MICROBIOLOGY



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Microbiology

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- Vibrio cholerae

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UNIT 1: INTRODUCTION TO MICROBIOLOGY AND PROKARYOTIC CELL ANATOMY

Microbiology is the study of microscopic organisms, those being unicellular (single cell), multicellular (cell colony), or acellular (lacking cells). As an application of microbiology, medical microbiology is often introduced with medical principles of immunology as microbiology and immunology. Otherwise, microbiology, virology, and immunology as basic sciences have greatly exceeded the medical variants, applied sciences.

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1: FUNDAMENTALS OF MICROBIOLOGY

1.1: Introduction to Microbiology
1.2: Cellular Organization - Prokaryotic and Eukaryotic Cells
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1.1: Introduction to Microbiology

Learning Objectives

1. State three harmful effects and four beneficial effects associated with the activities of microorganisms.
2. Define microbiota and microbiome.
3. Briefly describe two different beneficial things the human microbiome does for the normal function of our body.
4. State several diseases associated with a change in our "normal" microbiota.
5. List and recognize a description of the each of the 5 basic groups of microbes.

Microorganisms are the dominant life forms on earth, are found in almost every conceivable environment, and are essential to sustaining life on this planet. There are five basic groups of microorganisms:

- **Bacteria** are typically unicellular, microscopic, prokaryotic organisms that reproduce by binary fission.
- **Fungi (**yeasts and molds) are typically unicellular, microscopic, eukaryotic fungi that reproduce asexually by budding. Molds are typically filamentous, eukaryotic fungi that reproduce by producing asexual reproductive spores.
- **Viruses** are typically submicroscopic, acellular infectious particles that can only replicate inside a living host cell. The vast majority of viruses possess either DNA or RNA, but not both.
- **Protozoa** are typically unicellular, microscopic, eukaryotic organisms that lack a cell wall.
- **Algae** are typically eukaryotic microorganisms that carry out photosynthesis.

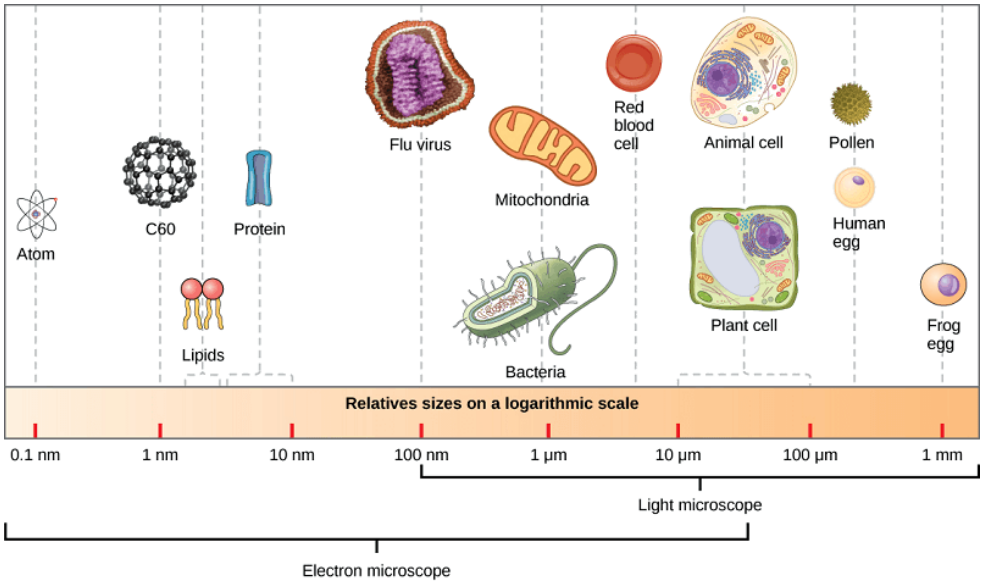
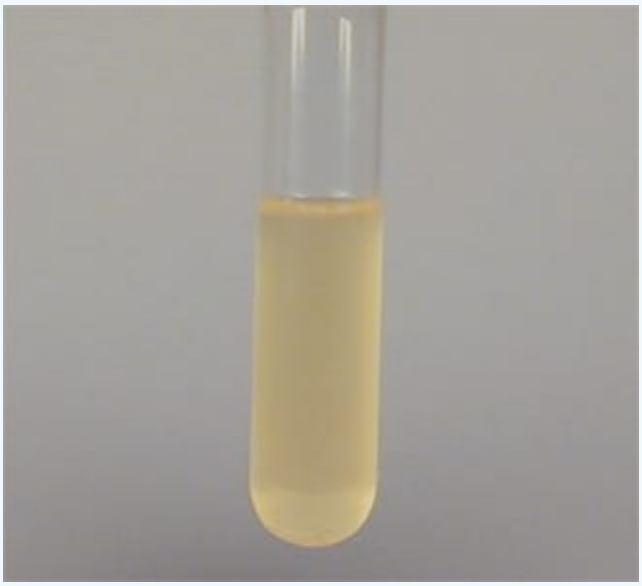


Figure 1.1.1: The size of a virus is very small relative to the size of cells and organelles.

To get us started on our introduction of microorganisms we will go through the following Think-Pair-Share Questions.

Exercise 1.1.1: Think-Pair-Share Questions



This tube contains 7 milliliters of a culture of *Escherichia coli*. The total number of bacteria in this tube is equal to:

a. The number of people in Baltimore city.
b. The number of people in Maryland.
c. The number of people in North America.
d. The number of people in the world.

Exercise 1.1.2: Think-Pair-Share Questions

Are microbes such as bacteria mostly beneficial or harmful? Briefly explain your answer.

Exercise 1.1.3: Think-Pair-Share Questions

- In what ways might microbes such as bacteria be beneficial?
- In what ways might microbes such as bacteria be harmful?

In this course we will be looking at various fundamental concepts of microbiology, with particular emphasis on their relationships to human health. The overall goal is to better understand the total picture of infectious diseases in terms of host-infectious agent interaction. We will look at various groups of microbes and learn what they might do to establish infection and harm the body, we will look at the body to see the ways in which it defends itself against these microbes, and we will learn what can be done to help the body in its defense efforts.

The Big Picture of Infectious Diseases

One of the most important things in microbiology is learining the "Big Picture of Infectious Diseases," which is the biological basis of host parasite interaction. There are four interlocking parts to this big picture:

A. **The microbe's side of the story - why some microbes have more potential to be harmful:** The overwhelming majority of microbes are harmless to humans and, in fact, many are beneficial, being key players in the recycling of nutrients in nature. We will look at the major groups of microbes, learn what they are composed of chemically and

structurally, and see how how they carry out their metabolism and reproduce. We will learn of a variety of factors some microbes may possess that play a role in increasing their ability to cause disease. Also we will learn how, through mutation, genetic recombination, and natural selection, microbes may adapt to resist our control attempts.

B. **The body's side of the story - ways in which the body is able to defend itself naturally against infectious disease agents:** Here will learn about the phenomenal defenses the body has available to defend itself against infectious disease agents, as well as altered body cells such as cancer cells and infected cells. The body is able to do this through the innate immune system and the adaptive immune system. Innate immune defenses are those you are born with and include anatomical barriers, mechanical removal, cytokines, pattern-recognition receptors, phagocytosis, inflammation, the complement pathways, and fever. The adaptive immune defenses are those you develop throughout your life and include antibody production and cell-mediated immunity.
C. **Ways in which we can artificially help the body defend itself by removing the microbes or enhancing body defenses:** We will learn how we can artificially help ourselves to avoid or reduce the risk of infection. Also we will learn ways in which we are able to artificially remove microbes from the body and its environment using agents such as antiseptics, disinfectants, physical agents such as heat and cold, antimicrobial chemotherapeutic chemicals, and antibiotics. Finally we will learn ways we are currently able to - or potentially in the future will be able to - improve or restore the body's immune responses through such techniques as immunization, adoptive immunotherapy, or immune modulation.
D. **Relationship between the Human Microbiome and Human Health:** The complex mutually beneficial symbiotic relationship between humans and their natural microbes is critical to good health. It is now recognized that the millions of genes associated with the normal flora or microbiota of the human body -especially in the intestinal tract - aid in the digestion of many foods, the regulation of multiple host metabolic pathways, and the regulation the body's immune defenses.

Benefits of Microbial Activity

Most people tend to think of microorganisms as harmful because of their roles in causing infectious diseases in humans and other animals, and agricultural loss as a result of infectious diseases of plants and the spoilage of food. The fact is, however, the vast majority of microorganisms are not harmful but rather beneficial. Without them there would be no life on earth. Therefore, we will start this course by looking at a few of the many benefits from microbial activity on this planet.

1. **Food production:** Many food products employ microorganisms in their production. These include the microbial fermentation processes used to produce yogurt, buttermilk, cheeses, alcoholic beverages, leavened breads, sauerkraut, pickles, and kimchi.
2. **Energy production and cleaning up the environment**: Methane, or natural gas, is a product of *methanogenic microorganisms*. Many aquatic microbes capture light energy and store it in molecules used as food then used by other organisms. Animal wastes, domestic refuse, biomass, and grain can be converted to biofuels such as ethanol and methane by microorganisms. In addition, through a process called bioremediation , some pollutants such pesticides, solvents, and oil spills can be cleaned up with the aid of microbes.
3. **Sustaining agriculture**: Through their roles in recycling nitrogen, carbon, and sulfur, microorganism are able to convert these essential elements into forms that can be used by plants in their growth. They are also essential in enabling ruminant animals such as cows and sheep to digest cellulose from the grasses they eat.
4. **Production of useful natural gene products or products from bioengineering**. Examples include specific enzymes, antibiotics, vaccines, and medications such as human insulin, interferons, and growth hormones.
5. **The human microbiota and microbiome**: Where we be without microorganisms? While the typical human body contains an estimated 37 trillion human cells, it also contains over 100 trillion bacteria and other microbes. The human body has 3 times as many bacterial cells as it does human cells! It is estimated the the mass of the human microbiota is 2.5 pounds.

The complex mutually beneficial symbiotic relationship between humans and their natural microbes is critical to good health. It is now recognized that the millions of genes associated with the microbiota of the human body -especially in the intestinal tract - aid in the digestion of many foods, the regulation of multiple host metabolic pathways, and the regulation the body's immune defenses. These collective microbes and their genes are referred to as the human microbiome. There are currently an estimated 5,000,000 - 10,000,000 genes from over 1000 species that constitute the human microbiome compared to the approximately 20,000 - 23,000 genes that make up the human genome. There are approximately 300 non-human genes in the human body for every human gene.

a. The mutually beneficial interaction between the human host and its resident microbiota is essential to human health. Microbial genes produce metabolites essential to the host while human genes contribute to development of the microbiota. The microbiome aids in the following:

1. The digestion of many foods, especially plant polysaccharides that would normally be indigestible by humans.
2. The regulation of many host metabolic pathways. The metabolism of many substrates in the human body is carried out by a combination of genes from both the microbiome and the human genome. Within the intestinal tract there is constant chemical communication not only between microbial species but also between microbial cells and human cells. Multiple factors, including diet, antibiotic use, disease, life style, and a person's environment can alter the composition of the microbiota within the gastrointestinal tract and, as a result, influence host biochemistry and the body's susceptibility to disease.
3. Metabolic disorders such as diabetes, nonalcoholic fatty liver disease, hypertension, obesity, gastric ulcers, colon cancer, and possibly some mood and behavior changes through hormone signaling have been linked to alterations in the microbiota.

b.

Summary

1. Microorganisms are typically too small to be seen with the naked eye.
2. Bacteria, fungi, viruses, protozoa, and algae are the major groups of microorganisms.
3. The vast majority of microorganisms are not harmful but rather beneficial.
4. Microbiota refers to all of the microorganisms that live in a particular environment.
5. A microbiome is the entire collection of genes found in all of the microbes associated with a particular host.
6. The microbiome of the human body - especially in the intestinal tract - aid in the digestion of many foods, the regulation of multiple host metabolic pathways, and the regulation the body's immune defenses.

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1.2: Cellular Organization - Prokaryotic and Eukaryotic Cells

Learning Objectives

1. Briefly describe why, in terms of differences in cell size, a eukaryotic cell is structurally more complex and compartmentalized than a cell that is prokaryotic.
2. When given a description, determine whether a cell is prokaryotic or eukaryotic and explain why.
3. Briefly state why viruses are not considered as prokaryotic nor eukaryotic.

According to the cell theory, the cell is the basic unit of life. All living organisms are composed of one or more cells. Based on the organization of their cellular structures, all living cells can be divided into two groups: prokaryotic and eukaryotic (also spelled procaryotic and eucaryotic). Animals, plants, fungi, protozoans, and algae all possess eukaryotic cell types. Only bacteria have prokaryotic cell types.

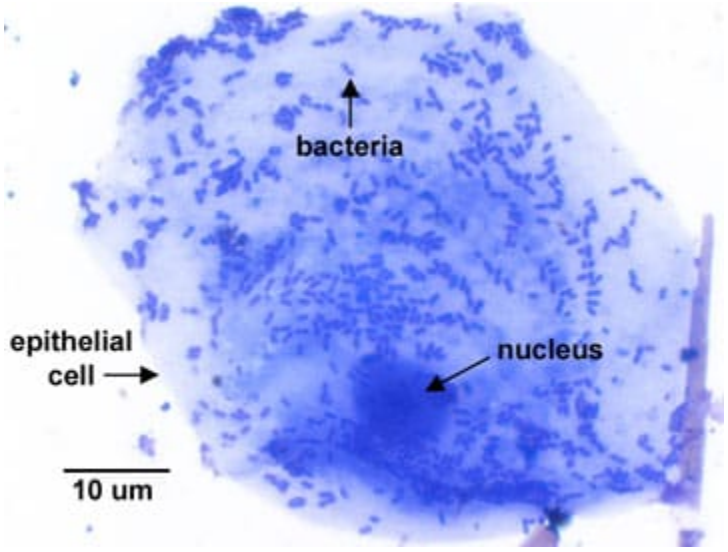


Figure 1.2.1: Bacteria on a Human Epithelial Cell from the Mouth. The bacteria are the small dark purple dots and dashes on the light blue cell. The oval purple mass in the center is the nucleus of the epithelial cell.

Prokaryotic cells are generally much smaller and more simple than eukaryotic (Figure 1.2.1). Prokaryotic cells are, in fact, able to be structurally more simple because of their small size. The smaller a cell, the greater is its surface-to-volume ratio (the surface area of a cell compared to its volume).

The surface area of a spherical object can be calculated using the following formula:

$$S = 4\,\pi\,r^2 \tag{1.2.1}$$

The volume of a spherical object can be calculated using the formula:

$$V = \frac{4}{3}\,\pi\,r^3 \tag{1.2.2}$$

For example, a spherical cell 1 micrometer (μm) in diameter - the average size of a coccus-shaped bacterium - has a surface-to-volume ratio of approximately 6:1, while a spherical cell having a diameter of 20 μm has a surface-to-volume ratio of approximately 0.3:1.

A large surface-to-volume ratio, as seen in smaller prokaryotic cells, means that nutrients can easily and rapidly reach any part of the cells interior. However, in the larger eukaryotic cell, the limited surface area when compared to its volume means nutrients cannot rapidly diffuse to all interior parts of the cell. That is why eukaryotic cells require a variety of specialized internal organelles to carry out metabolism, provide energy, and transport chemicals throughout the cell. Both, however, must carry out the same

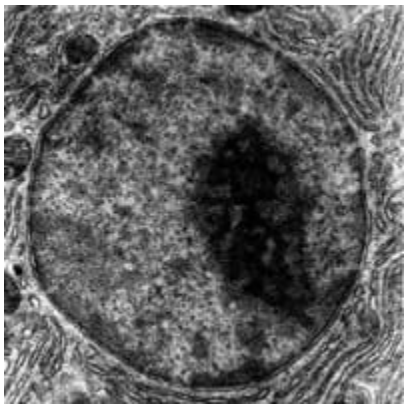
life processes. Some features distinguishing prokaryotic and eukaryotic cells are shown in Table 1.2.1. All of these features will be discussed in detail later in Unit 1.

Table 1.2.1: Eukaryotic Versus Prokaryotic Cells

Nuclear Body

eukaryotic cell

a. The nuclear body is bounded by a nuclear membrane having pores connecting it with the endoplasmic reticulum (see Figure 1.2.2 and Figure 1.2.3).
b. It contains one or more paired, linear chromosomes composed of deoxyribonucleic acid (DNA) associated with histone proteins).
c. A nucleolus is present. Ribosomal RNA (rRNA) is transcribed and assembled in the nucleolus.
d. The nuclear body is called a nucleus.



An electron micrograph of a cell nucleus, showing the darkly stained nucleolus. (Public Domain; US National Institute of General Medical Sciences/National Institutes of Health)

prokaryotic cell

a. The nuclear body is not bounded by a nuclear membrane (see Figure 1.2.4).
b. It usually contains one circular chromosome composed of deoxyribonucleic acid (DNA) associated with histone-like proteins.
c. There is no nucleolus.
d. The nuclear body is called a nucleoid .

Cell Division

eukaryotic cell

a. The nucleus divides by mitosis .
b. Haploid (1N) sex cells in diploid or 2N organisms are produced through meiosis .

For More Information: Review of Mitosis from Unit 7

prokaryotic cell

a. The cell usually divides by binary fission . There is no mitosis.
b. Prokaryotic cells are haploid. Meiosis is not needed.

Cytoplasmic Membrane - also known as a cell membrane or plasma membrane

eukaryotic cell

a. The cytoplasmic membrane (see Figure 1.2.2 and Figure 1.2.3) is a fluid phospholipid bilayer (see Figure 1.2.5) containing sterols (see Figure 1.2.6) .
b. The membrane is capable of endocytosis (phagocytosis and pinocytosis) and exocytosis .

prokaryotic cell

a. The cytoplasmic membrane (Figure 1.2.4) is a fluid phospholipid bilayer (Figure 1.2.5) that usually lacking sterols. Bacteria generally contain sterol-like molecules called hopanoids (Figure 1.2.7).

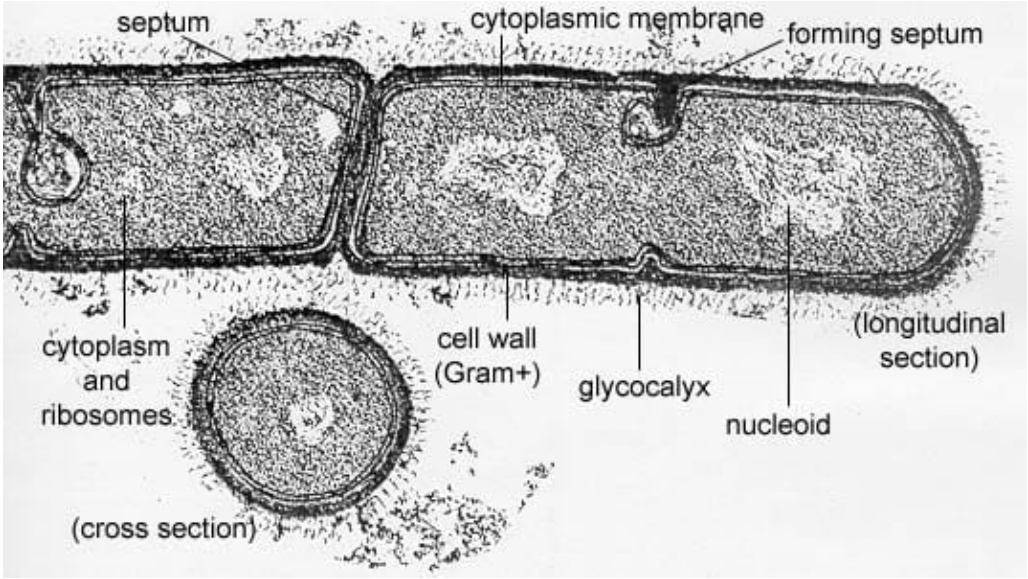


Figure 1.2.4: Prokaryotic Cell (Bacillus megaterium)

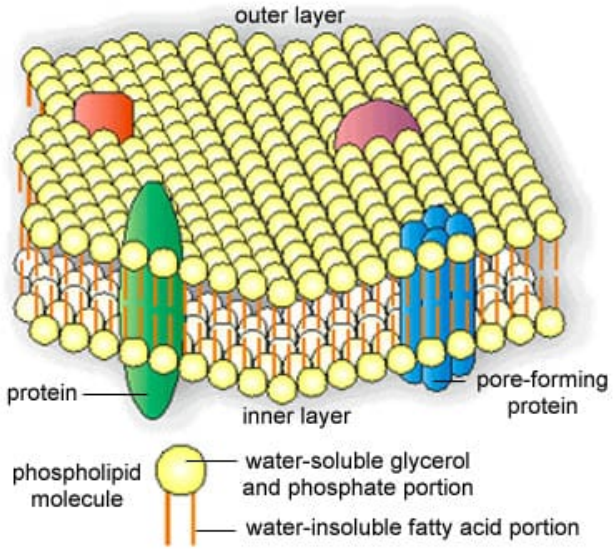


Figure 1.2.5: Diagram of a Cytoplasmic Membrane

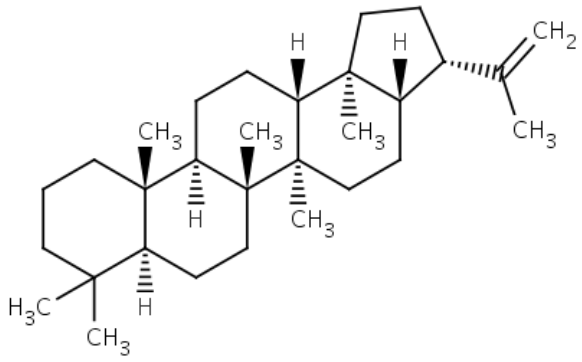


Figure 1.2.7: Sterol-like hopanoids are found in the cytoplasmic membrane of many bacteria.

b.The membrane is incapable of endocytosis and exocytosis.

Cytoplasmic Structures

eukaryotic cell

a. The ribosomes are composed of a 60S and a 40S subunit that come together during protein synthesis to form an 80S ribosome .

- Ribosomal subunit densities: 60S and 40S

b. Internal membrane-bound organelles such as mitochondria , endoplasmic reticulum , Golgi apparatus , vacuoles, and lysosomes are present (see Figure 1.2.2 and Figure 1.2.3).
c. Chloroplasts serve as organelles for photosynthesis.
d. A mitotic spindle involved in mitosis is present during cell division.
e. A cytoskeleton is present. It contains microtubules, actin micofilaments, and intermediate filaments. These collectively play a role in giving shape to cells, allowing for cell movement, movement of organelles within the cell and endocytosis, and cell division.

- Electron micrograph of a cytoplasmic membrane courtesy of Dennis Kunkel's Microscopy
- Electron micrograph of mitochondria courtesy of Dennis Kunkel's Microscopy
- Electron micrograph of rough endoplasmic reticulum courtesy of Dennis Kunkel's Microscopy
- Electron micrograph of a Golgi apparatus courtesy of Dennis Kunkel's Microscopy

prokaryotic cell

a. The ribosomes are composed of a 50S and a 30S subunit that come together during protein synthesis to form a 70S ribosome . See Figure 1.2.8.

- Ribosomal subunit densities: 50S and 30S

b. Internal membrane-bound organelles such as mitochondria, endoplasmic reticulum, Golgi apparatus, vacuoles, and lysosomes are absent (see Figure 1.2.4)
c. There are no chloroplasts. Photosynthesis usually takes place in infoldings or extensions derived from the cytoplasmic membrane.
d. There is no mitosis and no mitotic spindle.
e. The various structural filaments in the cytoplasm collectively make up the prokaryotic cytoskeleton. Cytoskeletal

filaments play essential roles in determining the shape of a bacterium (coccus, bacillus, or spiral) and are also critical in the process of cell division by binary fission and in determining bacterial polarity.

Prokaryotic cells with internal membrane-bound compartments?

Respiratory Enzymes and Electron Transport Chains

eukaryotic cell

- The electron transport system is located in the inner membrane of the mitochondria. It contributes to the production of ATP molecules via chemiosmosis.

-Electron micrograph of a mitochondrion from the Biology Department at the University of New Mexico.

Flash animation illustrating the development of proton motive force as a result of chemiosmosis and ATP production by ATP synthase.

html5 version of animation for iPad illustrating the development of proton motive force as a result of chemiosmosis and ATP production by ATP synthase.

prokaryotic cell

- The electron transport system is located in the cytoplasmic membrane. It contributes to the production of ATP molecules via chemiosmosis.

Flash animation illustrating ATP production by chemiosmosis during aerobic respiration in a prokaryotic bacterium.

html5 version of animation for iPad illustrating ATP production by chemiosmosis during aerobic respiration in a prokaryotic bacterium.

Cell Wall

eukaryotic cell

a. Plant cells, algae, and fungi have cell walls, usually composed of cellulose or chitin. Eukaryotic cell walls are never composed of peptidoglycan (see Figure 1.2.3).
b. Animal cells and protozoans lack cell walls (see Figure 1.2.2).

prokaryotic cell

a. With few exceptions, members of the domain *Bacteria* have cell walls composed of peptidoglycan (see Figure 1.2.4).
b. Members of the domain *Archae* have cell walls composed of protein, a complex carbohydrate, or unique molecules resembling but not the same as peptidoglycan.

Locomotor Organelles

eukaryotic cell

- Eukaryotic cells may have flagella or cilia. Flagella and cilia are organelles involved in locomotion and in eukaryotic cells consist of a distinct arrangement of sliding microtubules surrounded by a membrane. The microtubule arrangement is referred to as a 2X9+2 arrangement (see Figure 1.2.9).

- Electron micrograph of cilia showing microtubules courtesy of Dennis Kunkel's Microscopy
- YouTube movie of motile sperm.

prokaryotic cell

- Many prokaryotes have flagella, each composed of a single, rotating fibril and usually not surrounded by a membrane (see Figure 1.2.10). There are no cilia.

- Movie of motile *Rhodobacter spheroides* with fluorescent labelled-flagella. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

Representative Organisms

- eukaryotic cell: The domain *Eukarya*: animals, plants, algae, protozoans, and fungi (yeasts, molds, mushrooms).
- prokaryotic cell: The domain *Bacteria* and the domain *Archae*.

Since viruses are acellular- they contain no cellular organelles, cannot grow and divide, and carry out no independent metabolism - they are considered neither prokaryotic nor eukaryotic. Because viruses are not cells and have no cellular organelles, they can only replicate and assemble inside a living host cell. They turn the host cell into a factory for manufacturing viral parts and viral enzymes and assembling the viral components.

Viruses, which possess both living and nonliving characteristics, will be discussed in Unit 4. Recently, viruses have been declared as living entities based on the large number of protein folds encoded by viral genomes that are shared with the genomes of cells. This indicates that viruses likely arose from multiple ancient cells.

Summary

1. There are two basic types of cells in nature: prokaryotic and eukaryotic.
2. Prokaryotic cells are structurally simpler than eukaryotic cells.
3. The smaller a cell, the greater its surface to volume ratio.
4. The smaller the surface to volume ratio, the more structurally complex (compartmentalized) a cell needs to be in order to carry out life functions.
5. There are fundamental differences between prokaryotic and eukaryotic cells.
6. Bacteria are prokaryotic cells; fungi, protozoa, algae, plants, and animals are composed of eukaryotic cells.
7. Viruses are not cells so they are neither prokaryotic nor eukaryotic. They can replicate only inside a living cell.

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1.3: Classification - The Three Domain System

Learning Objectives

1. Define phylogeny.
2. Name the 3 Domains of the 3 Domain system of classification and recognize a description of each.
3. Name the four kingdoms of the Domain Eukarya and recognize a description of each.
4. Define horizontal gene transfer.

The Earth is 4.6 billion years old and microbial life is thought to have first appeared between 3.8 and 3.9 billion years ago; in fact, 80% of Earth's history was exclusively microbial life. Microbial life is still the dominant life form on Earth. It has been estimated that the total number of microbial cells on Earth on the order of 2.5 X 10^{30} cells, making it the major fraction of biomass on the planet.

Phylogeny refers to the evolutionary relationships between organisms. The Three Domain System, proposed by Woese and others, is an evolutionary model of phylogeny based on differences in the sequences of nucleotides in the cell's ribosomal RNAs (rRNA), as well as the cell's membrane lipid structure and its sensitivity to antibiotics. Comparing rRNA structure is especially useful. Because rRNA molecules throughout nature carry out the same function, their structure changes very little over time. Therefore similarities and dissimilarities in rRNA nucleotide sequences are a good indication of how related or unrelated different cells and organisms are.

There are various hypotheses as to the origin of prokaryotic and eukaryotic cells. Because all cells are similar in nature, it is generally thought that all cells came from a common ancestor cell termed the **last universal common ancestor (LUCA)**. These LUCAs eventually evolved into three different cell types, each representing a domain. The three domains are the *Archaea*, the *Bacteria*, and the *Eukarya*.

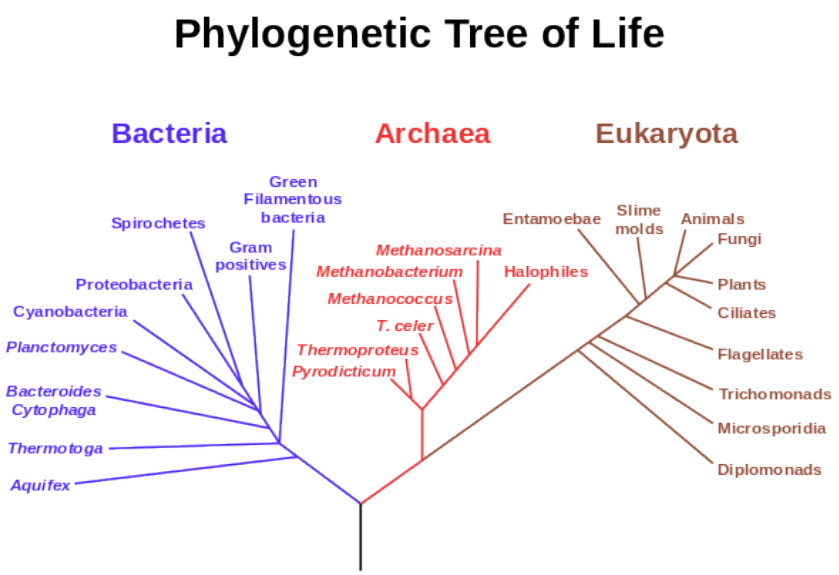


Figure 1.3.1: A phylogenetic tree based on rRNA data, showing the separation of bacteria, archaea, and eukaryota domains.

More recently various fusion hypotheses have begun to dominate the literature. One proposes that the diploid or 2N nature of the eukaryotic genome occurred after the fusion of two haploid or 1N prokaryotic cells. Others propose that the domains *Archaea* and *Eukarya* emerged from a common archaeal-eukaryotic ancestor that itself emerged from a member of the domain *Bacteria*. Some of the evidence behind this hypothesis is based on a "superphylum" of bacteria called PVC, members of which share some characteristics with both archaea and eukaryotes. There is growing evidence that eukaryotes may have originated within a subset of archaea. In any event, it is accepted today that there are three distinct domains of organisms in nature: *Bacteria, Archaea*, and *Eukarya*. A description of the three domains follows.

Domains?

There is a "superphylum" of bacteria called PVC, referring to the three members of that superphylum: the Planctomycetes, the Verrucomicrobia, and the Chlamydiae. Members of the PVC, while belonging to the domain *Bacteria*, show some features of the domains *Archaea* and *Eukarya*.

Some of these bacteria show cell compartmentalization wherein membranes surround portions of the cell interior, such as groups of ribosomes or DNA, similar to eukaryotic cells. Some divide by budding or contain sterols in their membranes, again similar to eukaryotes. Some lack peptidoglycan, similar to eukaryotes and archaea. It has been surmised that these bacteria migh be an intermediate step between an ancestor that emerged from a bacterium (domain *Bacteria*) and an archael-eukaryotic ancestor prior to its split into the domains *Archaea* and *Eukarya*.

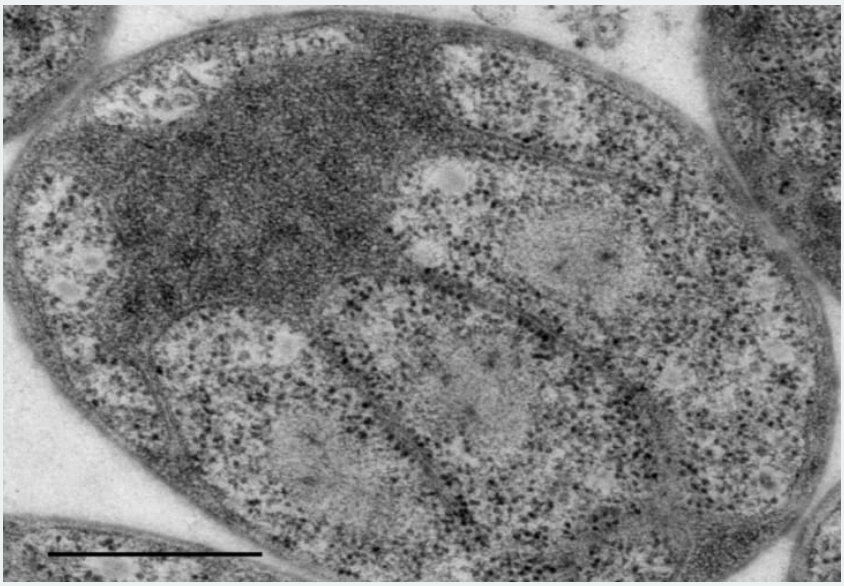


Figure 1.3.2: Electron micrograph of the bacterium Gemmata obscuriglobus, a planctomycete noted for its highly complex membrane morphology, illustrating representative morphologies. Scale bar = 500nm. Santarella-Mellwig R, Franke J, Jaedicke A, Gorjanacz M, Bauer U, Budd A, et al. (2010) The Compartmentalized Bacteria of the Planctomycetes-Verrucomicrobia-Chlamydiae Superphylum Have Membrane Coat-Like Proteins. PLoS Biol 8(1): e1000281. doi:10.1371/journal.pbio.1000281

The Archaea (archaebacteria)

The *Archaea* possess the following characteristics:

a. *Archaea* are prokaryotic cells.
b. Unlike the *Bacteria* and the *Eukarya*, the *Archaea* have membranes composed of branched hydrocarbon chains (many also containing rings within the hydrocarbon chains) attached to glycerol by ether linkages (Figure 1.3.3).
c. The cell walls of *Archaea* contain no peptidoglycan.
d. *Archaea* are not sensitive to some antibiotics that affect the *Bacteria*, but are sensitive to some antibiotics that affect the *Eukarya*.
e. *Archaea* contain rRNA that is unique to the *Archaea* as indicated by the presence molecular regions distinctly different from the rRNA of *Bacteria* and *Eukarya*.

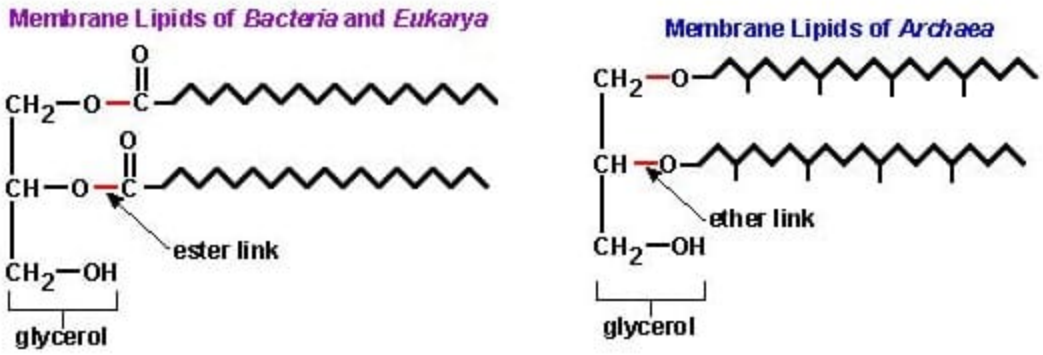


Figure 1.3.3: Membrane Lipids of Archaea, Bacteria, and Eukarya. The Bacteria and the Eukarya have membranes composed of unbranched fatty acid chains attached to glycerol by ester linkages. The Archaea have membranes composed of branched hydrocarbon chains attached to glycerol by ether linkages.

Archaea often live in extreme environments and include methanogens, extreme halophiles, and hyperthermophiles. One reason for this is that the ether-containing linkages in the *Archaea* membranes is more stabile than the ester-containing linkages in the *Bacteria* and *Eukarya* and are better able to withstand higher temperatures and stronger acid concentrations.

The *Bacteria* (eubacteria)

Bacteria (also known as eubacteria or "true bacteria") are prokaryotic cells that are common in human daily life, encounter many more times than the archaebacteria. Eubacteria can be found almost everywhere and kill thousands upon thousands of people each year, but also serve as antibiotics producers and food digesters in our stomachs. The *Bacteria* possess the following characteristics:

a. *Bacteria* are prokaryotic cells.
b. Like the *Eukarya*, they have membranes composed of unbranched fatty acid chains attached to glycerol by ester linkages (Figure 1.3.3).
c. The cell walls of *Bacteria*, unlike the *Archaea* and the Eukarya, contain peptidoglycan.
d. *Bacteria* are sensitive to traditional antibacterial antibiotics but are resistant to most antibiotics that affect *Eukarya*.
e. *Bacteria* contain rRNA that is unique to the *Bacteria* as indicated by the presence molecular regions distinctly different from the rRNA of *Archaea* and *Eukarya*.

Bacteria include mycoplasmas, cyanobacteria, Gram-positive bacteria, and Gram-negative bacteria.

The *Eukarya* (eukaryotes)

The *Eukarya* (also spelled *Eucarya*) possess the following characteristics:

a. *Eukarya* have eukaryotic cells.
b. Like the *Bacteria*, they have membranes composed of unbranched fatty acid chains attached to glycerol by ester linkages (Figure 1.3.3).
c. Not all *Eukarya* possess cells with a cell wall, but for those *Eukarya* having a cell wall, that wall contains no peptidoglycan.
d. *Eukarya* are resistant to traditional antibacterial antibiotics but are sensitive to most antibiotics that affect eukaryotic cells.
e. *Eukarya* contain rRNA that is unique to the *Eukarya* as indicated by the presence molecular regions distinctly different from the rRNA of *Archaea* and *Bacteria*.

The *Eukarya* are subdivided into the following four kingdoms:

1. Protista Kingdom: Protista are simple, predominately unicellular eukaryotic organisms. Examples includes slime molds, euglenoids, algae, and protozoans.
2. Fungi Kingdom: Fungi are unicellular or multicellular organisms with eukaryotic cell types. The cells have cell walls but are not organized into tissues. They do not carry out photosynthesis and obtain nutrients through absorption. Examples include sac fungi, club fungi, yeasts, and molds.

3. Plantae Kingdom: Plants are multicellular organisms composed of eukaryotic cells. The cells are organized into tissues and have cell walls. They obtain nutrients by photosynthesis and absorption. Examples include mosses, ferns, conifers, and flowering plants.
4. Animalia Kingdom: Animals are multicellular organisms composed of eukaryotic cells. The cells are organized into tissues and lack cell walls. They do not carry out photosynthesis and obtain nutrients primarily by ingestion. Examples include sponges, worms, insects, and vertebrates.

It used to be thought that the changes that allow microorganisms to adapt to new environments or alter their virulence capabilities was a relatively slow process occurring within an organism primarily through mutations, chromosomal rearrangements, gene deletions and gene duplications. Those changes would then be passed on to that microbe's progeny and natural selection would occur. This gene transfer from a parent organism to its offspring is called vertical gene transmission.

It is now known that microbial genes are transferred not only vertically from a parent organism to its progeny, but also horizontally to relatives that are only distantly related, e.g., other species and other genera. This latter process is known as horizontal gene transfer. Through mechanisms such as transformation, transduction, and conjugation, genetic elements such as plasmids, transposons, integrons, and even chromosomal DNA can readily be spread from one microorganism to another. As a result, the old three-branched "tree of life" in regard to microorganisms (Figure $1.3.1$) now appears to be more of a "net of life."

Microbes are known to live in remarkably diverse environments, many of which are extremely harsh. This amazing and rapid adaptability is a result of their ability to quickly modify their repertoire of protein functions by modifying, gaining, or losing their genes. This gene expansion predominantly takes place by horizontal transfer.

Summary

1. Phylogeny refers to the evolutionary relationships between organisms.
2. Organisms can be classified into one of three domains based on differences in the sequences of nucleotides in the cell's ribosomal RNAs (rRNA), the cell's membrane lipid structure, and its sensitivity to antibiotics.
3. The three domains are the Archaea, the Bacteria, and the Eukarya.
4. Prokaryotic organisms belong either to the domain Archaea or the domain Bacteria; organisms with eukaryotic cells belong to the domain Eukarya.
5. Microorganism transfer genes to other microorganisms through horizontal gene transfer - the transfer of DNA to an organism that is not its offspring.

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1.E: Fundamentals of Microbiology (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

1.1: Introduction to Microbiology

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. List 5 basic groups of microbes.
2. State 3 of the many benefits from microbial activity on this planet.
3. State 2 of the harmful effects associated with microbial activities.
4. Briefly describe two different beneficial things the human microbiome does for the normal function of our body.

1.2: Cellular Organization: Prokaryotic and Eukaryotic Cells

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. An electron micrograph of a cell shows a rigid cell wall, cytoplasmic membrane, nuclear body without a nuclear membrane, and no endoplasmic reticulum or mitochondria. Explain why it is or is not each of the following.
   a. a bacterium
   b. a yeast
   c. a virus
   d. an animal cell
2. Match the descriptions below with the best type of cellular organization.

   _____ no nuclear membrane, circular chromosome of DNA, no mitosis
   _____ capable of endocytosis, sterols in membrane, 80S ribosomes
   _____ mitochondria, Golgi apparatus, endoplasmic reticulum
   _____ cell wall contains peptidoglycan

   A. eukaryotic
   B. prokaryotic
3. Multiple Choice

1.3: Classification: The Three Domain System

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching

   ____ Eukaryotic cells. They have membranes composed of straight fatty acid chains attached to glycerol by ester linkages.If they possess cell walls, those walls contain no peptidoglycan.

   ____ Prokaryotic cells. They have membranes composed of branched hydrocarbon chains attached to glycerol by ether linkages and have cell walls that contain no peptidoglycan. They often live in extreme environments.

   ____ Prokaryotic cells. They have membranes composed of straight fatty acid chains attached to glycerol by ester linkages and have cell walls containing peptidoglycan.

A. *Archaea*
B. *Bacteria*
C. *Eukarya*

2. Matching

____ Simple, predominately unicellular eukaryotic organisms. Examples includes slime molds, euglenoids, algae, and protozoans.

_____ Multicellular organisms composed of eukaryotic cells. The cells are organized into tissues and lack cell walls. They do not carry out photosynthesis and obtain nutrients primarily by ingestion.

____ Multicellular organisms composed of eukaryotic cells. The cells are organized into tissues and have cell walls. They obtain nutrients by photosynthesis and absorption.

A. Fungi Kingdom
B. Protista Kingdom
C. Plantae Kingdom
D. Animalia Kingdom

3. Multiple Choice

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2.1: Sizes, Shapes, and Arrangements of Bacteria

Learning Objectives

1. List the three basic shapes of bacteria.
2. List and describe 5 different arrangements of cocci.
3. Define and give the abbreviation for the metric unit of length termed micrometer and state the average size of a coccus-shaped bacterium and a rod-shaped bacterium.
4. List and describe 2 different arrangements of bacilli.
5. List and describe 3 different spiral forms of bacteria.

Bacteria are prokaryotic, single-celled, microscopic organisms (Exceptions have been discovered that can reach sizes just visible to the naked eye. They include *Epulopiscium fishelsoni*, a bacillus-shaped bacterium that is typically 80 micrometers (µm) in diameter and 200-600 µm long, and *Thiomargarita namibiensis*, a spherical bacterium between 100 and 750 µm in diameter.)

a. generally much smaller than eukaryotic cells.
b. very complex despite their small size. Even though bacteria are single-celled organisms, they are able to communicate with one another through a process called quorum sensing. In this way they can function as a multicellular population rather than as individual bacteria. This will be discussed in greater detail in Unit 2.

For More Information: Bacterial Communication through Quorum Sensing

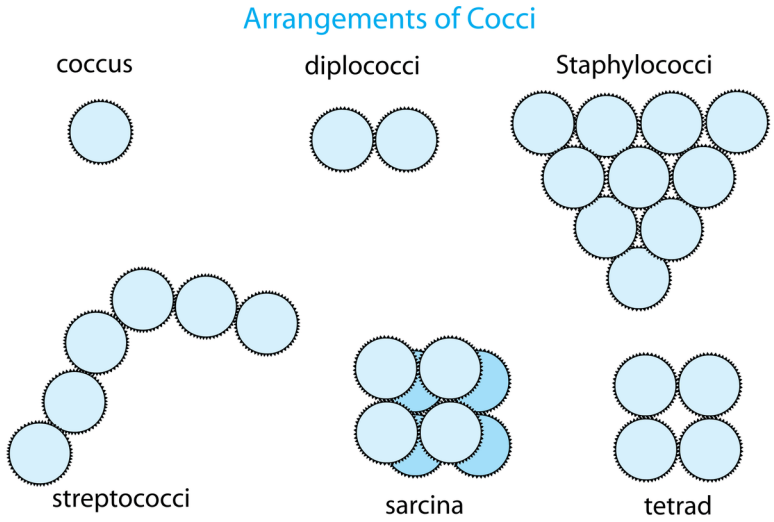


Figure 2.1.2.1.1: Arrangement of cocci bacteria. image used with permission from Mariana Ruiz.

a. Division in **one plane** produces either a diplococcus or streptococcus arrangement.

diplococcus: cocci arranged in pairs (see Figure 2.1.2)

- scanning electron micrograph of a *Streptococcus pneumoniae*, a diplococcus; courtesy of CDC
- scanning electron micrograph of a *Neisseria*, a diplococcus; courtesy of Dennis Kunkel's Microscopy

streptococcus: cocci arranged in chains (see Figure 2.1.3)

- scanning electron micrograph of a *Streptococcus pyogenes*, a streptococcus; courtesy of Dennis Kunkel's Microscopy
- transmission electron micrograph of *Streptococcus* from the Rockefeller University web page.

- scanning Electron Micrograph of *Enterococcus*

b. Division in **two planes** produces a tetrad arrangement.

tetrad: cocci arranged in squares of 4 (see Figure 2.1.4)

- scanning electron micrograph of *Micrococcus luteus* showing several tetrads

c. Division in **three planes** produces a sarcina arrangement.

sarcina: cocci in arranged cubes of 8 (see Figure 2.1.5)

d. Division in **random planes** produces a staphylococcus arrangement.

staphylococcus: cocci arranged in irregular, often grape-like clusters (see Figure 2.1.6)

- negative image of *Staphylococcus aureus*
- scanning electron micrograph of *Staphylococcus aureus*, a staphylococcus; courtesy of Dennis Kunkel's Microscopy
- Scanning electron micrograph of methicillin-resistant *Staphylococcus aureus* (MRSA); courtesy of CDC

An average coccus is about 0.5-1.0 micrometer (µm) in diameter. (A micrometer equals 1/1,000,000 of a meter.)

The rod or bacillus

Bacilli are rod-shaped bacteria. Bacilli all divide in one plane producing a bacillus, streptobacillus, or coccobacillus arrangement (see Figure 2.1.7).

a. **bacillus**: single bacilli (see Figure 2.1.8)
- scanning electron micrograph of a bacillus; courtesy of CDC
- scanning electron micrograph of *Escherichia coli* O157H7, a bacillus; courtesy of CDC

b. **streptobacillus**: bacilli arranged in chains (see Figure 2.1.9)

c. **coccobacillus**: oval and similar to a coccus (see Figure 2.1.9A and Figure 2.1.9B)

An average bacillus is 0.5-1.0 µm wide by 1.0-4.0 µm long.

The spiral

Spirals come in one of three **forms**, a vibrio, a spirillum, or a spirochete. (see Figure 2.1.10)

a. **vibrio**: a curved or comma-shaped rod (see Figure 2.1.11)

- scanning electron micrograph of a *Vibrio cholerae*, a vibrio; courtesy of Dennis Kunkel's Microscopy

b. **spirillum**: a thick, rigid spiral (see Figure 2.1.12)

c. **spirochete**: a thin, flexible spiral (see Figure 2.1.13)

- scanning electron micrograph of the spirochete *Leptospira*; courtesy of CDC
- scanning electron micrograph of the spirochete *Treponema pallidum*; courtesy of CDC

Spirals range in size from 1 µm to over 100 µm in length.

Exceptions to the above shapes

There are exceptions to the three basic shapes of coccus, bacillus, and spiral. They include sheathed, stalked, filamentous, square, star-shaped,

spindle-shaped, lobed, trichome-forming, and pleomorphic bacteria.

Ultrasmall Bacteria

Ultrasmall bacteria (150 could fit in a single Escherichia coli) have been discovered in groundwater that was passed through a filter with a pore size of 0.2 micrometers µm). They showed an **average length of only 323 nanometers**(nm) and an average width of 242 nm. They contain DNA, an average of 42 ribosomes per bacterium, and possessed pili . It is thought that they use these pili to attach to other bacteria from which they scavenge nutrients. Because the surface to volume ratio is even greater than in more traditional sized bacteria, they might be better designed to take up scarce nutrients from more nutrient-poor environments.

Concept map for Shapes and Arrangements of Bacteria

Summary

1. There are three basic shapes of bacteria: coccus, bacillus, and spiral.
2. Based on planes of division, the coccus shape can appear in several distinct arrangements: diplococcus, streptococcus, tetrad, sarcina, and staphylococcus.
3. The bacillus shape can appear as a single bacillus, a streptobacillus, or a coccobacillus.
4. The spiral shape can appear in several forms: vibrio, spirillum, and spirochete.
5. The metric unit micrometer (1/1,000,000 or 10^{-6} of a meter) is used to measure bacterial size.

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2.2: The Cytoplasmic Membrane

State the chemical composition and major function of the cytoplasmic membrane in bacteria.

- Briefly describe the fluid phospholipid bilayer arrangement of biological membranes.
- State the net flow of water when a cell is placed in an isotonic, hypertonic, or hypotonic environment and relate this to the solute concentration.
- Define the following means of transport:

  a. passive diffusion
  b. osmosis
  c. facilitated diffusion
  d. transport through channel proteins
  e. transport through uniporter
  f. active transport
  g. transport through antiporter
  h. transport through symporter
  i. the ABC transport system
  j. group translocation

- State how the antibiotic polymyxin and disinfectants such as orthophenylphenol, chlorhexidine, hexachlorophene, zephiran, and alcohol affect bacteria.
- Define binary fission and geometric progression and relate this to bacteria being able to astronomically increase their numbers in a relatively short period of time.
- Briefly describe the process of binary fission in bacteria, stating the functions of Par proteins, the divisome, and FtsZ proteins.

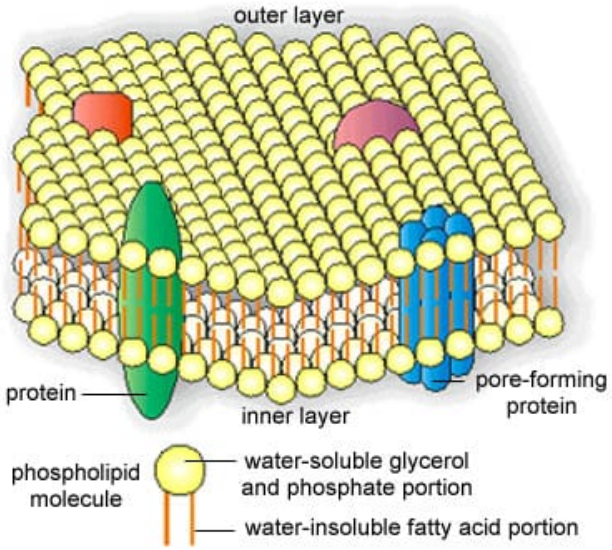


Figure 2.2.3A: Passive Diffusion Steps. Passive diffusion is the net movement of gases or small uncharge polar molecules across a phospholipid bilayer membrane from an area of higher concentration to an area of lower concentration . Examples of gases that cross membranes by passive diffusion include N_2, O_2, and CO_2; examples of small polar molecules include ethanol, H_2O, and urea.

All molecules and atoms possess kinetic energy (energy of motion). If the molecules or atoms are not evenly distributed on both sides of a membrane, the difference in their concentration forms a concentration gradient that represents a form of potential energy (stored energy). The net movement of these particles will therefore be down their concentration gradient - from the area of higher concentration to the area of lower concentration. Diffusion is powered by the potential energy of a concentration gradient and does not require the expenditure of metabolic energy.

Flash animation showing passive diffusion of oxygen.

html5 version of animation for iPad showing passive diffusion of oxygen.

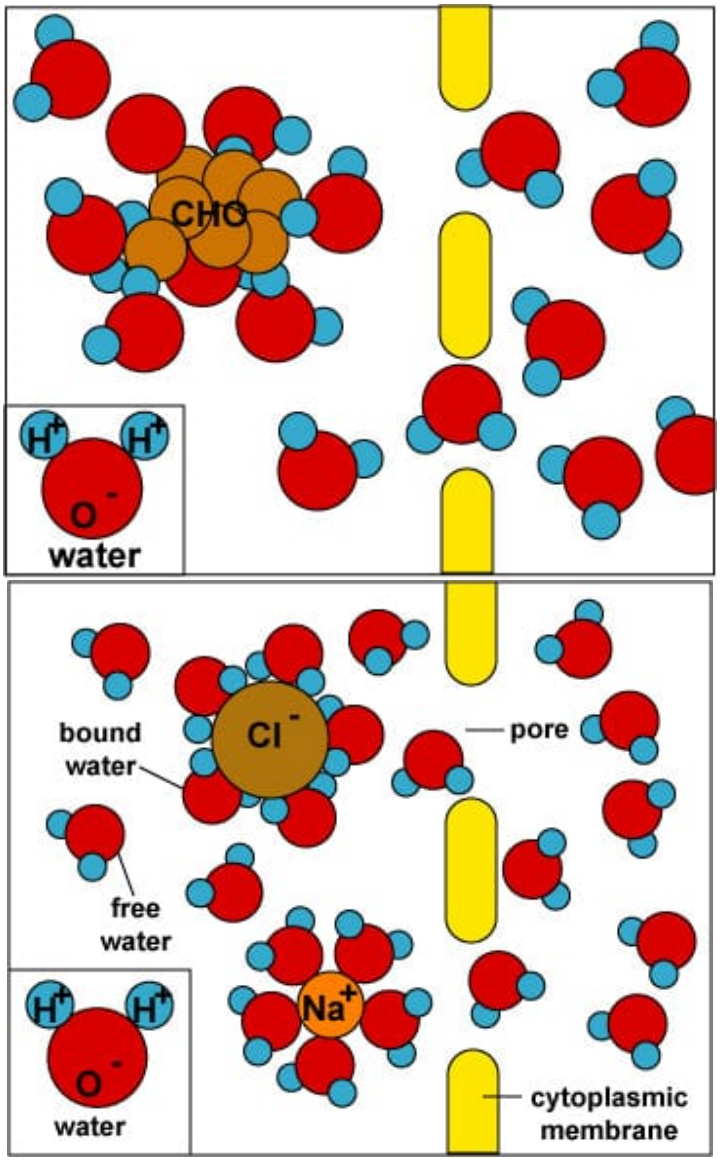


Figure 2.2.4: Osmosis. Free Water Passing Through Membrane Pores. (left) When a solute such as sugar dissolves in water, it forms weak hydrogen bonds with water molecules. While free, unbound water molecules are small enough to pass through the membrane and through membrane pores, water molecules bound to solute are not. (right) When an ionic solute such as NaCl dissolves in water, the Na^+ ion attracts the partial negative charge of the oxygen atom in the water molecule while the Cl^- ion attracts the partial positive charge of the warter's hydrogen. While free, unbound water molecules are small enough to pass through the membranr and through membrane pores, water molecules bound to solute are not.

A cell can find itself in one of three environments: isotonic, hypertonic, or hypotonic (the prefixes iso-, hyper-, and hypo- refer to the solute concentration).

- In an isotonic environment (Figure 2.2.5) both the water and solute concentration are the same inside and outside the cell and water goes into and out of the cell at an equal rate.

Flash animation showing osmosis in an isotonic environment.

http5 version of animation for iPad showing osmosis in an isotonic environment.

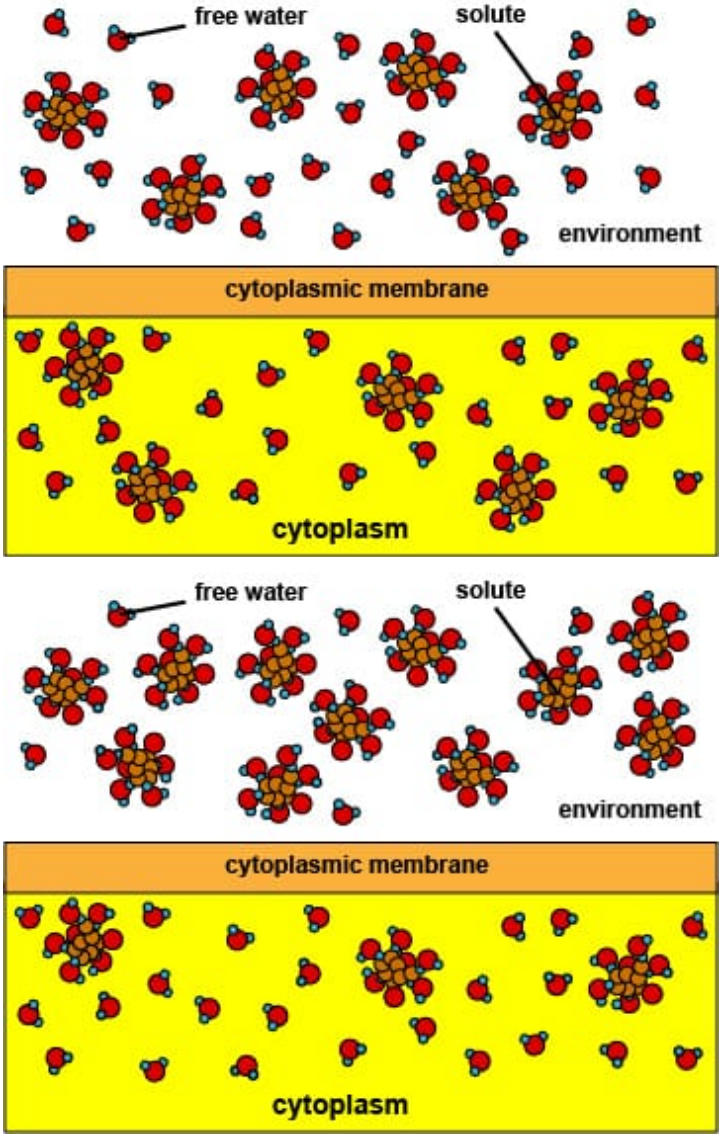


Figure 2.2.5: Osmosis (Cell in an Isotonic Environment). (left) In anisotonic environment, both the water and solute concentration are the same inside and outside the cell and water goes into and out of the cell at an equal rate. (right) If the environment surrounding the cell is hypertonic, the solute concentration is higher outside the cell, while the water concentration is greater inside the cell. The cytoplasm of the cell is hypotonic to the surrounding hypertonic environment. Water goes out of the cell.

- If the environment is hypertonic (Figure 2.2.6A and Figure 2.2.6B) the water concentration is greater inside the cell while the solute concentration is higher outside (the interior of the cell is hypotonic to the surrounding hypertonic environment). Water goes out of the cell.

Flash animation showing osmosis in a hypertonic environment.

html5 version of animation for iPad showing osmosis in a hypertonic environment.

- In an environment that is hypotonic (Figure 2.2.7) the water concentration is greater outside the cell and the solute concentration is higher inside (the interior of the cell is hypertonic to the hypotonic surroundings). Water goes into the cell.

Flash animation showing osmosis in a hypotonic environment.

html5 version of animation for iPad showing osmosis in a hypotonic environment.

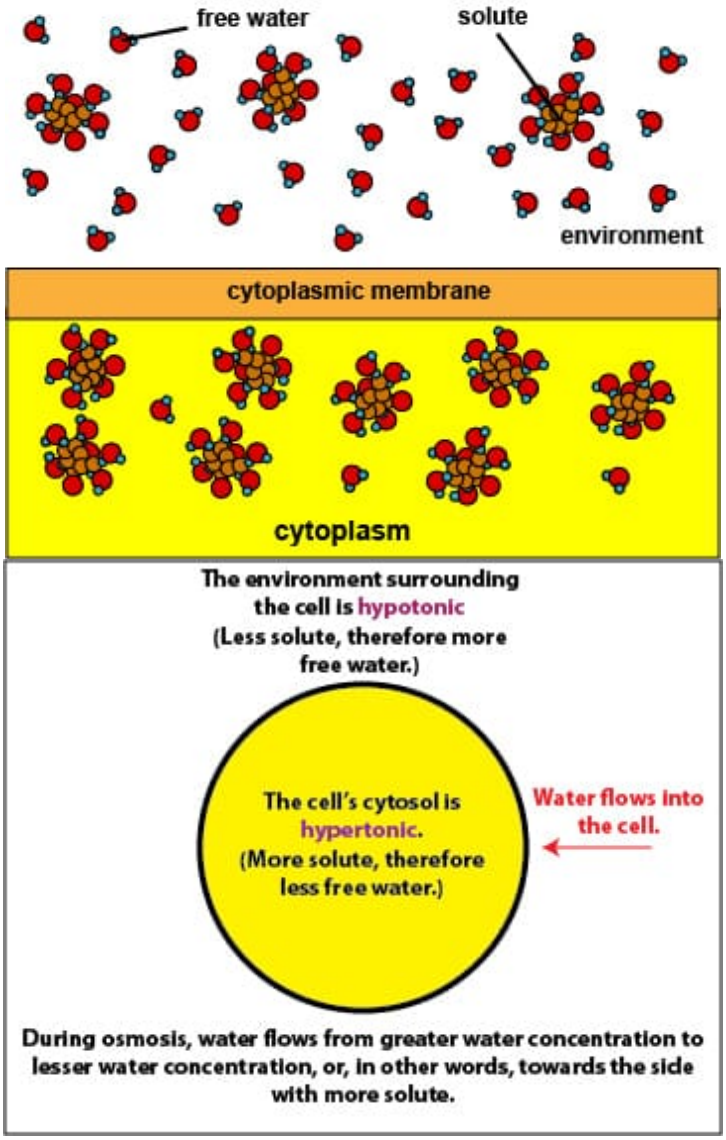


Figure 2.2.2.2.8: Transport of Substances Across a Membrane by Uniporters. Uniporters are transport proteins that transport a substance across a membrane down a concentration gradient from an area of greater concentration to lesser concentration. The transport is powered by the potential energy of a concentration gradient and does not require metabolic energy.

Flash animation showing transport by way of an uniporter.

html5 version of animation for iPad showing transport by way of an uniporter.

2. Channel proteins transport water or certain ions down either a concentration gradient, in the case of water, or an electric potential gradient in the case of certain ions, from an area of higher concentration to lower concentration (Figure 2.2.6B). While water molecules can directly cross the membrane by passive diffusion, as mentioned above, channel proteins called aquaporins can enhance their transport.

Flash animation showing transport of water across a membrane by channel proteins.

html5 version of animation for iPad showing transport of water across a membrane by channel proteins.

Active Transport

Active transport is a process whereby the cell uses both transport proteins and metabolic energy to transport substances across the membrane against the concentration gradient. In this way, active transport allows cells to accumulate needed substances even when the concentration is lower outside. Active transport enables bacteria to successfully compete with other organisms for limited nutrients in their natural habitat, and as will be seen in Unit 2, enables pathogens to compete with the body's own cells and normal flora bacteria for the same nutrients.

The energy is provided by proton motive force, the hydrolysis of ATP, or the breakdown of some other high-energy compound such as phosphoenolpyruvate (PEP). Proton motive force is an energy gradient resulting from hydrogen ions (protons) moving across the membrane from greater to lesser hydrogen ion concentration. ATP is the form of energy cells most commonly use to do cellular work. PEP is one of the intermediate high-energy phosphate compounds produced at the end of glycolysis.

For More Information: Review of Glycolysis from Unit 7

For More Information: Review of Proton Motive Force from Unit 7

For More Information: Review of ATP from Unit 7

Specific transport proteins (carrier proteins) are required in order to transport the majority of molecules a cell requires across its cytoplasmic membrane. This is because the concentration of nutrients in most natural environments is typically quite low. Transport proteins allow cells to accumulate nutrients from even a sparse environment. Transport proteins involved in active transport include antiporters, symporters, the proteins of the ATP-binding cassette (ABC) system, and the proteins involved in group translocation.

a. Antiporter: Antiporters are transport proteins that transport one substance across the membrane in one direction while simultaneously transporting a second substance across the membrane in the opposite direction (Figure 2.2.9A). Antiporters in bacteria generally use the potential energy of electrochemical gradients from protons (H^+), that is, proton motive force to co-transport ions, glucose, and amino acids against their concentration gradient (Figure 2.2.9B). Sodium ions (Na^+) and protons (H^+), for example, are co-transported across bacterial membranes by antiporters.

Flash animation showing transport by way of an antiporter.

html5 version of animation for iPad showing transport by way of an antiporter.

b. Symporter: Symporters are transport proteins that simultaneously transport two substances across the membrane in the same direction (Figure 2.2.10A). Symporters use the potential energy of electrochemical gradients from protons (H^+), that is, proton motive force to co-transport ions, glucose, and amino acids against their concentration gradient (Figure 2.2.10B). Sulfate (HSO_4^-) and protons (H^+) as well as phosphate (HPO_4^-) and protons (H^+) are co-transported across bacterial membranes by symporters.

Flash animation showing transport by way of a symporter.

html5 version of animation for iPad showing transport by way of a symporter.

c. ATP-binding cassette (ABC) system: An example of an ATP-dependent active transport found in various gram-negative bacteria is the ATP-binding cassette (ABC) system. This involves substrate-specific binding proteins located in the bacterial periplasm, the gel-like substance between the bacterial cell wall and cytoplasmic membrane. The periplasmic-binding protein picks up the substance to be transported and carries it to a membrane-spanning transport protein (Figure 2.2.11A). Meanwhile, an ATP-hydrolyzing protein breaks ATP down into ADP, phosphate, and energy (Figure 2.2.11B). It is this energy that powers the transport of the substrate, by way of the membrane-binding transporter, across the membrane (Figure 11C and Figure 2.2.11D) and into the cytoplasm. Examples of active transport include the transport of certain sugars and amino acids. Over 200 different ABC transport systems have been found in bacteria.

Flash animation showing an "ABC" transport system.

http5 version of animation for iPad showing an "ABC" transport system.

d. Group translocation is another form of active transport that can occur in prokaryotes. In this case, a substance is chemically altered during its transport across a membrane so that once inside, the cytoplasmic membrane becomes impermeable to that substance and it remains within the cell.

An example of group translocation in bacteria is the phosphotransferase system. A high-energy phosphate group from phosphoenolpyruvate (PEP) is transferred by a series of enzymes to glucose. The final enzyme both phosphorylates the glucose and transports it across the membrane as glucose 6-phosphate (Figure 2.2.12A through 12D). (This is actually the first step in glycolysis.) Other sugars that are transported by group translocation are mannose and fructose.

Flash animation showing group translocation.

html5 version of animation for iPad showing group translocation.

Functions of the cytoplasmic membrane other than selective permeability

A number of other functions are associated with the bacterial cytoplasmic membrane and associated proteins of a collection of cell division machinery known as the divisome. In fact, many of the functions associated with specialized internal membrane-bound organelles in eukaryotic cells are carried out generically in bacteria by the cytoplasmic membrane. Functions associated with the bacterial cytoplasmic membrane and/or the divisome include:

1. energy production. The electron transport system (Fig.) for bacteria with aerobic and anaerobic respiration, as well as photosynthesis for bacteria converting light energy into chemical energy is located in the cytoplasmic membrane.
2. motility. The motor that drives rotation of bacterial flagella (see Fig.) is located in the cytoplasmic membrane.
3. Movie of motile *Rhodobacter spheroides* with fluorescent labelled-flagella. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
4. waste removal. Waste by products of metabolism within the bacterium must exit through the cytoplasmic membrane.

5. formation of endospores (discussed later in this unit; see Fig. and animation).

Concept map for the cytoplasmic membrane, domain *Bacteria*.

Binary fission

Bacteria divide by binary fission wherein one bacterium splits into two. Therefore, bacteria increase their numbers by geometric progression whereby their population doubles every generation time. In general it is thought that during DNA replication (discussed in Unit 6), each strand of the replicating bacterial DNA attaches to proteins at what will become the cell division plane. For example, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells.

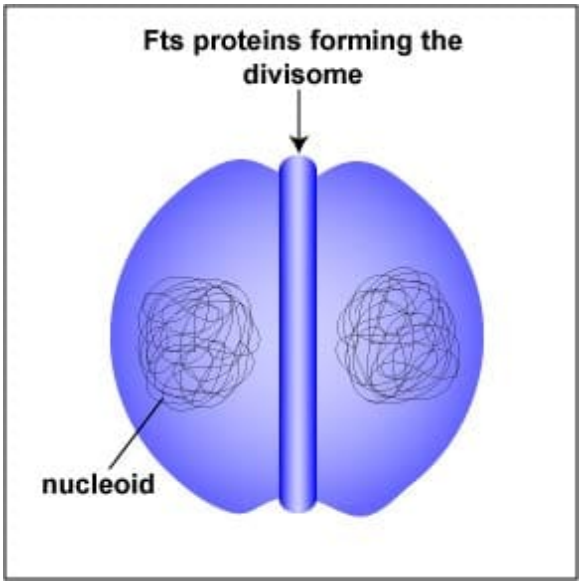


Figure 2.2.8**:** Bacterial Divisome.*In general it is thought that during DNA replication (discussed in Unit 6), each strand of the replicating bacterial DNA attaches to proteins at what will become the cell division plane. For example, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells. In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission. The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.*

In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission (Figure 2.2.1 and Figure 2.2.13).

- electron micrograph of a divisome: see under Bacterial Cell Division, Jon Beckwith's Lab.

The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum. The function of a number of divisome proteins have been identified, including:

- MinE: Directs formation of the FtsZ ring and divisome complex at the bacterium's division plane.
- FtsZ: Similar to tubulin in eukaryotic cells, FtsZ forms a constricting ring at the division site. As FtsZ depolymerizes, it directs an inward growth of the cell wall to form the division septum. It is found in both *Bacteria* and *Archaea*, as well as in mitochondria and chloroplasts.
- ZipA: A protein that connects the FtsZ ring to the bacterial cytoplasmic membrane.

- FtsA: An ATPase that breaks down ATP to provide energy for cell division and also helps connect the FtsZ ring to the bacterial cytoplasmic membrane.
- FtsK: Helps in separating the replicated bacterial chromosome.
- FtsI: Needed for peptidoglycan synthesis.

YouTube movie of binary fission in bacteria, #1.

YouTube movie of binary fission in bacteria, #2.

YouTube movie of fluorescing imaging of binary fission in bacteria.

- Scanning electron micrograph of dividing *Escherichia coli*; courtesy of CDC.

- Scanning electron micrograph of dividing *Salmonella typhimurium*; courtesy of CDC.

- To view an transmission electron micrograph of dividing streptococci, see the Rockefeller University home page.

Using Antimicrobial Agents that Alter the Cytoplasmic Membrane to Control Bacteria

As will be discussed later in Unit 2, a very few antibiotics, such as polymyxins and tyrocidins as well as many disinfectants and antiseptics, such as orthophenylphenol, chlorhexidine, hexachlorophene, zephiran, alcohol, triclosans, etc., used during disinfection alter the microbial cytoplasmic membranes and cause leakage of cellular needs.

For More Information: Preview of Chemotherapeutic Control of Bacteria from Unit 2.

For More Information: Preview of Using Chemical Agents to Control of Bacteria from Lab 19.

Summary

1. The bacterial cytoplasmic membrane is a fluid phospholipid bilayer that encloses the bacterial cytoplasm.
2. The cytoplasmic membrane is semipermeable and determines what molecules enter and leave the bacterial cell.
3. Passive diffusion is the net movement of gases or small uncharged polar molecules such as water across a membrane from an area of higher concentration to an area of lower concentration.
4. Passive diffusion is powered by the potential energy of a concentration gradient and does not require the expenditure of metabolic energy or the use of transport proteins.
5. Facilitated diffusion is powered by the potential energy of a concentration gradient and does not require the expenditure of metabolic energy, but it does require the use of transport proteins.
6. A solution refers to solute dissolved in a solvent.
7. Osmosis is the movement of water across a membrane from an area of higher water (lower solute) concentration to an area of lower water (higher solute) concentration by both passive diffusion and facilitated diffusion.
8. Active transport is a process whereby the cell uses both transport proteins and metabolic energy to transport substances across the membrane against the concentration gradient.
9. Most molecules and ions that a cell needs to concentrate within the cytoplasm in order to support life require active transport for entry into the cell.
10. In order to colonize any environment, a bacterium must be able to effectively use its transport systems to compete with other bacteria, as well as the cells of other organisms – such as human cells - for limited nutrients.
11. Bacteria divide by binary fission and increase their numbers by geometric progression.
12. Some antimicrobial agents alter the microbial cytoplasmic membranes and cause leakage of cellular needs.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following descriptions with the best answer.
2. Even though there is a lower concentration of a particular nutrient outside a bacterium than inside, the bacterium is still able to transport that nutrient into its cytoplasm. Explain how this might occur and what is required for this transport. *(ans)*
3. A bacterium is placed in a new environment and subsequently water flows out of the bacterium. Is this new environment isotonic, hypotonic, or hypertonic to the bacterium? Is the solute concentration higher inside the bacterium or outside? *(ans)*
4. Bacteria normally do not grow in jams and jellies. In terms of osmosis, what might explain this? *(ans)*
5. Define the following:
   a. binary fission (ans)
   b. geometric progression *(ans)*
6. State the functions of the following in bacterial cell division:
   a. Par proteins *(ans)*
   b. divisome *(ans)*
   c. FtsZ proteins *(ans)*
7. Multiple Choice *(ans)*

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2: THE PROKARYOTIC CELL - BACTERIA

2.1: Sizes, Shapes, and Arrangements of Bacteria

2.2: The Cytoplasmic Membrane

2.3: The Peptidoglycan Cell Wall

2.3A: The Gram-Positive Cell Wall

2.3B: The Gram-Negative Cell Wall

2.3C: The Acid-Fast Cell Wall

2.4: Cellular Components within the Cytoplasm

2.4A: Cytoplasm

2.4B: The Bacterial Chromosome and Nucleoid

2.4C: Plasmids and Transposons

2.4D: Ribosomes

2.4E: Endospores

2.4F: Inclusion Bodies and Organelles Used for Photosynthesis

2.5: Structures Outside the Cell Wall

2.5A: Glycocalyx (Capsules) and Biofilms

2.5B: Flagella

2.5C: Fimbriae and Pili

2.E: The Prokaryotic Cell: Bacteria (Exercises)

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2.3: THE PEPTIDOGLYCAN CELL WALL

Learning Objectives

1. State the three parts of a peptidoglycan monomer and state the function of peptidoglycan in bacteria.
2. Briefly describe how bacteria synthesize peptidoglycan, indicating the roles of autolysins, bactoprenols, transglycosylases, and transpeptidases.
3. Briefly describe how antibiotics such as penicillins, cephalosporins, and vancomycin affect bacteria and relate this to their cell wall synthesis.
4. State what color Gram-positive bacteria stain after Gram staining.
5. State what color Gram-negative bacteria stain after Gram staining.
6. State what color acid-fast bacteria stain after acid-fast staining.

The mycoplasmas are the only bacteria that naturally lack a cell wall. Mycoplasmas maintain a nearly even pressure between the outside environment and the cytoplasm by actively pumping out sodium ions. Their cytoplasmic membranes also contain sterols that most likely provide added strength. The remaining bacteria in the domain *Bacteria*, with the exception of a few bacteria such as the Chlamydias, have a semirigid cell wall containing peptidoglycan. (While bacteria belonging to the domain *Archaea* also have a semirigid cell wall, it is composed of chemicals distinct from peptidoglycan such as protein or pseudomurein. We will not take up the *Archaea* here.)

Function of Peptidoglycan

Peptidoglycan prevents osmotic lysis. As seen earlier under the cytoplasmic membrane, bacteria concentrate dissolved nutrients (solute) through active transport. As a result, the bacterium's cytoplasm is usually hypertonic to its surrounding environment and the net flow of free water is into the bacterium. Without a strong cell wall, the bacterium would burst from the osmotic pressure of the water flowing into the cell.

Structure and Composition of Peptidoglycan

With the exceptions above, members of the domain *Bacteria* have a cell wall containing a semirigid, tight knit molecular complex called peptidoglycan. Peptidoglycan, also called murein, is a vast polymer consisting of interlocking chains of identical peptidoglycan monomers (Figure 2.3.1). A peptidoglycan monomer consists of two joined amino sugars, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), with a pentapeptide coming off of the NAM (Figure 2.3.2). The types and the order of amino acids in the pentapeptide, while almost identical in gram-positive and gram-negative bacteria, show some slight variation among the domain *Bacteria*.

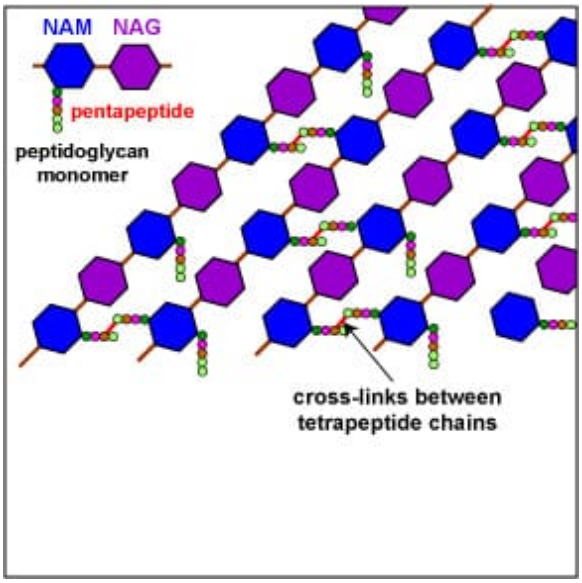


Figure 2.3.1: Peptidoglycan is composed of cross-linked chains of peptidoglycan monomers (NAG-NAM-pentapeptide). Transglycosylase enzymes join these monomers join together to form chains. Transpeptidase enzymes then cross-link the chains to provide strength to the cell wall and enable the bacterium to resist osmotic lysis. (left) In a peptidoglycan monomer of S. aureus, the pentapeptide coming off the NAM is composed of the amino acids L-alanine, D-glutamine, L-lysine, and two D-alanines. The peptide cross-link forms by formation of a short peptide interbridge consisting of 5 glycines. In the process the terminal D-alanine is cleaved from the pentapeptide to form a tetrapeptide in the peptidogycan. (right) In a peptidoglycan monomer of E. coli, the pentapeptide coming off the NAM is composed of the amino acids L-alanine, D-glutamic acid, meso-diaminopimelic acid, and two D-alanines. The peptide cross-link forms between the diaminopimelic acid of one peptide chain with the D-alanine of another and in the process the terminal D-alanine is cleaved from the pentapeptide to form a tetrapeptide in the peptidogycan.

The peptidoglycan monomers are synthesized in the cytosol of the bacterium where they attach to a membrane carrier molecule called bactoprenol. As discussed below, The bactoprenols transport the peptidoglycan monomers across the cytoplasmic membrane and work with the enzymes discussed below to insert the monomers into existing peptidoglycan enabling bacterial growth following binary fission.

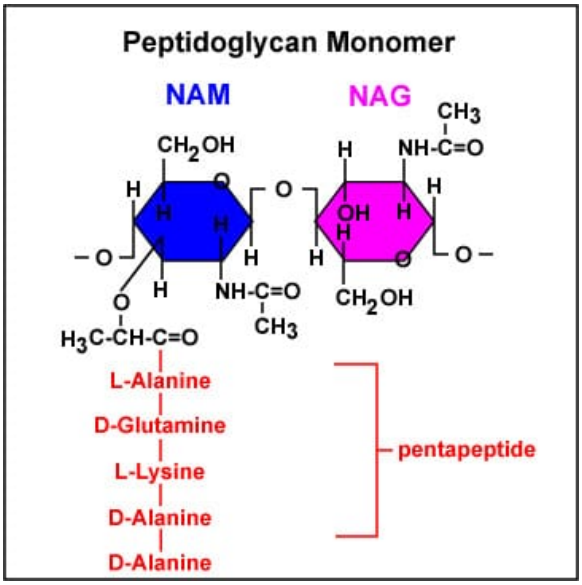


Figure 2.3.2: (left) A peptidoglycan monomer consists of two joined amino sugars, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), with a pentapeptide coming off of the NAM. In E. coli, the pentapeptide consists of the amino acids L-alanine, D-glutamic acid, meso diaminopimelic acid, and two D-alanines. (right) A peptidoglycan monomer consists of two joined amino sugars, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), with a pentapeptide coming off of the NAM. In S. aureus, the pentapeptide consists of the amino acids L-alanine, D-glutamine, L-lysine, and two D-alanines.

Once the new peptidoglycan monomers are inserted, glycosidic bonds then link these monomers into the growing chains of

peptidoglycan. These long sugar chains are then joined to one another by means of peptide cross-links between the peptides coming off of the NAMs. By linking the rows and layers of sugars together in this manner, the peptide cross-links provide tremendous strength to the cell wall, enabling it to function similar to a molecular chain link fence around the bacterium (see Figure 2.3.1).

Synthesis of Peptidoglycan

In order for bacteria to increase their size following binary fission, links in the peptidoglycan must be broken, new peptidoglycan monomers must be inserted, and the peptide cross links must be resealed. The following sequence of events occur:

Step 1. Bacterial enzymes called autolysins:

a) Break the glycosidic bonds between the peptidoglycan monomers at the point of growth along the existing peptidoglycan (see Figure 2.3.3, steps 1-3); and

b) Break the peptide cross-bridges that link the rows of sugars together (see Figure 2.3.3, steps 1-3).

Flash animation showing the synthesis of peptidoglycan.

html5 version of animation for iPad showing the synthesis of peptidoglycan.

Step 2. The peptidoglycan monomers are synthesized in the cytosol (see Figure 2.3.4, step-1 and Figure 2.3.4, step-2) and bind to bactoprenol. The bactoprenols transport the peptidoglycan monomers across the cytoplasmic membrane and interacts with transglycosidases to insert the monomers into existing peptidoglycan (see Figure 2.3.4, step-3, Figure 2.3.4, step-4, Figure 2.3.4, step-5, and Figure 2.3.4, step-6)

Flash animation showing the synthesis of peptidoglycan.

html5 version of animation for iPad showing the synthesis of peptidoglycan.

Step 3. Transglycosylase (transglycosidase) enzymes insert and link new peptidoglycan monomers into the breaks in the peptidoglycan (see Figure 2.3.5, step 1 and Figure 2.3.5, step 2).

Flash animation showing the synthesis of peptidoglycan.

html5 version of animation for iPad showing the synthesis of peptidoglycan.

Step 4. Finally, transpeptidase enzymes reform the peptide cross-links between the rows and layers of peptidoglycan to make the wall strong (see Figure 2.3.6, step 1 and see Figure 2.3.6, step 2).

In *Escherichia coli*, the terminal D-alanine is cleaved from the pentapeptides to form a tetrapeptides. This provides the energy to bond the D-alanine of one tetrapeptide to the diaminopimelic acid of another tetrapeptide (see Figure 2.3.1B). In the case of *Staphylococcus aureus*, the terminal D-alanine is cleaved from the pentapeptides to form a tetrapeptides. This provides the energy to bond a pentaglycine bridge (5 molecules of the amino acid glycine) from the D-alanine of one tetrapeptide to the L-lysine of another (see Figure 2.3.1A).

Exercise: Think-Pair-Share Questions

1. As we will see in Unit 2, the antibiotic bacitracin binds to bactoprenol after it inserts a peptidoglycan monomer into the growing bacterial cell wall.

   Explain how this can lead to the death of that bacterium.

2. As we will see in Unit 2, the penicillin antibiotics binds to the bacterial enzyme transpeptidase.

a. Explain how this can lead to the death of that bacterium.
b. Could this antibiotic be used to treat protozoan infections such as giardiasis and toxoplasmosis?

In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission (see Figure 2.3.1 and Figure 2.3.2).

The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.

Antimicrobial Agents that Inhibit Peptidoglycan Synthesis Causing Bacterial Lysis

Many antibiotics work by inhibiting normal synthesis of peptidoglycan in bacteria causing them to burst as a result of osmotic lysis. As just mentioned, in order for bacteria to increase their size following binary fission, enzymes called autolysins break the peptide cross links in the peptidoglycan, transglycosylase enzymes then insert and link new peptidoglycan monomers into the breaks in the peptidoglycan, and transpeptidase enzymes reform the peptide cross-links between the rows and layers of peptidoglycan to make the wall strong.

Interference with this process results in a weak cell wall and lysis of the bacterium from osmotic pressure. Examples include the penicillins (penicillin G, methicillin, oxacillin, ampicillin, amoxicillin, ticarcillin, etc.), the cephalosporins (cephalothin, cefazolin, cefoxitin, cefotaxime, cefaclor, cefoperazone, cefixime, ceftriaxone, cefuroxime, etc.), the carbapenems (imipenem, metropenem), the monobactems (aztreonem), the carbacephems (loracarbef), and the glycopeptides (vancomycin, teichoplanin).

- For example, penicillins and cephalosporins bind to the transpeptidase enzymes (also called penicillin-binding proteins) responsible for resealing the cell wall as new peptidoglycan monomers are added during bacterial cell growth. This blocks the transpeptidase enzymes from cross-linking the sugar chains and results in a weak cell wall and subsequent osmotic lysis of the bacterium (see Figure 2.3.8).

Flash animation illustrating how penicillins inhibit peptidoglycan synthesis.

html5 version of animation for ipad showing how penicillins inhibit the synthesis of peptidoglycan.

Flash animation showing how penicillins inhibit peptidoglycan synthesis.
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YouTube movie showing lysis of *E. coli* after exposure to a penicillin

Antimicrobial chemotherapy will be discussed in greater detail later in Unit 2 under Control of Bacteria by Using Antibiotics and Disinfectants.

For More Information: Preview of Chemotherapeutic Control of Bacteria from Unit 2.

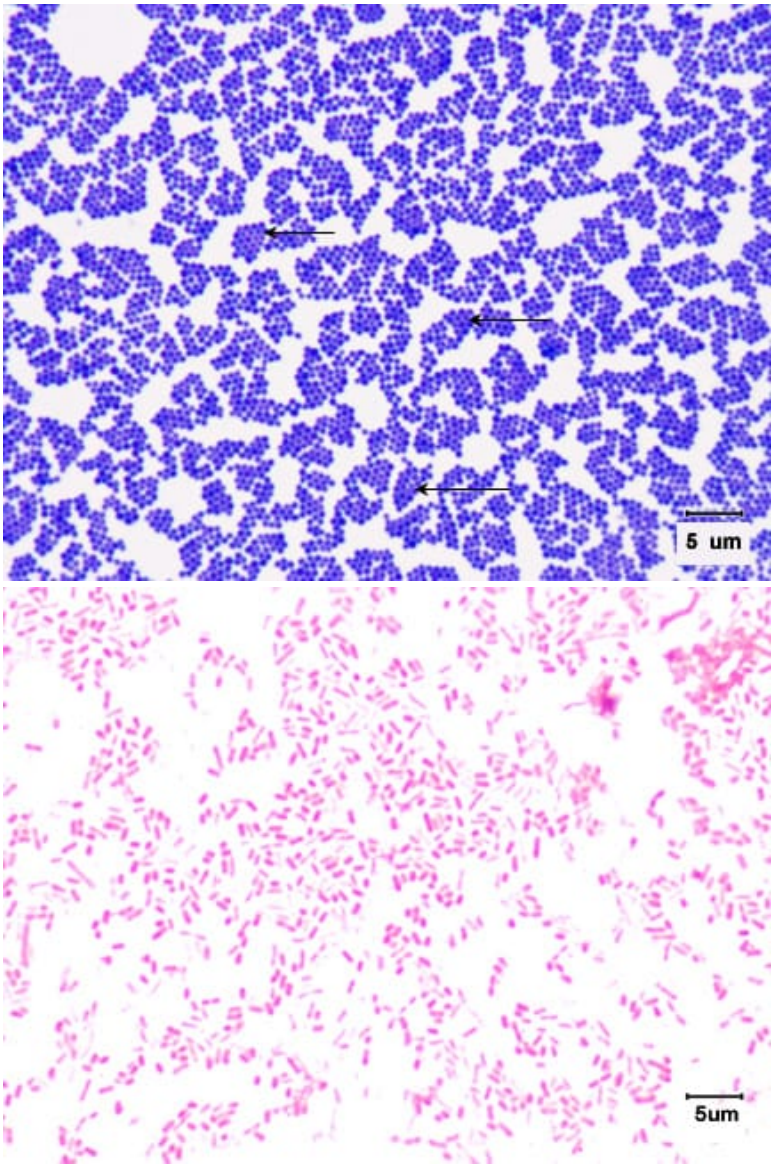
For More Information: Preview of Using Chemical Agents to Control of Bacteria from Lab 19.

Concept map for peptidoglycan and peptidoglycan synthesis.

Gram-Positive, Gram-Negative, and Acid-Fast Bacteria

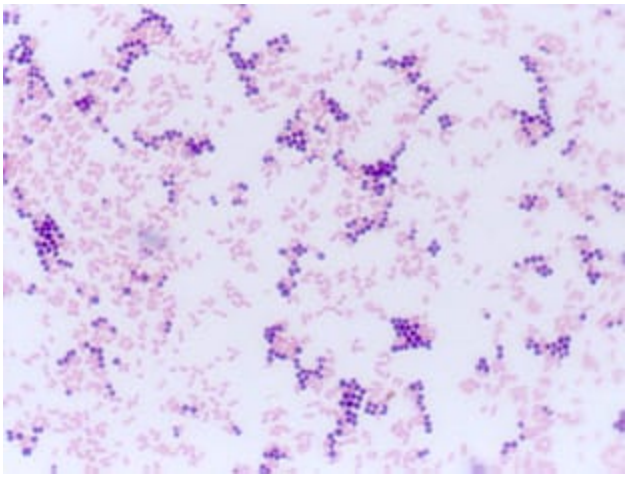
Most bacteria can be placed into one of three groups based on their color after specific staining procedures are performed: Gram-positive, Gram-negative, or acid-fast.

- **Gram-positive Bacteria**: These retain the initial dye crystal violet during the Gram stain procedure and appear purple when observed through the microscope. Common Gram-positive bacteria of medical importance include *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis,* and *Clostridium* species.



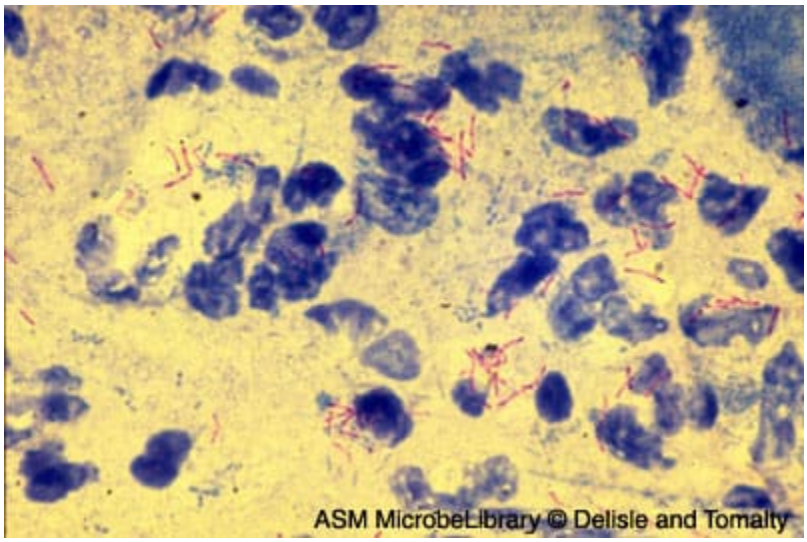
(left) Gram Stain of Staphylococcus aureus which are gram-positive (purple) cocci in clusters. (right) Gram Stain of Escherichia coli which are Gram-negative (pink) bacilli.

- **Gram-negative Bacteria**: These decolorize during the Gram stain procedure, pick up the counterstain safranin, and appear pink when observed through the microscope. Common Gram-negative bacteria of medical importance include *Salmonella* species, *Shigella* species, *Neisseria gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae, Proteus* species, and *Pseudomonas aeruginosa*. Also see gram stain of a mixture of gram-positive and gram-negative bacteria.



A Gram Stain of a Mixture of Gram-Positive and Gram-Negative Bacteria. Note Gram-negative (pink) bacilli and Gram-positive (purple) cocci.

- **acid-fast Bacteria**: These resist decolorization with an acid-alcohol mixture during the acid-fast stain procedure, retain the initial dye carbolfuchsin and appear red when observed through the microscope. Common acid-fast bacteria of medical importance include *Mycobacterium tuberculosis, Mycobacterium leprae,* and *Mycobacterium avium-intracellulare* complex.



Acid-Fast Stain of Mycobacterium tuberculosis in Sputum. Note the reddish acid-fast bacilli among the blue normal flora and white blood cells in the sputum that are not acid-fast.

These staining reactions are due to fundamental differences in their cell wall as will be discussed in Lab 6 and Lab 16. We will now look at each of these three bacterial cell wall types.

The S-layer

1. Structure and Composition

The most common cell wall in species of *Archaea* is a paracrystalline surface layer (S-layer). It consists of a regularly structured layer composed of interlocking glycoprotein or protein molecules. In electron micrographs, has a pattern resembling floor tiles. Although they vary with the species, S-layers generally have a thickness between 5 and 25 nm and possess identical pores with 2-8 nm in diameter. Several species of *Bacteria* have also been found to have S-layers.

To view electron micrographs of S-layers see the following:

- S-Layer Proteins, the Structural Biology Homepage at Karl-Franzens University in Austria.
- Characteristic Properties of S-layer Proteins, at Foresight Nanotech Institute in Austria.

2. Functions and Significance to Bacteria Causing Infections

The S-layer has been associated with a number of possible functions. These include the following:

a. The S-layer may protect bacteria from harmful enzymes, from changes in pH, from the predatory bacterium *Bdellovibrio*, a parasitic bacterium that actually uses its motility to penetrate other bacteria and replicate within their cytoplasm, and from bacteriophages.

b. The S-layer can function as an adhesin, enabling the bacterium to adhere to host cells and environmental surfaces, colonize, and resist flushing.

c. The S-layer may contribute to virulence by protecting the bacterium against complement attack and phagocytosis.

d. The S-layer may act as a as a coarse molecular sieve.

Summary

1. The vast majority of the domain Bacteria have a rigid cell wall composed of peptidoglycan.
2. The peptidoglycan cell wall surrounds the cytoplasmic membrane and prevents osmotic lysis.
3. Peptidoglycan is composed of interlocking chains of building blocks called peptidoglycan monomers.
4. In order to grow following binary fission, bacteria have to synthesize new peptidoglycan monomers in the cytoplasm, transport those monomers across the cytoplasmic membrane, put breaks in the existing cell wall so the monomers can be inserted, connect the monomers to the existing peptidoglycan, and cross-link the rows and layers of peptidoglycan.
5. Many antibiotics inhibit peptidoglycan synthesis in bacteria and lead to osmotic lysis of the bacteria.
6. Most bacteria can be placed into one of three groups based on their color after specific staining procedures are performed: Gram-positive, Gram-negative, or acid-fast. These staining reactions are due to fundamental differences in the bacterial cell wall.
7. Gram-positive bacteria stain purple after Gram staining while Gram-negative bacteria stain pink.
8. Acid-fast bacteria stain red after acid-fast staining.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. A monomer of peptidoglycan consists of _____, _____, and _____. *(ans)*
2. State the function of peptidoglycan in bacteria. *(ans)*
3. State the role of the following enzymes in peptidoglycan synthesis:
   a. autolysins *(ans)*
   b. bactoprenols *(ans)*
   c. transpeptidases *(ans)*
   d. transglycosylase *(ans)*
4. A penicillin is used to treat a bacterial infection. Describe the mechanism by which this antibiotic eventually kills the bacteria. *(ans)*
5. Gram-positive bacteria stain _____ *(ans)* after Gram staining while Gram-negative bacteria stain _____ *(ans)*.
6. Bacteria normally live in a hypotonic environment. Since water flows into a cell in an environment that is hypotonic, why don't the bacteria burst from osmotic pressure? *(ans)*
7. Multiple Choice *(ans)*

2.3A: The Gram-Positive Cell Wall
2.3B: The Gram-Negative Cell Wall
2.3C: The Acid-Fast Cell Wall

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2.3A: The Gram-Positive Cell Wall

State what color Gram-positive bacteria stain after the Gram stain procedure.

- Describe the composition of a Gram-positive cell wall and indicate the possible beneficial functions to the bacterium of peptidoglycan, teichoic acids, and surface proteins.
- Briefly describe how PAMPs of the Gram-positive cell wall can promote inflammation.
- State the function of bacterial adhesins, secretion systems, and invasins.
- Define antigen and epitope.

Highlighted Bacterium

1. Read the description of *Enterococcus*, andmatch the bacterium with the description of the organism and the infection it causes.

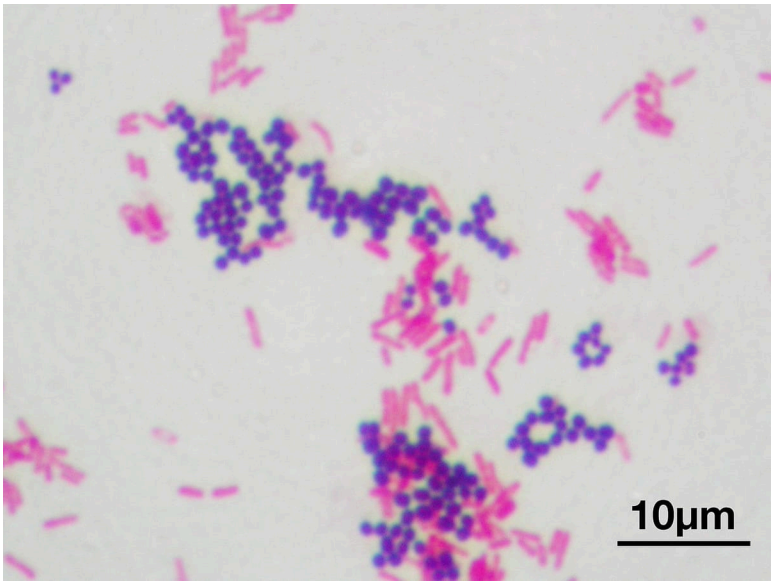


Figure 2.3A.2A.1: Gram Stain of *V*iolet stained gram-positive cocci and pink stained gram-negative rod-shaped bacteria. from Wikipedia (Y tambe).

For More Information: Preview of the Gram stain from Lab 6.

Flash animation illustrating the interaction of the Gram's stain reagents at a molecular level
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Common Gram-positive bacteria of medical importance include *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis,* and *Clostridium* species.

Structure and Composition of the Gram-Positive Cell Wall

1. In electron micrographs, the Gram-positive cell wall appears as a broad, dense wall 20-80 nm thick and consisting of numerous interconnecting layers of peptidoglycan (see Figs. 1A and 1B). Chemically, 60 to 90% of the Gram-positive cell wall is peptidoglycan. In Gram-positive bacteria it is thought that the peptidoglycan is laid down in cables of several cross-linked glycan

strands approximately 50 nm wide. These cables then themselves become cross-linked for further cell wall strength.

2. Interwoven in the cell wall of Gram-positive are teichoic acids and lipoteichoic acids. Teichoic acids extend through and beyond the rest of the cell wall and are polyalcohols composed of polymers of glycerol, phosphates, and the sugar alcohol ribitol and are covalently bound to the peptidoglycan. Teichoic acids covalently bound to cytoplasmic membrane lipids are called lipoteichoic acids (see Figure $2.3A.1$B).

3. The outer surface of the peptidoglycan is studded with surface proteins that differ with the strain and species of the bacterium (see Figure $2.3A.1$B).

4. The periplasm is the gelatinous material between the peptidoglycan and the cytoplasmic membrane.

For More Information: Peptidoglycan from Unit 1.

To view an electron micrograph of *Streptococcus* showing a Gram-positive cell wall, see the Rockefeller University web page.

Functions of the Gram-Positive Cell Wall Components

1. The peptidoglycan in the Gram-positive cell wall prevents osmotic lysis.

2. The teichoic acids probably help make the cell wall stronger (see Figure $2.3A.1$B).

3. The surface proteins (see Figure $2.3A.1$B) in the bacterial peptidoglycan, depending on the strain and species, carry out a variety of activities.

a. Some surface proteins function as enzymes.

b. Other proteins serve as adhesins. Adhesins enable the bacterium to adhere intimately to host calls and other surfaces in order to colonize those cells and resist flushing (See Figure $2.3A.2$).

Flash animation showing a bacterium using adhesins to adhere to a host cell.

html5 version of animation for iPad showing a bacterium using adhesins to adhere to a host cell.

c. Many bacteria involved in infection have the ability to co-opt the functions of host cells for the bacterium's own benefit. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication to the benefit of the bacteria. They do this by producing secretion systems such as the type 3 secretion system that produces hollow, needle-like tubes called injectisomes. Certain bacteria, for example, inject invasins into the cytoplasm of the host cell that enable the bacterium to enter that cell.

Flash animation showing bacteria secreting invasions into a non-immune host cell in order to enter that cell by phagocytosis.

html5 version of animation for iPad showing bacteria secreting invasions into a non-immune host cell in order to enter that cell by phagocytosis.

The role of these cell wall surface proteins will be discussed in greater detail later in Unit 3 under Bacterial Pathogenicity.

4. The periplasm contains enzymes for nutrient breakdown.

For More Information: The Ability to Adhere to Host Cells from Unit 3

For More Information: The Ability to Invade Host Cells from Unit 3

Concept map for the Gram-positive cell wall.

Significance of Gram-Positive Cell Wall Components to the Initiation of Body Defenses

The body has two immune systems: the innate immune system and the adaptive immune system.

1. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.

2. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life.

Initiation of Innate Immunity

In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometime referred to as microbe-associated molecular patterns or MAMPs.)

Fragments of peptidoglycan and teichoic acids are PAMPS associated with the cell wall of Gram-positive bacteria. In addition, bacteria and other microorganisms also possess mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar) that function as PAMPs. These mannose-rich glycans are common in microbial glycoproteins and glycolipids but rare in those of humans (see Figure 2.3A.3).

These PAMPS bind to pattern-recognition receptors or PRRs on a variety of defense cells of the body and trigger such innate immune defenses as inflammation, fever, and phagocytosis.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

Inflammation is the first response to infection and injury and is critical to body defense. Basically, the inflammatory response is an attempt by the body to restore and maintain homeostasis after injury. Most of the body defense elements are located in the blood, and inflammation is the means by which body defense cells and body defense chemicals leave the blood and enter the tissue around an injured or infected site.

Body defense cells such as macrophages, and dendritic cells have pattern recognition receptors such as toll-like receptors on their surface that are specific for the peptidoglycan fragments and lipoteichoic acids in the Gram-positive cell wall and/or to NODs in their cytoplasm that are specific for peptidoglycan fragments.

The binding of these cell wall components to their corresponding pattern recognition receptors triggers the macrophages to release various defense regulatory chemicals called cytokines, including IL-1, IL-6, IL-8, TNF-alpha, and PAF. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the

coagulation pathway (see Figure 2.3A.4).

For More Information: Cytokines from Unit 5

For More Information: Inflammation from Unit 5

The peptidoglycan and teichoic acids also activate the alternative complement pathway and the lectin pathway, innate immune defense pathways that play a variety of roles in body defense.

For More Information: The Complement Pathways from Unit 5

Innate immunity will be discussed in greater detail in Unit 5.

Concept map for the Gram-positive cell wall.

Initiation of Adaptive Immunity

Proteins and polysaccharides associated with the Gram-positive cell wall function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity : Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against cell wall antigens can stick bacteria to phagocytes, a process called opsonization. Antibodies made against cell wall adhesins can prevent bacteria from adhering to and colonizing host cells.

2. Cell-mediated immunity : Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Significance of Gram-Positive Cell Wall Components to Bacterial Pathogenicity

During severe systemic infections with large numbers of bacteria present, however, high levels of Gram-positive PAMPs are released resulting in excessive cytokine production by the macrophages and other cells and this, in turn, can harm the body (see Figure 2.3A.5).

Flash animation illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

For More Information: Inflammatory Gram-PositiveCell Wall Components from Unit 3

For More Information: Cytokines from Unit 5

For More Information: Inflammation from Unit 5

Summary

1. Because of the nature of their cell wall, Gram-positive bacteria stain purple after Gram staining.
2. The Gram-positive cell wall consists of many interconnected layers of peptidoglycan and lacks an outer membrane.
3. Peptidoglycan prevents osmotic lysis in the hypotonic environment in which most bacteria live.
4. Teichoic acids and lipoteichoic acids are interwoven through the peptidoglycan layers.
5. Surface proteins embedded in the cell wall can function as adhesins, secretion systems, and enzymes.
6. The Gram-positive cell wall activates both the body's innate immune defenses and its adaptive immune defenses.
7. The body activates innate immunity by recognizing molecules unique to microorganisms that are not associated with human cells called pathogen-associated molecular patterns or PAMPs. PAMPs bind to Pattern-recognition receptors (PRRs) on defense cells to trigger the production of inflammatory cytokines.
8. Inflammation is the means by which the body delivers defense cells and defense molecules to an infection site,however, excessive inflammation can be harmful and even deadly to the body.
9. PAMPs associated with the Gram-positive cell wall include peptidoglycan monomers, teichoic acids, lipoteichoic acids, and mannose-rich sugar chains.
10. An antigen is a molecular shape that reacts with antigen receptors on lymphocytes to initiate an adaptive immune response.
11. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what color Gram-positive bacteria appear after the Gram stain procedure. (ans)
2. Describe the structure and appearance of a Gram-positive cell wall. *(ans)*
3. State the beneficial function to the bacterium of the following components of the gram-positive cell wall:
   a. peptidoglycan *(ans)*
   b. teichoic acids *(ans)*
   c. adhesins *(ans)*

d. invasins *(ans)*

4. Briefly describe how PAMPs of the Gram-positive cell wall can promote inflammation. *(ans)*
5. Define antigen. *(ans)*

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2.3B: The Gram-Negative Cell Wall

State what color Gram-negative bacteria stain after the Gram stain procedure.

- Describe the composition of a Gram-negative cell wall and indicate the possible beneficial functions to the bacterium of peptidoglycan, the outer membrane, lipopolysaccharides, porins, and surface proteins.
- Briefly describe how LPS and other PAMPs of the Gram-negative cell wall can promote inflammation.
- State the function of bacterial adhesins, secretion systems, and invasins.
- Define periplasm.
- Define antigen and epitope.

Highlighted Bacterium

1. Read the description of *Escherichia coli*, and match the bacterium with the description of the organism and the infection it causes.

Highlighted Disease: Urinary Tract Infections (UTIs)

1. Define the following:
   a. urethritis
   b. cystitis
   c. pyelonephritis
2. Name at least 4 risk factors for UTIs.
3. Name the most common bacterium to cause UTIs; name at least 3 other bacteria that commonly cause UTIs.
4. Name at least 3 common symptoms of UTIs.

We will now look at the Gram-negative bacterial cell wall. As mentioned in the previous section on peptidoglycan, Gram-negative bacteria are those that decolorize during the Gram stain procedure, pick up the counterstain safranin, and appear pink (Figure $2.3B.2$B.1).

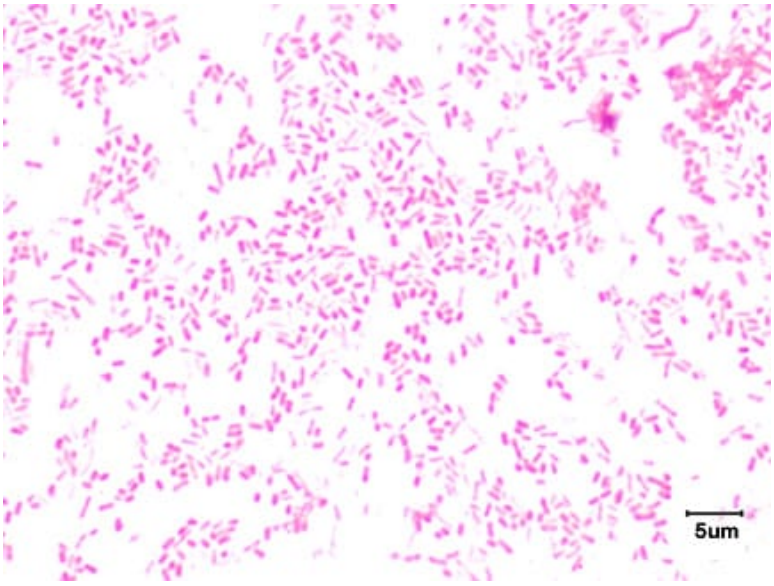


Figure $2.3B.2$B.1: Gram Stain of *Escherichia coli*. Note Gram-negative (pink) bacilli.

Common Gram-negative bacteria of medical importance include *Salmonella* species, *Shigella* species, *Neisseria gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae, Proteus* species, and *Pseudomonas aeruginosa*.

Escherichia coli

Organism

- *Escherichia coli* is a moderately-sized Gram-negative bacillus.
- Possess a peritrichous arrangement of flagella.
- Facultative anaerobe.

Habitat

- Normal flora of the intestinal tract in humans and animals.

Source

- Usually the patient's own fecal flora; some transmission is patient-to-patient.

Clinical Disease

- *E. coli* causes around 80 percent of all uncomplicated **urinary tract infections** (UTIs) and more than 50 percent of nosocomial UTIs. UTIs account for more than 7, 000,000 physician office visits per year in the U.S. Between 35 and 40 percent of all nosocomial infections, about 900,000 per year in the U.S., are UTIs and are usually associated with urinary catheterization.
- *E. coli* causes **wound infections**, usually a result of fecal contamination of external wounds or a result of wounds that cause trauma to the intestinal tract, such as surgical wounds, gunshot wounds, knife wounds, etc.
- *E. coli* is by far the most common Gram-negative bacterium causing sepsis. **Septicemia** is a result of bacteria getting into the blood. They are usually introduced into the blood from some other infection site, such as an infected kidney, wound, or lung. There are approximately 500,000 cases of septicemia per year in the U.S. and the mortality rate is between 20 and 50 percent. Approximately 45 percent of the cases of septicemia are due to Gram-negative bacteria. *Klebsiella, Proteus, Enterobacter, Serratia*, and *E. coli*, are all common gram-negative bacteria causing septicemia.
- *E. coli*, along with group B streptococci, are the leading cause of **neonatal meningitis**.
- While *E. coli* is one of the dominant normal flora in the intestinal tract of humans and animals, some strains can cause **gastroenteritis**, an infection of the intestinal tract.
  - Enterotoxigenc *E. coli* (ETEC) produce enterotoxins that cause the loss of sodium ions and water from the small intestines resulting in a watery diarrhea. Over half of all travelers' diarrhea is due to ETEC; almost 80,000 cases a year in the U.S.
  - Enteropathogenic *E. coli* (EPEC) cause an endemic diarrhea in areas of the developing world, especially in infants younger than 6 months. The bacterium disrupts the normal microvilli on the epithelial cells of the small intestines resulting in maladsorbtion and diarrhea.
  - Enteroaggregative *E. coli* (EAEC) is a cause of persistant diarrhea in developing countries. It probably causes diarrhea by adhering to mucosal epithelial cells of the small intestines and interfering with their function.
  - Enteroinvasive *E. coli* (EIEC) invade and kill epithelial cells of the large intestines causing a dysentery-type syndrome similar to *Shigella* common in underdeveloped countries.
  - Enterohemorrhagic *E. coli* (EHEC), such as *E. coli* 0157:H7, produce a shiga-like toxin that kills epithelial cells of the large intestines causing hemorrhagic colitis, a bloody diarrhea. In rare cases, the shiga-toxin enters the blood and is carried to the kidneys where, usually in children, it damages vascular cells and causes hemolytic uremic syndrome. *E. coli* 0157:H7 is thought to cause more than 20,000 infections and up to 250 deaths per year in the U.S.
  - Diffuse aggreegative *E. coli*(DAEC) causes watery diarrhea in infants 1-5 years of age. They stimulate elongation of the microvilli on the epithelial cells lining the small intestines.

- For More Information: The Gram Stain from Lab 6.
- Flash animation illustrating the interaction of the Gram's stain reagents at a molecular level © Daniel Cavanaugh, Mark Keen, authors, Licensed for use, ASM MicrobeLibrary.

- Highlighted Infection: Urinary Tract Infections (UTIs)

Structure and Composition of the Gram-Negative Cell Wall

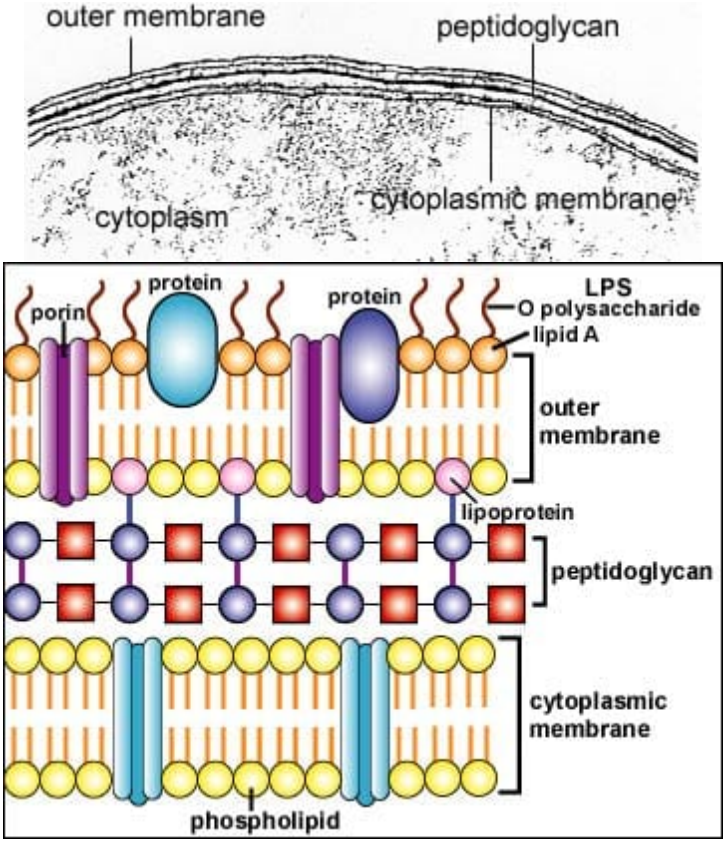


Figure $2.3B.1$B) span the outer membrane. The porins function as channels for the entry and exit of solutes through the outer membrane of the Gram-negative cell wall. The outer membrane of the Gram-negative cell wall is studded with surface proteins that differ with the strain and species of the bacterium.

The periplasm is the gelatinous material between the outer membrane, the peptidoglycan, and the cytoplasmic membrane. This periplasmic space is about 15nm wide and contains a variety of hydrolytic enzymes for nutrient breakdown, periplasmic binding proteins for transport via the ATP-binding cassette (ABC) system, and chemoreceptors for chemotaxis (discussed under Bacterial Flagella later in this Unit).

Concept map for the Gram-negative cell wall.

Functions of the Gram-Negative Cell Wall Components

Flash animation showing a bacterium using adhesins to adhere to a host cell.

html5 version of animation for iPad showing a bacterium using adhesins to adhere to a host cell.

Flash animation showing a bacterium using adhesins to resist being flushed out of the urethra.

html5 version of animation for iPad showing a bacterium using adhesins to resist being flushed out of the urethra.

Flash animation showing a bacterium without adhesins being flushed out of the urethra.

html5 version of animation for iPad showing a bacterium without adhesins being flushed out of the urethra.

c. Many bacteria involved in infection have the ability to **co-opt the functions of host cells for the bacterium's own benefit**. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication to the benefit of the bacteria. They do this by producing secretion systems such as the type 3 secretion system that produces hollow, needle-like tubes called **injectisomes**. Certain bacteria, for example, inject **invasins** into the cytoplasm of the host cell that enable the bacterium to **enter that cell.**

html5 version of animation for iPad showing a bacterium secreting invasions in order to penetrete non-immune host cells.

The role of these cell wall surface proteins will be discussed in greater detail later in Unit 3 under Bacterial Pathogenicity.

For More Information: The Ability to Adhere to Host Cells from Unit 3

For More Information: The Ability to Invade Host Cells from Unit 3

4. The **periplasm** contains **enzymes for nutrient breakdown** as well as **periplasmic binding proteins to facilitate the transfer of nutrients across the cytoplasmic membrane**.

Concept map for the Gram-negative cell wall.

The Role of Gram-Negative Cell Wall Components to the Initiation of Body Defenses

The body has two immune systems: the innate immune system and the adaptive immune system. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life.

Initiation of Innate Immunity

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometime referred to as microbe-associated molecular patterns or MAMPs.)

LPS, porins, and fragments of peptidoglycan are PAMPs associated with the cell wall of Gram-negative bacteria. In addition, bacteria and other microorganisms also possess mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar) that function as PAMPs. These mannose-rich glycans are common in microbial glycoproteins and glycolipids but rare in those of humans (Figure $2.3B.3$).

These PAMPS bind to pattern-recognition receptors or PRRs on a variety of defense cells of the body and triggers innate immune

defenses such as inflammation , fever, and phagocytosis.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

Inflammation is the first response to infection and injury and is critical to body defense. Basically, the inflammatory response is an attempt by the body to restore and maintain homeostasis after injury. Most of the body defense elements are located in the blood, and inflammation is the means by which body defense cells and body defense chemicals leave the blood and enter the tissue around an injured or infected site.

Body defense cells called macrophages, and dendritic cells have pattern recognition receptors such as toll-like receptors on their surface that are specific for the peptidoglycan fragments and LPS in the Gram-negative cell wall and/or to NODs in their cytoplasm that are specific for peptidoglycan fragments. The binding of these cell wall components to their corresponding pattern recognition receptors triggers the macrophages to release various defense regulatory chemicals called cytokines, including IL-1, IL-6, IL-8, TNF-alpha, and PAF. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway (Figure $2.3B.4$).

The LPS binds to a LPS-binding protein circulating in the blood and this complex, in turn, binds to a receptor molecule (CD_{14}) found on the surface of body defense cells called macrophages. This is thought to promote the ability of the toll-like receptor pair TLR-4/TLR4 to respond to the LPS. The binding of these cell wall components to their corresponding pattern recognition receptors triggers macrophages to release various defense regulatory chemicals called cytokines, including IL-1, IL-6, IL-8, TNF-alpha, and PAF. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway (Figure $2.3B.4$).

Flash animation showing the release of LPS from the cell wall of a gram negative bacterium and its subsequent binding to pattern-recognition receptors on a macrophage.

html5 version of animation for iPad showing the release of LPS from the cell wall of a gram negative bacterium and its subsequent binding to pattern-recognition receptors on a macrophage.

For More Information: Cytokines from Unit 5

For More Information: Inflammation from Unit 5

Concept map for the Gram-negative cell wall.

Explain how the body is able to recognize these bacteria and eventually send phagocytes and defense molecules to the infected site.

- How might this mechanism lead to the symptoms of the infection?

The LPS also activates the alternative complement pathway and the lectin pathway, innate defense pathways that play a variety of roles in body defense.

Innate immunity will be discussed in greater detail in Unit 5.

For More Information: The Complement Pathways from Unit 5

Initiation of Adaptive Immunity

Proteins and polysaccharides associated with the Gram-negative cell wall function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against cell wall antigens can stick bacteria to phagocytes, a process called opsonization. Antibodies made against cell wall adhesins can prevent bacteria from adhering to and colonizing host cells.
2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Significance of Gram-Negative Cell Wall Components to Bacterial Pathogenicity

The lipid A portion of the LPS portion in the outer membrane is also known as endotoxin. During severe systemic infections with large numbers of bacteria present, high levels of LPS are released resulting in excessive cytokine production by the macrophages and other cells and this, in turn, can harm the body (Figure $2.3B.5$).

For More Information: Endotoxin from Unit 3

Concept map for the Gram-negative cell wall.

Summary

1. Because of the nature of their cell wall, Gram-negative bacteria stain pink after Gram staining.
2. The Gram-negative cell wall consists of 2-3 interconnected layers of peptidoglycan surrounded by an outer membrane.
3. Peptidoglycan prevents osmotic lysis in the hypotonic environment in which most bacteria live.

4. The outer membrane is a semipermeable structure that contains pore-forming proteins called porins that allow nutrients to pass through the outer membrane.
5. Surface proteins embedded in the cell wall can function as adhesins, secretion systems, and enzymes.
6. The Gram-negative cell wall activates both the body's innate immune defenses and its adaptive immune defenses.
7. The body activates innate immunity by recognizing molecules unique to microorganisms that are not associated with human cells called pathogen-associated molecular patterns or PAMPs. PAMPs bind to Pattern-recognition receptors (PRRs) on defense cells to trigger the production of inflammatory cytokines.
8. Inflammation is the means by which the body delivers defense cells and defense molecules to an infection site, however, excessive inflammation, can be harmful and even deadly to the body.
9. PAMPs associated with the Gram-negative cell wall include peptidoglycan monomers, lipopolysaccharide (LPS), porins, and mannose-rich sugar chains.
10. An antigen is a molecular shape that reacts with antigen receptors on lymphocytes to initiate an adaptive immune response.
11. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what color Gram-negative bacteria appear after the Gram stain procedure. (ans)
2. Describe the structure and appearance of a Gram-negative cell wall. *(ans)*
3. State the beneficial function to the bacterium of the following components of the gram-negative cell wall:
   a. peptidoglycan *(ans)*
   b. outer membrane *(ans)*
   c. adhesins *(ans)*
   d. invasins *(ans)*
4. Briefly describe how the LPS (endotoxin) of the Gram-negative cell wall can promote inflammation. *(ans)*
5. Define epitope. *(ans)*
6. When Gram-negative bacteria enter the blood and cause septicemia, most of the harm to the body is due to a massive inflammatory response. What might explain this? *(ans)*

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2.3C: The Acid-Fast Cell Wall

Fundamental Statements for this Learning Object:

In this section on Prokaryotic Cell Anatomy we are looking at the various anatomical parts that make up a bacterium. As mentioned in the introduction to this section, a typical bacterium usually consists of:

- a cytoplasmic membrane surrounded by a peptidoglycan cell wall and maybe an outer membrane;
- a fluid cytoplasm containing a nuclear region (nucleoid) and numerous ribosomes; and
- often various external structures such as a glycocalyx, flagella, and pili.

There are three primary types of bacterial cell wall: Gram-positive, Gram-negative, and acid-fast. We will now look at the acid-fast cell wall.

Acid-fast bacteria stain poorly with the Gram stain procedure, appearing weakly Gram-positive or Gram-variable. They are usually characterized using the acid-fast staining procedure. As mentioned in the previous section on peptidoglycan, bacteria with an acid-fast cell wall resist decolorization with an acid-alcohol mixture during the acid-fast staining procedure , retain the initial dye carbol fuchsin and appear red (Figure $2.3C.1; left$). Common acid-fast bacteria of medical importance include *Mycobacterium tuberculosis, Mycobacterium leprae,Mycobacterium avium-intracellulare* complex, and *Nocardia* species.

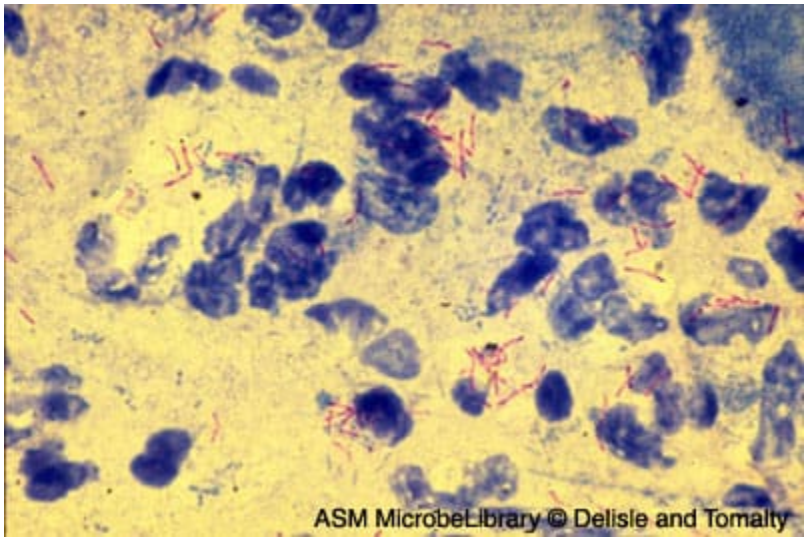


Figure $2.3C.1$**:** (left) Scanning Electron Micrograph of Mycobacterium tuberculosis. Image provided by Dr. Ray Butler and Janice Carr. Courtesy of the Centers for Disease Control and Prevention. (right) Acid-Fast Stain of Mycobacterium tuberculosis in Sputum. Note the reddish acid-fast bacilli among the blue normal flora and white blood cells in the sputum that are not acid-fast.

Structure and Composition of the Acid-Fast Cell Wall

Acid-fast bacteria are gram-positive, but in addition to peptidoglycan, the outer membrane or envelope of the acid-fast cell wall of contains large amounts of glycolipids, especially mycolic acids that in the genus *Mycobacterium*, make up approximately 60% of the acid-fast cell wall (Figure $2.3C.2$).

- **Layer 1:** The acid-fast cell wall of *Mycobacterium* has a thin, inner layer of peptidoglycan.
- **Layer 2:** The peptidoglycan layer is, in turn, linked to arabinogalactan (D-arabinose and D-galactose).
- **Layer 3:** The arabinogalactan is then linked to an outer membrane containing high-molecular weight mycolic acids. The arabinogalactan/mycolic acid layer is overlaid with a layer of polypeptides and mycolic acids consisting of free lipids, glycolipids, and peptidoglycolipids. Other glycolipids include lipoarabinomannan and phosphatidyinositol mannosides (PIM). Like the outer membrane of the gram-negative cell wall, porins are required to transport small hydrophilic molecules through

the outer membrane of the acid-fast cell wall.

- **Layer 4:** The outer surface of the acid-fast cell wall is studded with surface proteins that differ with the strain and species of the bacterium.
- **Layer 5:**The periplasm is the gelatinous material between the peptidoglycan and the cytoplasmic membrane.

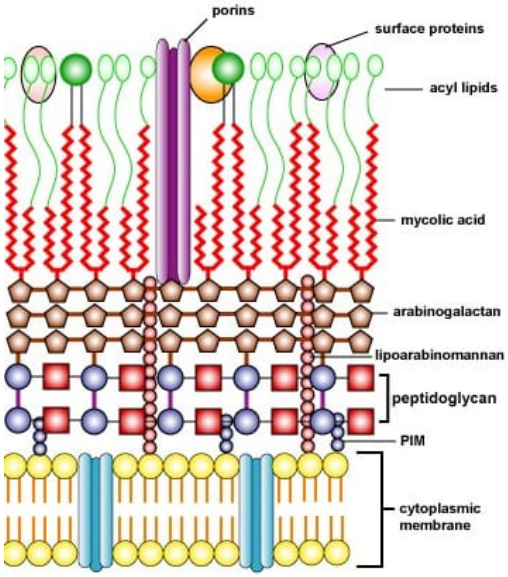


Figure $2.3C.2$**:** Structure of an Acid-Fast Cell Wall. In addition to peptidoglycan, the acid-fast cell wall of Mycobacterium contains a large amount of glycolipids, especially mycolic acids. The peptidoglycan layer is linked to arabinogalactan (D-arabinose and D-galactose) which is then linked to high-molecular weight mycolic acids. The arabinogalactan/mycolic acid layer is overlaid with a layer of polypeptides and mycolic acids consisting of free lipids, glycolipids, and peptidoglycolipids. Other glycolipids include lipoarabinomannan and phosphatidyinositol mannosides (PIM). Like the outer membrane of the gram-negative cell wall, porins are required to transport small hydrophilic molecules through the outer membrane of the acid-fast cell wall. Because of its unique cell wall, when it is stained by the acid-fast procedure, it will resist decolorization with acid-alcohol and stain red, the color of the initial stain, carbol fuchsin. With the exception of a very few other acid-fast bacteria such as Nocardia, all other bacteria will be decolorized and stain blue, the color of the methylene blue counterstain.

Functions of the Acid-Fast Cell Wall Components

- **Layer 1:** The peptidoglycan prevents osmotic lysis.
- **Layer 2:** The arabinogalactan layer is linked to both the peptidoglycan and to the mycolic acid outer membrane and probably provides additional strength to the cell wall.
- **Layer 3:** The mycolic acids and other glycolipids also impede the entry of chemicals causing the organisms to grow slowly and be more resistant to chemical agents and lysosomal components of phagocytes than most bacteria (Figure $2.3C.2$). There are far fewer porins in the acid-fast cell wall compared to the gram-negative cell wall and the pores are much longer. This is thought to contribute significantly to the lower permeability of acid-fast bacteria.
- **Layer 4:**The surface proteins in the acid-fast cell wall, depending on the strain and species, carry out a variety of activities, including functioning as enzymes and serving as *adhesin*s, which enable the bacterium to adhere intimately to host cells and other surfaces in order to colonize and resist flushing.
- **Layer 15** The periplasm contains enzymes for nutrient breakdown.

Exercise: Think-Pair-Share Questions

Mycobacterium tuberculosis is a very slow growing bacterium with a generation time often measured in days to weeks. It is also resistant to the vast majority of antibiotics that are commonly effective against other bacteria and treatment is typically with a combination of drugs for up to 9 months.

Based on what we just learned, explain what might account for these two characteristics.

Significance of Acid-Fast Cell Wall Components to the Initiation of Body Defenses

The body has two immune systems: the innate immune system and the adaptive immune system.

1. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.
2. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life.

Initiation of Innate Immunity

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. Pathogenic *Mycobacterium* species such as *Mycobacterium tuberculosis* and *Mycobacterium leprae* release mycolic acid, arabinogalactan, and peptidoglycan fragments from their acid-fast cell wall. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometime referred to as microbe-associated molecular patterns or MAMPs.)

These PAMPS bind to pattern-recognition receptors or PRRs on a variety of defense cells of the body causing them to synthesize and secrete a variety of proteins called cytokines. These cytokines can, in turn promote innate immune defenses such as inflammation , phagocytosis, activation of the complement pathways , and activation of the coagulation pathway .

Inflammation is the first response to infection and injury and is critical to body defense. Basically, the inflammatory response is an attempt by the body to restore and maintain homeostasis after injury. Most of the body defense elements are located in the blood, and inflammation is the means by which body defense cells and body defense chemicals leave the blood and enter the tissue around an injured or infected site.

Body defense cells called macrophages , and dendritic cells have pattern recognition receptors such as toll-like receptors on their surface that are specific for the peptidoglycan fragments and mycolic acids in the acid-fast cell wall and/or to NODs in their cytoplasm that are specific for peptidoglycan fragments. The binding of these cell wall components to their corresponding pattern recognition receptors triggers the macrophages to release various defense regulatory chemicals called cytokines, including IL-1 and TNF-alpha. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway.

Innate immunity will be discussed in greater detail in Unit 5.

Initiation of Adaptive Immunity

Proteins and polysaccharides associated with the acid-fast cell wall function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes . An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes.
2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

Significance of Acid-Fast Cell Wall Components to Bacterial Pathogenicity

Most of the damage in the lungs during tuberculosis is thought to be due to the inflammatory effects from excessive TNF-alpha production, along with the release of toxic lysosomal components of the macrophages trying to kill the *Mycobacterium tuberculosis*.

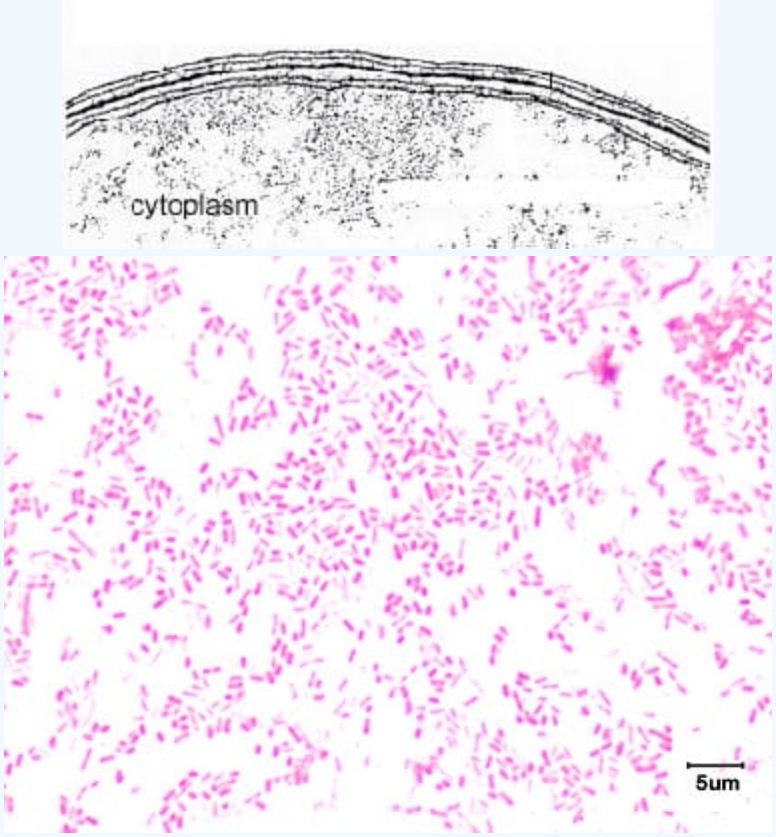
> Click on this link, read the description of *Mycobacterium tuberculosis*, and be able to match the bacterium with its description on an exam.

Antimicrobial Agents that Inhibit Acid-Fast Cell Wall Synthesis to Control *Mycobacterium* Species

INH (isoniazid) blocks the incorporation of mycolic acid into acid-fast cell walls while ethambutol interferes with the incorporation of arabinoglactan (Figure $2.3C.2$). Both inhibit synthesis of the acid-fast cell wall. Pyrazinamide inhibits fatty acid synthesis in *Mycobacterium tuberculosis*.

Think-Pair-Share Questions

Look at the following transmission electron micrograph and Gram stain of the same bacterium.



(left) Transmission electron micrograph: (right) Gram stain

1. Is this organism Gram-positive, Gram-negative, or acid-fast?
2. How can you tell? State all reasons.

Summary

1. Because of the nature of their cell wall, acid-fast bacteria stain red after acid-fast staining.
2. The genus Mycobacterium and the genus Nocardia are among the few bacteria possessing an acid-fast cell wall.
3. The acid-fast cell wall consists of a thin, inner layer of peptidoglycan linked to a layer of arabinogalactin, which in turn is linked to an outer membrane containing mycolic acids and overlaid with a variety of polypeptides and glycolipids.
4. Porins are required to transport small hydrophilic molecules through the outer membrane of the acid-fast cell wall.
5. The acid-fast cell wall activates both the body's innate immune defenses and its adaptive immune defenses.
6. The body activates innate immunity by recognizing molecules unique to microorganisms that are not associated with human cells called pathogen-associated molecular patterns or PAMPs. PAMPs bind to Pattern-recognition receptors (PRRs) on defense cells to trigger the production of inflammatory cytokines.
7. Inflammation is the means by which the body delivers defense cells and defense molecules to an infection site, however, excessive inflammation, can be harmful and even deadly to the body.
8. PAMPs associated with the acid-fast cell wall include peptidoglycan monomers, arabinogalactin, and mycolic acids.
9. An antigen is a molecular shape that reacts with antigen receptors on lymphocytes to initiate an adaptive immune response.
10. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens.
11. A few antimicrobial chemotherapeutic agents inhibit acid-fast cell wall synthesis

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what color acid-fast bacteria appear after the acid-fast stain procedure. *(ans)*
2. Describe the structure and appearance of an acid-fast cell wall. *(ans)*
3. State the beneficial function to the bacterium of the following components of the acid-fast cell wall:
   a. peptidoglycan *(ans)*
   b. mycolic acid and other glycolipids *(ans)*
   c. porins *(ans)*
4. *Mycobacterium tuberculosis* is much more resistant to antibiotics and disinfectants than most other bacteria. It also grows much more slowly. Why might this be? *(ans)*
5. Multiple Choice Cell Wall Quiz *(ans)*

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2.4: CELLULAR COMPONENTS WITHIN THE CYTOPLASM

Name the various structures that may be located within the cytoplasm of bacteria.

In this section on Prokaryotic Cell Anatomy we are looking at the various anatomical parts that make up a bacterium. As mentioned in the introduction to this section, a typical bacterium usually consists of:

- a cytoplasmic membrane surrounded by a peptidoglycan cell wall and maybe an outer membrane;
- a fluid cytoplasm containing a nuclear region (nucleoid) and numerous ribosomes; and
- often various external structures such as a glycocalyx, flagella, and pili.



-  Topic hierarchy 

2.4A: Cytoplasm

2.4B: The Bacterial Chromosome and Nucleoid

2.4C: Plasmids and Transposons

2.4D: Ribosomes

2.4E: Endospores

2.4F: Inclusion Bodies and Organelles Used for Photosynthesis

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2.4A: Cytoplasm

Define the following:

a. exoenzymes
b. endoenzymes.
c. cytosol

- State the primary function of the bacterial cytoplasm.
- Define the following:

a. metabolism
b. catabolic reactions
c. anabolic reactions.

We will now look at the bacterial cytoplasm. In bacteria, the cytoplasm refers to everything enclosed by the cytoplasmic membrane. About 80% of the cytoplasm of bacteria is composed of water. Within the cytoplasm can be found nucleic acids (DNA and RNA), enzymes and amino acids, carbohydrates, lipids, inorganic ions, and many low molecular weight compounds. The liquid component of the cytoplasm is called the cytosol. Some groups of bacteria produce cytoplasmic inclusion bodies that carry out specialized cellular functions.

Functions

While bacteria secrete exoenzymes to hydrolize macromolecules into smaller molecules capable of being transported across the cytoplasmic membrane, the cytoplasm is the site of most bacterial metabolism. This includes catabolic reactions in which molecules are broken down in order to obtain building block molecules for more complex cellular molecules and macromolecules, and anabolic reactions used to synthesize cellular molecules and macromolecules. The chemical reactions occuring within the bacterium are under the control of endoenzymes.

The various structurural filaments in the cytoplasm collectively make up the prokaryotic cytoskeleton. Prokaryotic cells possess analogs for all of the cytoskeletal proteins found in eukaryotic cells, as well as cytoskeletal proteins with no eukaryotic homologues. Cytoskeletal filaments play essential roles in determining the shape of a bacterium (coccus, bacillus, or spiral) and are also critical in the process of cell division by binary fission and in determining bacterial polarity.

Summary

1. In bacteria, the cytoplasm refers to anything enclosed by the cytoplasmic membrane.
2. The liquid portion of the cytoplasm is called the cytosol.
3. The cytoplasm is the site of most bacterial metabolism.
4. During catabolic reactions larger molecules are broken down to obtain cellular building block molecules and energy; during anabolic reactions cellular molecules and macromolecules are synthesized.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ Enzymes that function within the bacterium. (ans)

   _____ Chemical reactions in which more complex molecules are synthesized. *(ans)*

   _____ Chemical reactions in which more complex molecules are broken down into smaller, more simple molecules. *(ans)*

A. Metabolism
B. Catabolic reactions
C. Anabolic reactions
D. Exoenzymes
E. Endoenzymes

2. State the primary function of bacterial cytoplasm. *(ans)*

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2.4B: The Bacterial Chromosome and Nucleoid

Learning Objectives

1. Define genome.
2. Describe the composition of the bacterial chromosome.
3. Name the enzymes that enables bacterial DNA to become circular, supercoiled, and unwind during DNA replication.
4. Briefly describe the process of DNA replication.
5. State the function of the following enzymes in bacterial DNA replication:
    a. DNA polymeraseIII
    b. DNA polymerase II
    c. DNA helicase
    d. primase
    e. DNA ligase
6. State the function of DNA.
7. In terms of protein synthesis, briefly describe the process of transcription and translation.
8. Briefly state how the following antibacterial chemotherapeutic agents affect bacteria:
    a. fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.)
    b. trimethoprim and sulfamethoxazole

We will now look at the bacterial chromosome located in the nuclear region called the nucleoid.

A. Structure and Composition of the Bacterial Chromosome

The term genome refers to the sum of an organism's genetic material. The bacterial genome is composed of a single molecule of chromosomal deoxyribonucleic acid or DNA and is located in a region of the bacterial cytoplasm visible when viewed with an electron microscope called the nucleoid. Unlike the eukaryotic nucleus, the bacterial nucleoid has no nuclear membrane or nucleoli.

In general it is thought that during DNA replication, each strand of the replicating bacterial DNA attaches to proteins at what will become the cell division plane. For example, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells (Figure $2.4B.1$).

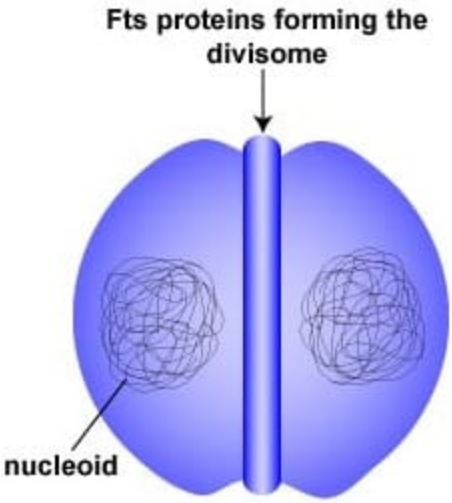


Figure $2.4B.1$**:** Bacterial Division. In general it is thought that during DNA replication, each strand of the replicating bacterial DNA attaches to proteins at what will become the cell division plane. For example, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells. In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission. The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.

In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission. The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.

Since bacteria are haploid, that is they have only one chromosome and only reproduce asexually, there is also no meiosis in bacteria.

The bacterial chromosome is one long, single molecule of double stranded, helical, supercoiled DNA. In most bacteria, the two ends of the double-stranded DNA covalently bond together to form both a physical and genetic circle. The chromosome is generally around 1000 µm long and frequently contains as many as 3500 genes (Figure $2.4B.2$). *E. coli*, a bacterium that is 2-3 µm in length, has a chromosome approximately 1400 µm long.

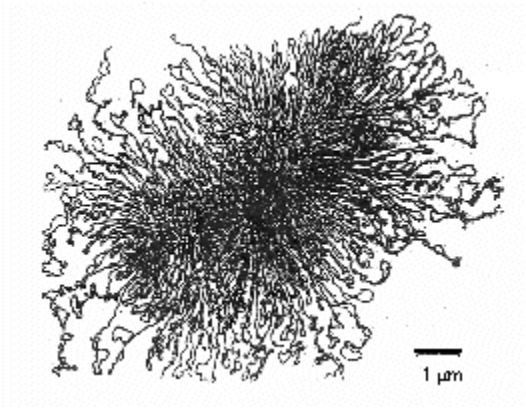


Figure $2.4B.2$**:** Electron Micrograph of a Bacterial Chromosome

To enable a macromolecule this large to fit within the bacterium, histone-like proteins bind to the DNA, segregating the DNA molecule into around 50 chromosomal domains and making it more compact. A DNA topoisomerase enzyme called DNA gyrase then supercoils each domain around itself, forming a compacted mass of DNA approximately 0.2 µm in diameter. In actively growing bacteria, projections of the nucleoid extend into the cytoplasm. Presumably, these projections contain DNA that is being transcribed into mRNA.Supercoils are both inserted and removed by *topoisomerases*.

DNA topoisomerases are, therefore, essential in the unwinding, replication, and rewinding of the circular, supercoiled bacterial DNA. In order for the long molecule of DNA to fit within the bacterium, the DNA must be supercoiled. However, this supercoiled DNA must be uncoiled and relaxed in order for DNA polymerase to bind for DNA replication and RNA polymerase to bind for transcription of the DNA. For example, a topoisomerase called DNA gyrase catalyzes the negative supercoiling of the circular DNA found in bacteria. Topoisomerase IV, on the other hand, is involved in the relaxation of the supercoiled circular DNA, enabling the separation of the interlinked daughter chromosomes at the end of bacterial DNA replication.

B. DNA Replication in Bacteria

In general, DNA is replicated by uncoiling of the helix, strand separation by breaking of the hydrogen bonds between the complementary strands, and synthesis of two new strands by complementary base pairing. Replication begins at a specific site in the DNA called the origin of replication (*ori*C).

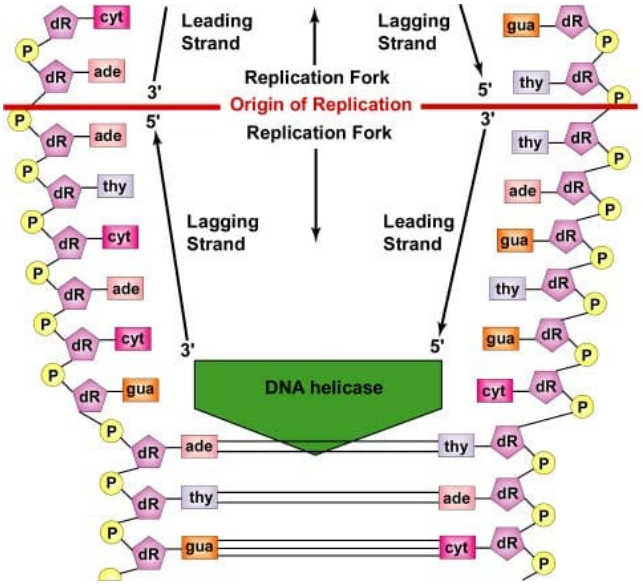


Figure $2.4B.3$**:** DNA Replication by Complementary Base Pairing: Unwinding by DNA Helicase. Replication begins at a specific site in the DNA called the origin of replication. Unwinding enzymes called DNA helicases cause the two parent DNA strands to unwind and separate from one another in both directions at this site to form two "Y"-shaped replication forks. These replication forks are the actual site of DNA copying. During replication within the fork, helix destabilizing proteins (not shown here) bind to the single-stranded regions preventing the strands from rejoining.

DNA replication is bidirectional from the origin of replication. To begin DNA replication, unwinding enzymes called DNA helicases cause short segments of the two parent DNA strands to unwind and separate from one another at the origin of replication to form two "Y"-shaped replication forks. These replication forks are the actual site of DNA copying (Figure $2.4B.3$). All the proteins involved in DNA replication aggregate at the replication forks to form a replication complex called a replisome (Figure $2.4B.4$).

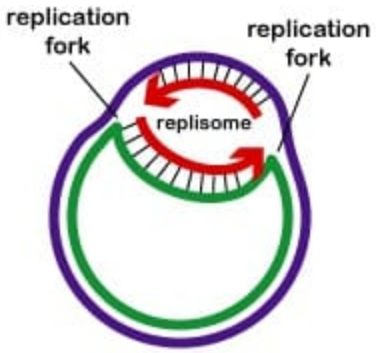


Figure $2.4B.4$**:** Bidirectional Circular DNA Replication in Bacteria. DNA replication (arrows) occurs in both directions from the origin of replication in the circular DNA found in most bacteria. All the proteins involved in DNA replication aggregate at the replication forks to form a replication complex called a replisome. The lagging DNA strand loops out from the leading strand and this enables the replisome to move along both strands pulling the DNA through as replication occurs. It is the actual DNA, not the DNA polymerase that moves during bacterial DNA replication.

Single-strand binding proteins bind to the single-stranded regions so the two strands do not rejoin. Unwinding of the double-stranded helix generates positive supercoils ahead of the replication fork. Enzymes called *topoisomerases* counteract this by producing breaks in the DNA and then rejoin them to form negative supercoils in order to relieve this stress in the helical molecule during replication.

As the strands continue to unwind and separate in both directions around the entire DNA molecule, new complementary strands are produced by the hydrogen bonding of free DNA nucleotides with those on each parent strand. As the new nucleotides line up opposite each parent strand by hydrogen bonding, enzymes called DNA polymerases join the nucleotides by way of phosphodiester bonds. Actually, the nucleotides lining up by complementary base pairing are deoxynucleotide triphosphates, composed of a nitrogenous base, deoxyribose, and three phosphates. As the phosphodiester bond forms between the 5' phosphate group of the new nucleotide and the 3' OH of the last nucleotide in the DNA strand, two of the phosphates are removed providing energy for bonding (see Figure $2.4B.6$). In the end, each parent strand serves as a template to synthesize a complementary copy of itself, resulting in the formation of two identical DNA molecules (see Figure $2.4B.7$). In bacteria, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells. Fts proteins, such as FtsK in the divisome, also help in separating the replicated bacterial chromosome.

GIF animation illustrating DNA replication by complementary base pairing

In reality, DNA replication is more complicated than this because of the nature of the DNA polymerases. DNA polymerase enzymes are only able to join the phosphate group at the 5' carbon of a new nucleotide to the hydroxyl (OH) group of the 3' carbon of a nucleotide already in the chain. As a result, DNA can only be synthesized in a 5' to 3' direction while copying a parent strand running in a 3' to 5' direction.

Each DNA strand has two ends. The 5' end of the DNA is the one with the terminal phosphate group on the 5' carbon of the deoxyribose; the 3' end is the one with a terminal hydroxyl (OH) group on the deoxyribose of the 3' carbon of the deoxyribose (see Figure $2.4B.8$). The two strands are antiparallel, that is they run in opposite directions. Therefore, one parent strand - the one running 3' to 5' and called the leading strand - can be copied directly down its entire length (see Figure $2.4B.9$). However, the other parent strand - the one running 5' to 3' and called the lagging strand - must be copied discontinuously in short fragments (Okazaki fragments) of around 100-1000 nucleotides each as the DNA unwinds. This occurs, as mentioned above, at the replisome. The lagging DNA strand loops out from the leading strand and this enables the replisome to move along both strands pulling the DNA through as replication occurs. It is the actual DNA, not the DNA polymerase that moves during bacterial DNA replication (see Figure $2.4B.5$).

In addition, DNA polymerase enzymes cannot begin a new DNA chain from scratch. They can only attach new nucleotides onto 3' OH group of a nucleotide in a preexisting strand. Therefore, to start the synthesis of the leading strand and each DNA fragment of the lagging strand, an RNA polymerase complex called a primase is required. The primase, which is capable of joining RNA nucleotides without requiring a preexisting strand of nucleic acid, first adds several comlementary RNA nucleotides opposite the DNA nucleotides on the parent strand. This forms what is called an RNA primer (see Figure $2.4B.10$).

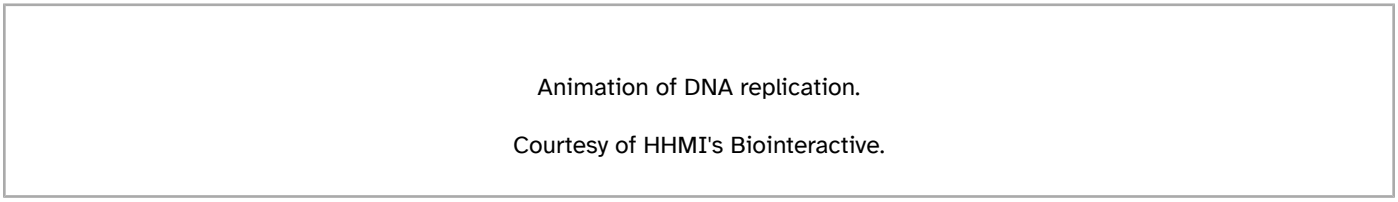
DNA polymerase III then replaces the primase and is able to add DNA nucleotides to the RNA primer (see Figure $2.4B.11$). Later, DNA polymerase II digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA

nucleotides to fill the gap (see Figure $2.4B.12$). Finally, the DNA fragments themselves are hooked together by the enzyme DNA ligase (see Figure $2.4B.9$). Yet even with this complicated procedure, a 1000 micrometer-long macromolecule of tightly-packed, supercoiled DNA can make an exact copy of itself in only about 10 minutes time under optimum conditions, inserting nucleotides at a rate of about 1000 nucleotides per second!

YouTube movie illustrating DNA replication in prokaryotic cells, #1.

YouTube movie illustrating DNA replication in prokaryotic cells, #2.

GIF animation illustrating the replication of leading and lagging strands of DNA



Animation of DNA replication.

Courtesy of HHMI's Biointeractive.

For More Information: Review of Prokaryotic DNA Replication from Unit 7

C. Functions of the Bacterial Chromosome

The chromosome is the genetic material of the bacterium. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA, and ribosomal RNA (rRNA). Messenger RNA is then translated into protein at the ribosomes.

- **Transcription:** Ribonucleic acid (RNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene. Although genes are present on both strands of DNA, only one strand is transcribed for any given gene. Following transcription of genes into mRNA, 30S and 50S ribosomal subunits attach to the mRNA and tRNA inserts the correct amino acids which are subsequently joined to form a polypeptide or a protein through a process called translation.
- **Translation**: During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message." This is done by the anticodon portion of the tRNA molecules complementary base pairing with the codons along the mRNA.

In general then, DNA determines what proteins and enzymes an organism can synthesize and, therefore, what chemical reactions it is able to carry out.

D. The Bacterial Epigenome

The epigenome refers to a variety of chemical compounds that modify the genome typically by adding a methyl (CH_3) group to the nucleotide base adenine at specific locations along the DNA molecule. This methylation can, in turn, either repress or activate transcription of specific genes. By basically turning genes on or off, the epigenome enables the bacterial genome to interact with and respond to the bacterium's environment. The epigenome can be inherited just like the genome.

All cells, including human cells, possess an epigenome. Just as the bacterial epigenome can affect the bacterial genome, bacteria, can affect our epigenome and subsequently modify the function of our genome by causing either DNA methylation of nucleotides or by modifying our histone proteins. The resulting modification can either help activate various genes involved in immune defenses, or, in the case of some pathogens, suppress immune response genes.

E. Significance of the Chromosome to the Initiation of Body Defense

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The

body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Bacterial and viral genomes contain a high frequency of unmethylated cytosine-guanine (CpG) dinucleotide sequences (a cytosine lacking a methyl or CH_3 group and located adjacent to a guanine). Mammalian DNA has a low frequency of cytosine-guanine dinucleotides and most are methylated. These unmethylated cytosine-guanine dinucleotide sequences in bacterial DNA are PAMPS that bind to pattern-recognition receptors on a variety of defense cells of the body and triggers innate immune defenses such as inflammation, fever, and phagocytosis.

F. Antimicrobial Agents that Inhibiting Normal Nucleic Acid Replication in Bacteria

Some antibacterial chemotherapeutic affect bacteria by inhibiting normal nucleic acid replication.

- The fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.) work by inhibiting one or more of the topoisomerases, the enzymes needed for bacterial nucleic acid synthesis.
- Co-trimoxazole, a combination of sulfamethoxazole and trimethoprim, block enzymes in the bacteria pathway required for the synthesis of tetrahydrofolic acid, a cofactor needed for bacteria to make the nucleotide bases thymine, guanine, uracil, and adenine. Without the tetrahydrofolic acid, the bacteria cannot synthesize DNA or RNA.

Antimicrobial chemotherapy will be discussed in greater detail later in Unit 2 under Control of Bacteria by Using Antibiotics and Disinfectants.

Exercise: Think-Pair-Share Questions

As we are learning, pathogen-associated molecular patterns (PAMPs) are microbial molecules many microbes share but are not found as a part of the human body and are able to initiate innate immune responses. Examples thus far include peptidoglycan fragments, lipopolysaccharide in the gram-negative cell wall, and lipoteichoic acids in the gram-positive cell wall, molecules that human cells lack. Bacterial and viral genomes also act as PAMPs.

Our cells also have DNA and RNA. How can bacterial and viral genomes initiate innate immunity when our genomes do not?

Summary

1. The genome is the sum of an organism's genetic material.
2. Bacteria contain a single chromosome of double-stranded deoxyribonucleic acid (DNA).
3. The region of the bacterial cytoplasm where the chromosome is located and visible when viewed with an electron microscope called the nucleoid.
4. The bacterial chromosome is typically a physical and genetic circle, becomes supercoiled,and is not surrounded by a nuclear membrane.
5. Bacteria do not carry out mitosis or meiosis.
6. DNA topoisomerase enzymes are used to supercoil and relax the bacterial chromosome during DNA replication and transcription.
7. Like eukaryotic DNA, prokaryotic DNA replicates by sequential unwinding of the two DNA parent strands and the subsequent complementary base pairing of DNA nucleotides with each parent strand.
8. During DNA replication the nitrogenous base adenine forms hydrogen bonds with thymine and guanine forms hydrogen bonds with cytosine.
9. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA). Messenger RNA is then translated into protein at the ribosomes.
10. During transcription, ribonucleic acid (RNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene.
11. During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message."

12. Bacterial and viral genomes act as PAMPs to stimulate innate immunity.
13. Some antibacterial chemotherapeutic agents inhibiting normal nucleic acid replication in bacteria.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. The sum of an organism's genetic material is called its_____. *(ans)*
2. Bacterial enzymes involved in in the unwinding, replication, and rewinding of the circular, supercoiled bacterial DNA called _____. *(ans)*
3. Describe the general composition of the chromosome in most bacteria. *(ans)*
4. Briefly describe the process of DNA replication. *(ans)*
5. State what enzyme carries out the following functions during DNA replication.
    a. Unwinds the helical DNA by breaking the hydrogen bonds between complementary bases. *(ans)*
    b. Synthesizes a short RNA primer at the beginning of each origin of replication. *(ans)*
    c. Adds DNA nucleotides to the RNA primer. *(ans)*
    d. Digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides. *(ans)*
    e. Links the DNA fragments of the lagging strand together. *(ans)*
6. State the overall function of DNA. *(ans)*
7. Define transcription. *(ans)*
8. Define translation. *(ans)*
9. Ciprofloxacin (*Cipro*) is used to treat a variety of bacterial infections. How does it stop bacteria from growing? *(ans)*
10. Multiple Choice *(ans)*

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2.4C: Plasmids and Transposons

Learning Objectives

1. Describe plasmids and indicate their possible benefit to bacteria.
2. State the function of the following:
   a. transposons
   b. integrons
   c. episome
   d. conjugative plasmid
3. State the most common way plasmids are transmitted from one bacterium to another.
4. Define horizontal gene transfer.

In addition to the bacterial chromosome, many bacteria often contain small nonchromosomal DNA molecules called plasmids. Plasmids usually contain between 5 and 100 genes. Plasmids are not essential for normal bacterial growth and bacteria may lose or gain them without harm. They can, however, provide an advantage under certain environmental conditions. For example, under normal environmental growth conditions, bacteria are not usually exposed to antibiotics and having a plasmid coding for an enzyme capable of denaturing a particular antibiotic is of no value. However, if that bacterium finds itself in the body when the particular antibiotic that the plasmid-coded enzyme is able to degrade is being given to treat an infection, the bacterium containing the plasmid is able to survive and grow.

Structure and Composition

Plasmids are small molecules of double stranded, helical, non-chromosomal DNA. In most plasmids the two ends of the double-stranded DNA molecule that make up plasmids covalently bond together forming a physical circle. Some plasmids, however, have linear DNA. Plasmids replicate independently of the host chromosome, but some plasmids, called episomes, are able to insert or integrate into the host cell's chromosome where their replication is then regulated by the chromosome.

Although some plasmids can be transmitted from one bacterium to another by transformation and by generalized transduction, the most common mechanism of plasmid transfer is conjugation. Plasmids that can be transmitted by cell-to-cell contact are called conjugative plasmids. They contain genes coding for proteins involved in both DNA transfer and and the formation of mating pairs.

Functions

Plasmids code for synthesis of a few proteins not coded for by the bacterial chromosome. For example, R-plasmids, found in some Gram-negative bacteria, often have genes coding for both production of a conjugation pilus (discussed later in this unit) and multiple antibiotic resistance. Through a process called conjugation, the conjugation pilus enables the bacterium to transfer a copy of the R-plasmids to other bacteria, making them also multiple antibiotic resistant and able to produce a conjugation pilus. In addition, some exotoxins, such as the tetanus exotoxin, *Escherichia coli* enterotoxin, and *E. coli* shiga toxin discussed later in Unit 2 under Bacterial Pathogenicity, are also coded for by plasmids. Thousands of different plasmids are known to exist.

Transposons

Transposons (transposable elements or "jumping genes") are small pieces of DNA that encode enzymes that transpose the transposon, that is, move it from one DNA location to another, either on the same molecule of DNA or on a different molecule. Transposons may be found as part of a bacterium's nucleoid (conjugative transposons) or in plasmids and are usually between one and twelve genes long. A transposon contains a number of genes, coding for antibiotic resistance or other traits, flanked at both ends by insertion sequences coding for an enzyme called transpoase. Transpoase is the enzyme that catalyzes the cutting and resealing of the DNA during transposition. Thus, such transposons are able to cut themselves out of a bacterial nucleoid or a plasmid and insert themselves into another nucleoid or plasmid and contribute in the transmission of antibiotic resistance among a population of bacteria.

Plasmids can also acquire a number of different antibiotic resistance genes by means of integrons. Integrons are transposons that can carry multiple gene clusters called gene cassettes that move as a unit from one piece of DNA to another. An enzyme called integrase enables these gene cassettes to integrate and accumulate within the integron. In this way, a number of different antibiotic resistance genes can be transferred as a unit from one bacterium to another.

Plasmids and conjugative transposons are very important in horizontal gene transfer in bacteria. Horizontal gene transfer , also known as lateral gene transfer, is a process in which an organism transfers genetic material to another organism that is not its offspring. The ability of *Bacteria* and *Archaea* to adapt to new environments as a part of bacterial evolution most frequently results from the acquisition of new genes through horizontal gene transfer rather than by the alteration of gene functions through mutations. (It is estimated that as much as 20% of the genome of *Escherichia coli* originated from horizontal gene transfer.)

Horizontal gene transfer is able to cause rather large-scale changes in a bacterial genome. For example, certain bacteria contain multiple virulence genes called pathogenicity islands that are located on large, unstable regions of the bacterial genome. These pathogenicity islands can be transmitted to other bacteria by horizontal gene transfer. However, if these transferred genes provide no selective advantage to the bacteria that acquire them, they are usually lost by deletion. In this way the size of the bacterium's genome can remain approximately the same size over time.

CRISPR

Because bacteria are always taking in new DNA from horizontal gene transfer or being infected by bacteriophages, bacteria have developed a system for removing viral nucleic acid or DNA from self-serving or harmful plasmids. This system represents a type of adaptive immunity in bacteria, and is carried out by clustered, regularly interspaced, short palindromic repeat (CRISPR) sequences and CRISPR-associated (Cas) proteins that possess nuclease activity. The CRISPR/Cas system targets specific foreign DNA sequences in bacteria for destruction.

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Video: YouTube Movie of the CRISPER/Cas9 System in Bacteria (www.youtube.com/v/ZsxIU5-s5Ds)

Applications of CRISPR technology has now become a common tool used in molecular biology for CRISPR/nuclease mediated genome editing (genetic engineering) in a wide variety of different cell types. Molecular biologists are now beginning to use this to carry out highly efficient, targeted alterations of genome sequence and gene expression and hope to eventually use it to repair damaged or dysfunctional genes.

Exercise: Think-Pair-Share Questions

An F^+ plasmid is a conjugative plasmid that codes strictly for the ability to produce a conjugation pilus and a mating pair.

State what medically significant event might occur if a transposon located in the nucleoid of a normal flora intestinal bacterium and containing genes for antibiotic resistance were to cut out of the bacterium's nucleoid and insert into the F^+ plasmid.

Summary

1. Many bacteria often contain small nonchromosomal DNA molecules called plasmids.
2. While plasmids are not essential for normal bacterial growth and bacteria may lose or gain them without harm, they can provide an advantage under certain environmental conditions.
3. Plasmids code for synthesis of a few proteins not coded for by the bacterial chromosome.
4. Transposons (jumping genes) are small pieces of DNA that encode enzymes that enable the transposon to, move from one

DNA location to another.
5. Transposons may be found as part of a bacterium's chromosome or in plasmids
6. Integrons are transposons that can carry multiple gene clusters called gene cassettes that move as a unit from one piece of DNA to another
7. Horizontal gene transfer is a process in which an organism transfers genetic material to another cell that is not its offspring.
8. Horizontal gene transfer is able to cause rather large-scale changes in a bacterial genome.
9. The ability of Bacteria and Archaea to adapt to new environments as a part of bacterial evolution, most frequently results from the acquisition of new genes through horizontal gene transfer rather than by the alteration of gene functions through mutations.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe plasmids and indicate their possible benefit to bacteria. *(ans)*
2. State why R-plasmids are presenting quite a problem today in treating many Gram-negative infections. *(ans)*
3. _____ are small pieces of DNA that encode enzymes that cut segments of DNA from a location in a bacterial chromosome or in a plasmid and insert it into another chromosome or plasmid. These segments of translocated DNA often contain genes for antibiotic resistance. *(ans)*
4. The genes coding for antibiotic resistance in bacterial plasmids frequently change over time, enabling the bacterium to resist new antibiotics. What might account for this? *(ans)*
5. State the most common way plasmids are transmitted from one bacterium to another. *(ans)*
6. Define horizontal gene transfer. *(ans)*
7. Multiple Choice *(ans)*

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2.4D: Ribosomes

Learning Objectives

1. Describe the structure and chemical composition of bacterial ribosomes and state their function.
2. In terms of protein synthesis, briefly describe the process of transcription and translation.
3. State, in a general sense, how antibiotics like neomycin, tetracycline, doxycycline, erythromycin, and azithromycin affect bacterial growth.

Ribosome Structure and Composition

Ribosomes are composed of ribosomal RNA (rRNA) and protein. Prokaryotic cells have three types of rRNA: 16S rRNA, 23S rRNA, and 5S rRNA. Like transfer RNA (tRNA), rRNAs use intrastrand H-bonding between complementary nucleotide bases to form complex folded structures. Ribosomes are composed of two subunits with densities of 50S and 30S ("S" refers to a unit of density called the Svedberg unit). The 30S subunit contains 16S rRNA and 21 proteins; the 50S subunit contains 5S and 23S rRNA and 31 proteins.The two subunits combine during protein synthesis to form a complete 70S ribosome about 25nm in diameter. A typical bacterium may have as many as 15,000 ribosomes.

The Density of Ribosomal Subunits

Ribosomes are composed of two subunits that come together to translate messenger RNA (mRNA) into polypeptides and proteins during translation and are typically described in terms of their density. Density is the mass of a molecule or particle divided by its volume and is measured in Svedberg (S) units, a unit of density corresponding to the relative rate of sedimentation during ultra-high-speed centrifugation. The greater the S-value, the more dense the particle.

Ribosomal subunits are composed of ribosomal RNA (rRNA) and proteins. Ribosomal subunits with different S-values are composed of different molecules of rRNA, as well as different proteins. Remember that RNA is a polymer of ribonucleotides containing the nitrogenous base adenine, uracil, guanine, or cytosine. Different molecules of rRNA are of different lengths and have a different order of these ribonucleotide bases. Because rRNA is single stranded, many of the rRNA nucleotide bases are involved in intrastrand hydrogen bonds and this is what gives the rRNA molecule its specific shape (see Figure $2.4D.1$). The shape, in turn, helps determine its function - much like the the interactions between amino acids in a protein determine that protein's shape and function (see Figure $2.4D.2$).

Illustration of a 16S rRNA in *Escherichia coli*

Animation of a 16S rRNA

Illustration of the enzyme catalase

Prokaryotic ribosomes, for example, are composed of two subunits with densities of 50S and 30S. The 30S subunit contains 16S rRNA 1540 nucleotides long and 21 proteins; the 50S subunit contains a 5S rRNA 120 nucleotides long, a 23S rRNA 2900 nucleotides long, and 31 proteins. The two subunits combine during protein synthesis to form a complete 70S ribosome.

Eukaryotic ribosomal subunits have densities of 60S and 40S because they contain different rRNA molecules and proteins than prokaryotic ribosomal subunits. In most eukaryotes, the 40S subunit contains an 18S rRNA 1900 nucleotides long and approximately 33 proteins; the 60S subunit contains a 5S rRNA 120 nucleotides long, a 5.8S rRNA 160 nucleotides long, a 28S rRNA 4700 nucleotides long, and approximately 49 proteins. The two subunits combine during protein synthesis to form a complete 80S ribosome about 25nm in diameter.

Because of this difference in specific rRNAs and proteins the resulting "shape," there are drugs that can bind either to a 30S or 50S ribosomal subunit of a prokaryotic ribosome and subsequently block its function but are unable to bind to the equivalent 40S or 60S subunit of a eukaryotic ribosome.

Ribosome Functions

Ribosomes function as a workbench for protein synthesis, that is, they receive and translate genetic instructions for the formation of specific proteins. During protein synthesis, mRNA attaches to the 30s subunit and amino acid-carrying transfer RNAs (tRNA) attach to the 50s subunit (Figure $2.4D.1$). Protein synthesis is discussed in detail in Unit 6.

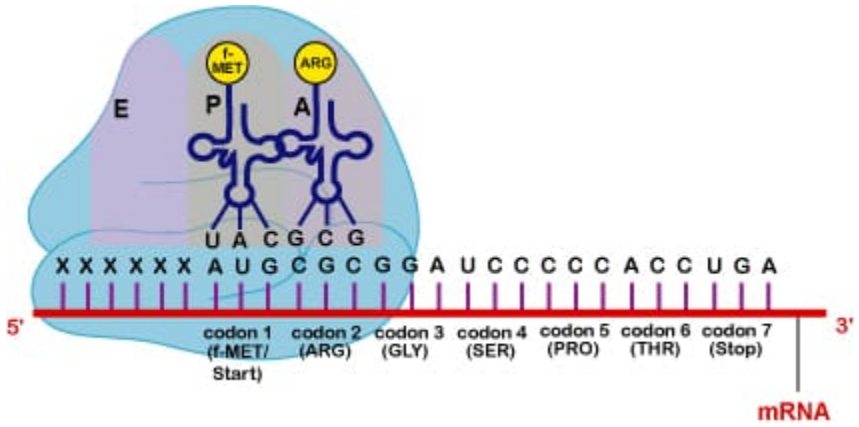


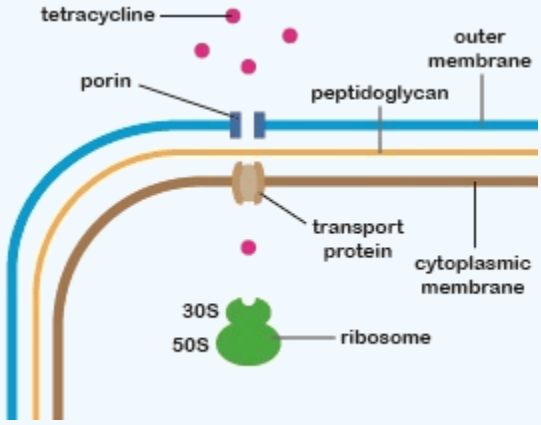
Figure $2.4D.1$: 70S Ribosome During Translation. The 70S prokaryotic ribosome consists of a 50S and a 30S subunit. "S" refers to a unit of density called the Svedberg unit.

The chromosome is the genetic material of the bacterium. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA, and ribosomal RNA (rRNA). Messenger RNA is then translated into protein at the ribosomes.

- **Transcription:** Ribonucleic acid (RNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene. Although genes are present on both strands of DNA, only one strand is transcribed for any given gene. Following transcription of genes into mRNA, 30S and 50S ribosomal subunits attach to the mRNA and tRNA inserts the correct amino acids which are subsequently joined to form a polypeptide or a protein through a process called translation.
- **Translation:** During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message." This is done by the anticodon portion of the tRNA molecules complementary base pairing with the codons along the mRNA.

Exercise: Think-Pair-Share Questions

In order for any of the tetracycline group of antibiotics to inhibit Gram-negative bacterial growth, they must enter the cytoplasm of that bacterium and bind to the 30S subunit of its ribosomes.



Earlier we learned the composition and functions of both the Gram-negative cell wall and the cytoplasmic membrane. We have also previously learned how the order of deoxyribonucleotide bases in DNA determines the order of ribonucleotide bases in rRNA which, in turn, determines the 3-dimensional shape of that RNA. Likewise, the order of deoxyribonucleotide bases in DNA determines the order of amino acids in a protein or enzyme which determines the 3-dimensional shape of that protein.

Considering all of this and using the illustration above, think of three physical changes that could occur within the bacterium as a result of acquiring new or altered genes through mutation or horizontal gene transfer that could enable the bacterium to resist that tetracycline.

Antimicrobial Agents that Alter Prokaryotic Ribosomal Subunits and Block Translation in Bacteria

Many antibiotics alter bacterial ribosomes, interfering with translation and thereby causing faulty protein synthesis. The portion of the ribosome to which the antibiotic binds determines how translation is effected. For example:

- The **tetracyclines** (tetracycline, doxycycline, demeclocycline, minocycline, etc.) bind reversibly to the 30S subunit, distorting it in such a way that the anticodons of charged tRNAs cannot align properly with the codons of the mRNA.
- The **macrolides** (erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc.) bind reversibly to the 50S subunit. They appear to inhibit elongation of the protein by preventing the enzyme peptidyltransferase from forming peptide bonds between the amino acids. They may also prevent the transfer of the peptidyl tRNA from the A-site to the P-site.

Antimicrobial chemotherapy will be discussed in greater detail later in Unit 2 under Control of Bacteria by Using Antibiotics and Disinfectants.

Summary

1. Ribosomes are composed of ribosomal RNA (rRNA) and protein.
2. Bacterial ribosomes are composed of two subunits with densities of 50S and 30S, as opposed to 60S and 40S in eukaryotic cells.
3. Ribosomes function as a workbench for protein synthesis whereby they receive and translate genetic instructions for the formation of specific proteins.
4. During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message."
5. Many antibiotics bind to either the 30S or the 50S subunit of bacterial ribosomes, interfering with translation and thereby causing faulty protein synthesis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe bacterial ribosomes. *(ans)*
2. State the function of ribosomes. *(ans)*
3. Define translation. *(ans)*
4. State, in a general sense, how antibiotics like neomycin, tetracycline, doxycycline, erythromycin, and azithromycin affect bacterial growth. *(ans)*
5. The tetracyclines (tetracycline, doxycycline) are antibiotics that bind to the 30S subunit of bacterial ribosomes. The macrolides (erythromycin, azithromycin, clarithromycin) are antibiotics that bind to the 50S subunit of bacterial ribosomes. Why won't these antibiotics be effective for fungal, protozoal, or viral infections? *(ans)*
6. Multiple Choice *(ans)*

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2.4E: Endospores

Name 2 common genera of bacteria capable of producing endospores and state which is an obligate anaerobe.

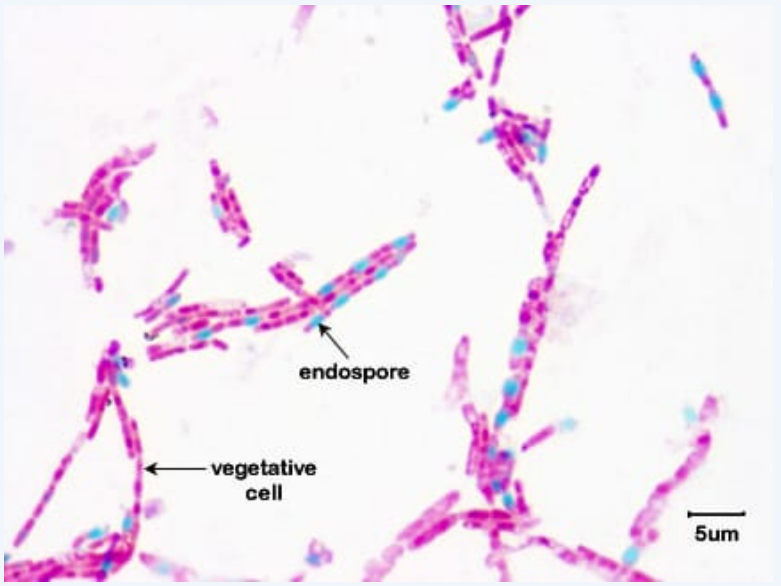
- Briefly discuss the function of a bacterial endospore.
- Describe the structure of a bacterial endospore.
- Define sporulation and germination.
- Name three infections that may be transmitted to humans by endospores.

Highlighted Bacterium

1. Read the description of *Clostridium tetani* and match the bacterium with the description of the organism and the infection it causes.

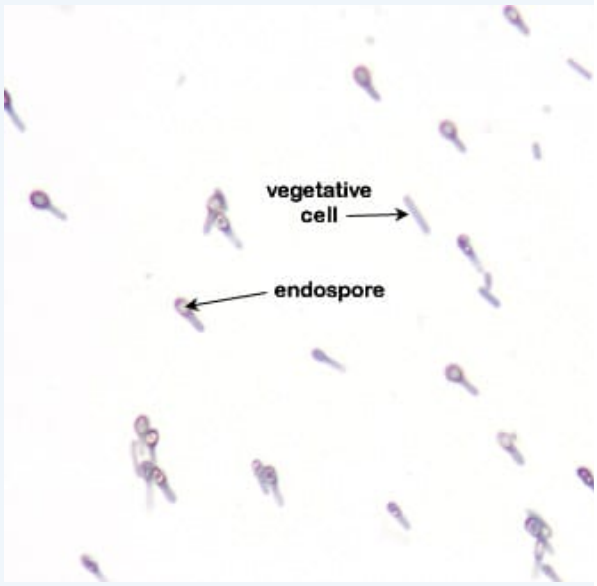
Endospores are dormant alternate life forms produced by the genus *Bacillus*, the genus *Clostridium*, and a number other genera of bacteria, including *Desulfotomaculum, Sporosarcina, Sporolactobacillus, Oscillospira,* and *Thermoactinomyces*. *Bacillus* species (see Figure $2.4E.1$) are obligate aerobes that live in soil while *Clostridium* species (see Figure $2.4E.2$) are obligate anaerobes often found as normal flora of the gastrointestinal tract in animals.

Figure $2.4E.1$: Endospore stain of *Bacillus megaterium*



Note green endospores within pink bacilli.

Figure $2.4E.2$: Endospore stain of *Clostridium*



Note the endospore within the rod gives the bacter racquet" shape (arrows).

- Scanning electron micrograph of *Clostridium botulinum* with endospore; courtesy of Dennis Kunkel's Microscopy.

Formation of Endospores

Under conditions of starvation, especially the lack of carbon and nitrogen sources, a single endospores form within some of the bacteria. The process is called sporulation .

First the DNA replicates (Figure $2.4E.3$, step 1)and a cytoplasmic membrane septum forms at one end of the cell (Figure $2.4E.3$. step 3). A second layer of cytoplasmic membrane then forms around one of the DNA molecules (Figure $2.4E.3$, step 4) - the one that will become part of the endospore - to form a forespore (Figure $2.4E.3$, step 5). Both of these membrane layers then synthesize peptidoglycan in the space between them to form the first protective coat, the cortex (Figure $2.4E.3$, step 6) that lies adjacent to the germ cell wall that will eventually form the cell wall of the bacterium upon germination.

Calcium dipocolinate is also incorporated into the forming endospore. A spore coat composed of a keratin-like protein then forms around the cortex (Figure $2.4E.3$, step 7). Sometimes an outer membrane composed of lipid and protein and called an exosporium is also seen (Figure $2.4E.3$, step 8).

Finally, the remainder of the bacterium is degraded and the endospore is released (Figure $2.4E.3$, step 9). Sporulation generally takes around 15 hours. The process is summarized in Figure $2.4E.3$.

GIF animation showing endospore formation

GIF animation showing endospore germination

YouTube animation of endospore formation by Global Institute of Medical Sciences

- Scanning electron micrograph of *Bacillus anthracis* endospores; courtesy of CDC.

Endospore Structure (see Figure $2.4E.3$, step 10)

The completed endospore consists of multiple layers of resistant coats (including a cortex, a spore coat, and sometimes an exosporium) surrounding a nucleoid, some ribosomes, RNA molecules, and enzymes.

- To view an electron micrograph of an endospore of *Bacillus stearothermophilus*, see the Microbe Zoo web page of Michigan State University.

(Some bacteria produce spore-like structures distinct from endospores. Exospores are heat resistant spores produced by a budding process in members of the genus *Metylosinus* and *Rhodomicrobium*. Cysts are resistant to drying and are formed singly within vegetative cells by *Azotobacter, Myxococcus*, and *Sporocytophaga*. Conidia are heat-susceptible asexual reproductive spores produced by various genera of branching bacteria belonging to the group Actinomycetes.)

Function of Endospores

An endospore is not a reproductive structure but rather a resistant, dormant survival form of the organism. Endospores are quite resistant to high temperatures (including boiling), most disinfectants, low energy radiation, drying, etc. The endospore can then survive until a variety of environmental stimuli trigger germination , allowing outgrowth of a single vegetative bacterium as shown in Fig 3, step 11 and step 12 and in Figure $2.4E.4$. Viable endospores have reportedly been isolated from the GI tract of a bee embedded in amber between 25 and 40 million years ago. Viable endospores of a halophilic (salt-loving) bacterium have also reportedly been isolated from fluid inclusions in salt crystals dating back over 250 million years!

Bacterial endospores are resistant to antibiotics, most disinfectants, and physical agents such as radiation, boiling, and drying. The impermeability of the spore coat is thought to be responsible for the endospore's resistance to chemicals. The heat resistance of endospores is due to a variety of factors:

- Calcium-dipicolinate, abundant within the endospore, may stabilize and protect the endospore's DNA.
- Small acid-soluble proteins (SASPs) saturate the endospore's DNA and protect it from heat, drying, chemicals, and radiation. They also function as a carbon and energy source for the development of a vegetative bacterium during germination.
- The cortex may osmotically remove water from the interior of the endospore and the dehydration that results is thought to be very important in the endospore's resistance to heat and radiation.

- Finally, DNA repair enzymes contained within the endospore are able to repair damaged DNA during germination.

, its oxygen requirements, where it normally lives, and what its exotoxin does, explain the sequence of events that led to the person contracting botulism and dying.

Endospores and Infectious Disease

Although harmless themselves until they germinate, they are involved in the transmission of some diseases to humans. Infections transmitted to humans by endospores include:

- Anthrax, caused by Bacillus anthracis; endospores can be inhaled, ingested, or enter wounds where they germinate and the vegetative bacteria subsequently replicate.
- Tetanus, caused by *Clostridium tetani*; endospores enter anaerobic wounds where they germinate and the vegetative bacteria subsequently replicate.
- Botulism, caused by *Clostridium botulinum*; endospores enter the anaerobic environment of improperly canned food where they germinate and subsequently replicate.
- Gas gangrene, caused by *Clostridium perfringens*); endospores enter anaerobic wounds where they germinate and the vegetative bacteria subsequently replicate.
- Pseudomembranous colitis (*Clostridium difficile*); antibiotics destroy the normal microbiota of the intestines that keep the growth of *C. difficile* in check while the endospores of *C. difficile* survive and subsequently germinate and replicate before the microbiota is restored.

Concept map for Bacterial Endospores

Summary

1. Endospores are dormant alternate life forms produced by a few genera of bacteria.
2. The genus Bacillus (an obligate aerobe often living in the soil) and the genus Clostridium (an obligate anaerobe living in the gastrointestinal tract of animals) produce endospores.
3. Under conditions of starvation, a single endospore forms within a bacterium through a process called sporulation, after which the remainder of the bacterium is degraded.
4. The completed endospore consists of multiple layers of resistant coats (including a cortex, a spore coat, and sometimes an exosporium) surrounding a nucleoid, some ribosomes, RNA molecules, and enzymes.
5. Endospores are quite resistant to high temperatures (including boiling), most disinfectants, low energy radiation, and drying.
6. The endospore survives until a variety of environmental stimuli trigger germination, allowing outgrowth of a single vegetative bacterium.
7. Infectious diseases such as anthrax, tetanus, gas gangrene, botulism, and pseudomembranous colitis are transmitted to humans by endospores.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Name 2 common genera of bacteria capable of producing endospores and state which is an obligate anaerobe. (ans)
2. Briefly discuss the function of a bacterial endospore. *(ans)*
3. The emergence of a vegetative bacterium from an endospore is called _____. *(ans)*
4. Name three infections transmitted to humans by bacterial endospores. *(ans)*
5. Botulism is caused by *Clostridium botulinum*, a bacterium that is normal flora of the intestinal tract of grazing animals. A person home-canned some green beans by boiling the beans and placing them in jars and screwing on lids. The lids popped

down indicating a vacuum had formed within the jar. Upon ingesting these beans the person contracted botulism. Based on what was learned about *Clostridium*, explain. *(ans)*

6. Multiple Choice *(ans)*

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2.4F: Inclusion Bodies and Organelles Used for Photosynthesis

Name three major types of photosynthetic bacteria and briefly describe where its photosynthetic system is located.

- State the function of the following inclusion bodies:

A. cyanophycin granules
B. carboxysomes
C. gas vacuoles
D. polyhydroxybutyrate and glycogen granules
E. magnetosomes
F. volutin granules and sulfur granules

There are several major groups of photosynthetic bacteria: cyanobacteria, purple bacteria, green sulfur bacteria, green nonsulfur bacteria, heliobacteria, and acidobacteria. Comparing the cyanobacteria, the purple bacteria, and the green bacteria:

The cyanobacteria carry out oxygenic photosynthesis, that is, they use water as an electron donor and generate oxygen during photosynthesis. The photosynthetic system is located in an extensive thylakoid membrane system that is lined with particles called phycobilisomes that contain light-harvesting phycobiliproteins.

- Photograph of the cyanobacteria *Anabaena*.

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2.5: STRUCTURES OUTSIDE THE CELL WALL

The overall purpose of this Learning Object is to list the various cellular components that are often found external to the bacterial cell wall.

In this section on Prokaryotic Cell Anatomy we are looking at the various anatomical parts that make up a bacterium. We will now look at the following structures located outside the cell wall of many bacteria: (1) glycocalyx (capsule) and S-layer, (2) flagella, and (3) pili.



-  Topic hierarchy 

2.5A: Glycocalyx (Capsules) and Biofilms

2.5B: Flagella

2.5C: Fimbriae and Pili

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2.5A: Glycocalyx (Capsules) and Biofilms

State the chemical composition and 2 common functions of a bacterial glycocalyx.

- Briefly describe the following steps in phagocytosis:

  a. unenhanced attachment
  b. enhanced attachment
  c. engulfment
  d. destruction

- Briefly describe how a capsule might initially enable some bacteria to resist being phagocytosed by white blood cells.
- Define biofilm and state at least 3 advantages of biofilm formation to bacteria.

Highlighted Bacterium

1. Read the description of *Strepococcus pneumoniae* and match the bacterium with the description of the organism and the infection it causes.

All bacteria secrete some sort of glycocalyx (Capsules and Slime Layers), an outer viscous covering of fibers extending from the bacterium (see Figure $2.5A.1$, Figure $2.5A.2$, and Figure $2.5A.3$). If it appears as an extensive, tightly bound accumulation of gelatinous material adhering to the cell wall, it is called a capsule as shown in the photomicrograph in Figure $2.5A.2$. If the glycocalyx appears unorganized and more loosely attached, it is referred to as a slime layer.

Structure and Composition

The glycocalyx is usually a viscous polysaccharide or polypeptide slime. Actual production of a glycocalyx often depends on environmental conditions.

- A capsule stain of *Streptococcus lactis*.

Functions and Significance to Bacterial Pathogenicity

Although a number of functions have been associated with the glycocalyx, such as protecting bacteria against drying, trap nutrients, etc., for our purposes there are two very important functions. The glycocalyx enables certain bacteria to resist phagocytic engulfment by white blood cells in the body or protozoans in soil and water. The glycocalyx also enables some bacteria to adhere to environmental surfaces (rocks, root hairs, teeth, etc.), colonize, and resist flushing.

1. Preview of the Steps in Phagocytosis

As will be seen in Unit 5, there are several steps involved in phagocytosis.

a. Attachment

First the surface of the microbe must be attached to the cytoplasmic membrane of the phagocyte. Attachment of microorganisms is necessary for ingestion and may be unenhanced or enhanced.

- Unenhanced attachment is a general recognition of what are called pathogen-associated molecular patterns or PAMPs - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, and glucans common in microbial cell walls but not found on human cells - by means of glycoprotein known as endocytic pattern-recognition receptors on the surface of the phagocytes (see Figure $2.5A.4$).

Flash animation illustrating the function of endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating the function of endocytic pattern-recognition receptors on phagocytes.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

- Enhanced attachment is the attachment of microbes to phagocytes by way of an antibody molecule called IgG or proteins produced during the complement pathways called C3b and C4b (see Figure $2.5A.5$). Molecules such as IgG and C3b that promote enhanced attachment are called opsonins and the process is called opsonization. Enhanced attachment is much more specific and efficient than unenhanced.

  Flash animation illustrating the function of enhanced attachment by way of IgG.

  html5 version of animation for iPad illustrating the function of enhanced attachment by way of IgG.

  For More Information: Antibodies from Unit 6

  For More Information: The Benefits of the Complement Pathways from Unit 5

b. Engulfment

Following attachment, polymerization and then depolymerization of actin filaments send pseudopods out to engulf the microbe (see Figure $2.5A.6$) and place it in a vesicle called a phagosome (see Figure $2.5A.7$).

Flash animation summarizing phagocytosis through unenhanced attachment.

html5 version of animation for iPad summarizing phagocytosis through unenhanced attachment.

Flash animation summarizing phagocytosis through enhanced attachment.

html5 version of animation for iPad summarizing phagocytosis through enhanced attachment.

You Tube Movie illustrating bacterial phagocytosis by a neutrophil.

You Tube Movie illustrating a neutrophil phagocytosing MRSA

YouTube movie showing phagocytosis of yeast by a white blood cell.

You Tube animation summarizing phagocytosis by a macrophage.

c. Destruction

Finally, lysosomes, containing digestive enzymes and microbicidal chemicals, fuse with the phagosome containing the ingested microbe and the microbe is destroyed (see Figure 2.5A.8).

Role of the Glycocalyx in Resisting Phagocytosis

Capsules enable bacteria to resist phagocytosis. For example, capsules can resist unenhanced attachment by preventing the glycoprotein receptors on phagocytes from recognizing the bacterial cell wall components and mannose-containing carbohydrates (see Figure 2.5A.10). Also, some capsules simply cover the C3b that does bind to the bacterial surface and prevent the C3b receptor on phagocytes from making contact with the C3b (see Figure 2.5A.9). This will be discussed in greater detail later in Unit 3 under Bacterial Pathogenesis.

Flash animation illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

Examples of bacteria that use their capsule to resist phagocytic engulfment include *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Bacillus anthracis* , and *Bordetella pertussis*.

- Encapsulated rod-shaped bacteria in an infected gall bladder.

For More Information: The Ability to Resist Phagocytic Engulfment from Unit 3

The body's immune defenses, however, can eventually get around the capsule by producing opsonizing antibodies (IgG) against the capsule. The antibody then sticks the capsule to the phagocyte. In vaccines against pneumococccal pneumonia and *Haemophilus influenzae* type b, it is capsular polysaccharide that is given as the antigen in order to stimulate the body to make opsonizing antibodies against the encapsulated bacterium.

Flash animation showing phagocytosis of an encapsulated bacterium through opsonization.

html5 version of animation for iPad showing phagocytosis of an encapsulated bacterium through opsonization.

- Movie of an encapsulated bacterium resisting engulfment by a neutrophil. Phagocytosis. © James Sullivan, author. Licensed for use, ASM MicrobeLibrary.

Normally when bacteria first enter the body, the innate immune defenses bind PAMPs on the bacterial cell wall to endocytic PRRs on the body's phagocytes and the organism is phagocytosed. Explain why the child's innate phagocytic defense was unable to remove the *S. pneumoniae*.

- The pneumococcal conjugate vaccine, PCV13 or Prevnar 13® is currently recommended for all children under 5 years of age. Why might prior vaccination with this vaccine have enabled the child to to remove the *S. pneumoniae* via phagocytosis?

3. Role of the Glycocalyx in Adhering to and Colonizing Environmental Surfaces

The glycocalyx also enables some bacteria to adhere to environmental surfaces (rocks, root hairs, teeth, etc.), colonize, and resist flushing. For example, many normal flora bacteria produce a capsular polysaccharide matrix or glycocalyx to form a biofilm on host tissue (see Figure 2.5A.3) as discussed below.

Significance of the glycocalyx in the Initiation of Body Defense

Initiation of Adaptive Immunity

Polysaccharides or polypeptides associated with the bacterial glycocalyx or capsule function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against capsular antigens can stick bacteria to phagocytes, a process called opsonization.

2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

Biofilms

Many pathogenic bacteria, as well as normal flora and many environmental bacteria, form complex bacterial communities as biofilms. Biofilms are groups of bacteria attached to a surface and enclosed in a common secreted adhesive matrix, typically polysaccharide in nature. Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing (discussed later in Unit 2) and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. By living as a community of bacteria as a biofilm, these bacteria are better able to:

- resist attack by antibiotics;
- trap nutrients for bacterial growth and remain in a favorable niche;
- adhere to environmental surfaces and resist flushing;
- live in close association and communicate with other bacteria in the biofilm; and
- resist phagocytosis and attack by the body's complement pathways.

Biofilms are, therefore, functional, interacting, and growing bacterial communities. Biofilms even contain their own water channels for delivering water and nutrients throughout the biofilm community.

- Electron micrograph of a biofilm of *Haemophilus influenzae* from Biomedcentral.com
- Photomicrograph of a biofilm with water channels from Centers for Disease Control and Prevention Rodney M. Donlan: "Biofilms: Microbial Life on Surfaces"

- Biofilm of *Pseudomonas aeruginosa* from the Ausubel Lab, Department of Molecular Biology, Massachusetts General Hospital

To initiate biofilm formation, planktonic bacteria (free individual bacteria not in a biofilm) contact an environmental surface through their motility or by random collision. These planktonic bacteria then attach to that surface using pili or cell wall adhesins. This attachment then signals the expression of genes involved in quorum sensing and, ultimately, biofilm formation. As the biofilm matrix is secreted, motile bacteria lose their flagella and become nonmotile.

Planktonic *Pseudomonas aeruginosa*, for example, uses its polar flagellum to move through water or mucus and make contact with a solid surface such as the body's mucous membranes. It then can use pili and cell wall adhesins to attach to the epithelial cells of the mucous membrane. Attachment activates signaling and quorum sensing genes to eventually enable the population of *P. aeruginosa* to start synthesizing a polysaccharide biofilm composed of alginate. As the biofilm grows, the bacteria lose their flagella to become nonmotile and secrete a variety of enzymes that enable the population to obtain nutrients from the host cells. Eventually the biofilm mushrooms up and develops water channels to deliver water and nutrients to all the bacteria within the biofilm. As the biofilm begins to get too crowded with bacteria, quorum sensing enables some of the *Pseudomonas* to again produce flagella, escape the biofilm, and colonize a new location (See Figs. 11A-11G).

Streptococcus mutans, and *Streptococcus sobrinus*, two bacteria implicated in initiating dental caries, break down sucrose into glucose and fructose. *Streptococcus mutans* can uses an enzyme called dextransucrase to convert sucrose into a sticky polysaccharide called dextran that forms a biofilm enabling the bacteria to adhere to the enamel of the tooth and form plaque. This will be discussed in greater detail later in Unit 2 under Bacterial Pathogenicity. *S. mutans* and *S. sobrinus* also ferment glucose in order to produce energy. The fermentation of glucose results in the production of lactic acid that is released onto the surface of the tooth and initiates decay.

- Scanning electron micrograph of *Streptococcus* growing in the enamel of a tooth.© Lloyd Simonson, author. Licensed for use, ASM MicrobeLibrary.
- Scanning electron micrograph of dental plaque.© H. Busscher, H. van der Mei, W. Jongebloed, R Bos, authors. Licensed for use, ASM MicrobeLibrary.
- Scanning electron micrograph of *Staphylococcus aureus* forming a biofilm in an indwelling catheter courtesy of CDC.
- Biofilm of *Staphylococcus aureus* from Montana State University

A number of biofilm-forming bacteria, such as uropathogenic *Escherichia coli* (UPEC), enterohemorrhagic *E. coli* (EHEC), *Citrobacter* species, *Salmonella* species, and *Mycobacterium tuberculosis* are able to produce amyloid fibers that can play a role in such processes as attachment to host cells, invasion of host cells, and biofilm formation. Curli is an example of such an amyloid fiber produced by UPEC and *Salmonella*.

Many chronic and difficult-to-treat infections are caused by bacteria in biofilms. Within biofilms, bacteria grow more slowly, exhibit different gene expression than free planktonic bacteria, and are more resistant to antimicrobial agents such as antibiotics because of the reduced ability of these chemicals to penetrate the dense biofilms matrix. Biofilms have been implicated in tuberculosis, kidney stones, *Staphylococcus* infections, Legionnaires' disease, and periodontal disease. It is further estimated that as many as 10 million people a year in the US may develop biofilm-associated infections as a result of invasive medical procedures and surgical implants.

You Tube movie and animation: What are Biofilms?

Concept map for Glycocalyx and Biofilms

Summary

1. All bacteria secrete some sort of glycocalyx, an outer viscous covering of fibers extending from the bacterium.
2. An extensive, tightly bound glycocalyx adhering to the cell wall is called a capsule.
3. Phagocytosis involves several distinct steps including attachment of the microbe to the phagocyte through unenhanced or enhanced attachment, ingestion of the microbe and its placement into a phagosome, and the destruction of the microbe after fusion of lysosomes with the phagosome.

4. Capsules enable bacteria to resist unenhanced attachment by covering up bacterial PAMPs so they are unable to bind to endocytic pattern-recognition receptors.
5. The glycocalyx also enables some bacteria to adhere to environmental surfaces, colonize, and resist flushing.
6. The body's adaptive immune defenses can eventually overcome bacterial capsules by producing opsonizing antibodies (IgG) against the capsule that are able to stick the capsule to the phagocyte.
7. Biofilms are groups of bacteria attached to a surface and enclosed in a common secreted adhesive matrix and are functional, interacting, and growing bacterial communities.
8. Most bacteria in nature exist as biofilm populations.
9. Many chronic and difficult-to-treat infections are caused by bacteria in biofilms.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State two common functions associated with the bacterial glycocalyx. (ans)
2. Briefly describe how a bacterial capsule might block phagocytosis. *(ans)*
3. State three possible functions associated with a bacterial biofilm. *(ans)*
4. Multiple Choice *(ans)*

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2.5B: Flagella

Describe the basic structure of a bacterial flagellum and state its function.

- State what provides the energy for bacterial flagellar rotation.
- Define the following flagellar arrangements:

  a. monotrichous
  b. lophotrichous
  c. amphitrichous
  d. peritrichous
  e. axial filaments

- Define taxis.
- Compare and contrast how bacteria with peritrichous flagella and bacteria with polar flagella carry out taxis.
- State how bacterial flagella may play a role in the initiation of innate immune defenses.
- Briefly describe how bacterial flagella and chemotaxis may play a role in the pathogenocity of some bacteri

Highlighted Bacterium

1. Read the description of *Treponema pallidum* and match the bacterium with the description of the organism and the infection it causes.

Why might having flagella better enable those bacteria to cause disease?

- Our defense cells have a surface PRR called TLR-5 that recognizes bacterial flagellin. In terms of preventing infection, why is this an advantage?
- Most pathogenic spirochetes such as Treponema pallidum and Borrelia burgdorferi disseminate from the original infection site. How are they able to do this?

Structure and Composition of Flagella

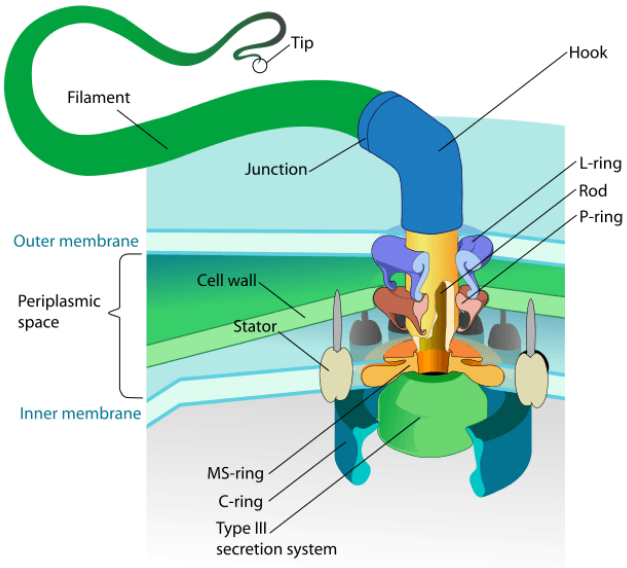


Figure $2.5B.4$B.1: A flagellum (plural: flagella) is a long, slender projection from the cell body, whose function is to propel a unicellular or small multicellular organism. The depicted type of flagellum is found in bacteria such as E. coli and Salmonella, and rotates like a propeller when the bacterium swims. The bacterial movement can be divided into 2 kinds: run, resulting from a counterclockwise rotation of the flagellum, and tumbling, from a clockwise rotation of the flagellum. from Wikipedia (LadyofHats)

1. The filament is the rigid, helical structure that extends from the cell surface. It is composed of the protein flagellin arranged in helical chains so as to form a hollow core. During synthesis of the flagellar filament, flagellin molecules coming off of the ribosomes are transported through the hollow core of the filament where they attach to the growing tip of the filament causing it to lengthen. With the exception of a few bacteria, such as *Bdellovibrio* and *Vibrio cholerae*, the flagellar filament is not surrounded by a sheath (see Figure 2.5B.1).
2. The hook is a flexible coupling between the filament and the basal body (see Figure 2.5B.1).
3. The basal body consists of a rod and a series of rings that anchor the flagellum to the cell wall and the cytoplasmic membrane (see Figure 2.5B.1). Unlike eukaryotic flagella, the bacterial flagellum has no internal fibrils and does not flex. Instead, the basal body acts as a rotary molecular motor, enabling the flagellum to rotate and propel the bacterium through the surrounding fluid. In fact, the flagellar motor rotates very rapidly. (Some flagella can rotate up to 300 revolutions per second!)

The MotA and MotB proteins form the stator of the flagellar motor and function to generate torque for rotation of the flagellum. The MS and C rings function as the rotor. (See Figure 2.5B.1). Energy for rotation comes from the proton motive force provided by protons moving through the Mot proteins along a concentration gradient from the peptidoglycan and periplasm towards the cytoplasm.

For More Information: Review of Proton Motive Force from Unit 7

- Electron micrograph and illustration of the basal body of bacterial flagella; Cover photo of *Molecular Biology of the Cell*, May 1, 2000.
- Animation of a rotating bacterial flagellum from the ARN Molecular Museum
- YouTube movie of the assembly and rotation of a bacterial flagellum

Bacteria flagella (see Figure 2.5B.2 and Figure 2.5B.3) are 10-20 µm long and between 0.01 and 0.02 µm in diameter.

Flagellar Arrangements (see Figure 2.5B.4)

1. monotrichous: a single flagellum, usually at one pole

- Scanning electron micrograph showing monotrichous flagellum of *Vibrio*; courtesy of CDC.

2. amphitrichous: a single flagellum at both ends of the organism

3. lophotrichous: two or more flagella at one or both poles

- Scanning electron micrograph of *Helicobacter pylori* showing lophotrichous arrangement of flagella ; from Science Photolab.com

4. peritrichous: flagella over the entire surface

- Scanning electron micrograph of *Proteus vulgaris* showing peritrichous arrangement of flagella and pili; from fineartamerica.com

5. axial filaments: internal flagella found only in the spirochetes. Axial filaments are composed of from two to over a hundred axial fibrils (or endoflagella) that extend from both ends of the bacterium between the outer membrane and the cell wall, often overlapping in the center of the cell. (see Figure 2.5B.5 and Figure 2.5B.6). A popular theory as to the mechanism behind spirochete motility presumes that as the endoflagella rotate in the periplasmic space between the outer membrane and the cell wall, this could cause the corkscrew-shaped outer membrane of the spirochete to rotate and propel the bacterium through the surrounding fluid.

- Axial filaments of the spirochete Leptospira; Midlands Technical College, Bio 255 course site

Concept map for Bacterial Flagella

Functions

Flagella are the organelles of locomotion for most of the bacteria that are capable of motility. Two proteins in the flagellar motor, called MotA and MotB, form a proton channel through the cytoplasmic membrane and rotation of the flagellum is driven by a proton gradient. This driving proton motive force occurs as protons accumulating in the space between the cytoplasmic membrane and the cell wall as a result of the electron transport system travel through the channel back into the bacterium's cytoplasm. Most bacterial flagella can rotate both counterclockwise and clockwise and this rotation contributes to the bacterium's ability to change direction as it swims. A protein switch in the molecular motor of the basal body controls the direction of rotation.

1. A bacterium with peritrichous flagella:

If a bacterium has a peritrichous arrangement of flagella, counterclockwise rotation of the flagella causes them to form a single bundle that propels the bacterium in long, straight or curved runs without a change in direction. Counterclockwise rotation causes the flagellum to exhibit a left-handed helix. During a run, that lasts about one second, the bacterium moves 10 - 20 times its length before it stops. This occurs when some of the the flagella rotate clockwise, disengage from the bundle, and trigger a tumbling motion. Clockwise rotation causes the flagellum to assume a right-handed helix. A tumble only lasts about one-tenth of a second and no real forward progress is made. After a “tumble”, the direction of the next bacterial run is random because every time the bacterium stops swimming, Brownian motion and fluid currents cause the bacterium to reorient in a new direction.

Movie of swimming *Escherichia coli* as seen with phase contrast microscopy. Flagella are not visible with under phase contrast microscopy. Note runs and tumbles. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
Movie of motile *Escherichia coli* with fluorescent labelled-flagella #1. This technique allows the the flagella to be seen as the bacteria swim. Note some flagella leaving the flagellar bundle to initiate tumbling. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
Movie of motile *Escherichia coli* with fluorescent labelled-flagella #2. This technique allows the the flagella to be seen as the bacteria swim. Note some flagella leaving the flagellar bundle to initiate tumbling. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
Movie of tethered *Escherichia coli* showing that the bacterial flagella rotate. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

When bacteria with a peritrichous arrangement grow on a nutrient-rich solid surface, they can exhibit a swarming motility wherein the bacteria elongate, synthesize additional flagella, secrete wetting agents, and move across the surface in coordinated manner.

Movie of swarming motility of *Escherichia coli*. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

2. A bacterium with polar flagella:

Most bacteria with polar flagella, like the peritrichous above, can rotate their flagella both clockwise and counterclockwise. If the flagellum is rotating counterclockwise, it pushes the bacterium forward. When it rotates clockwise, it pulls the bacterium backward. These bacteria change direction by changing the rotation of their flagella.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Video 2.5B.4B.1: Phase contrast movie of motile Pseudomonas. Pseudomonas has a single polar flagellum that can rotate both counterclockwise and clockwise but is not visible under phase contrast microscopy (http://www.youtube.com/embed/EWj2TGsTQEI).

Movie of *Spirillum volutans*, a spiral-shaped bacterium with a bundle of flagella at either end.
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

Some bacteria with polar flagella can only rotate their flagellum clockwise. In this case, clockwise rotation pushes the bacterium forward. Every time the bacterium stops, Brownian motion and fluid currents cause the bacterium to reorient in a new direction.

Movie of *Rhodobacter spheroides* with fluorescent-labelled flagella.
The flagellum can only rotate clockwise.
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

Concept map for Bacterial Flagella

Taxis

Around half of all known bacteria are motile. Motility serves to keep bacteria in an optimum environment via taxis. Taxis is a motile response to an environmental stimulus. Bacteria can respond to chemicals (chemotaxis), light (phototaxis), osmotic pressure (osmotaxis), oxygen (aerotaxis), and temperature (thermotaxis). Chemotaxis is a response to a chemical gradient of attractant or repellent molecules in the bacterium's environment.

- In an environment that lacks a gradient of attractant or repellent, the bacterium moves randomly. In this way the bacterium keeps searching for a gradient.
- In an environment that has a gradient of attractant or repellent, the net movement of the bacterium is towards the attractant or away from the repellent.

For More Information: Chemotaxis in *Escherichia coli*

Chemotaxis is regulated by chemoreceptors located in the cytoplasmic membrane or periplasm of the bacterium bind chemical attractants or repellents. In most cases, this leads to either the methylation or demethylation of methyl-accepting chemotaxis proteins (MCPs) that in turn, eventually trigger either a counterclockwise or clockwise rotation of the flagellum. An increasing concentration of attractant or decreasing concentration of repellent (both conditions beneficial) causes less tumbling and longer runs; a decreasing concentration of attractant or increasing concentration of repellent (both conditions harmful) causes normal tumbling and a greater chance of reorienting in a "better" direction. As a result, the organism's net movement is toward the optimum environment..

Significance of Flagella in the Initiation of Body Defense

Initiation of Innate Immunity

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

The protein flagellin in bacterial flagella is a PAMP that binds to pattern-recognition receptors or PRRs on a variety of defense cells of the body and triggers innate immune defenses such as inflammation, fever, and phagocytosis.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

Initiation of Adaptive Immunity

Proteins associated with bacterial flagella function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against flagellar antigens can stick bacteria to phagocytes, a process called opsonization. They can also interfere with bacterial motility.
2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Significance of Motility to Bacterial Pathogenicity

Motility and chemotaxis probably help some intestinal pathogens to move through the mucous layer so they can attach to the epithelial cells of the mucous membranes. In fact, many bacteria that can colonize the mucous membranes of the bladder and the intestines are motile. Motility probably helps these bacteria move through the mucus in places where it is less viscous.

Flash animation showing a motile bacterium contacting a host cell by swimming through the mucus.

html5 version of animation for iPad showing a motile bacterium contacting a host cell by swimming through the mucus.

Motility and chemotaxis also enable spirochetes to move through viscous environments and penetrate cell membranes. Examples include *Treponema pallidum (inf)*, *Leptospira (inf)*, and *Borrelia burgdorferi*) *(inf)*. Because of their thinness, their internal flagella (axial filaments), and their motility, spirochetes are more readily able to penetrate host mucous membranes, skin abrasions, etc., and enter the body. Motility and invasins may also enable the spirochetes to penetrate deeper in tissue and enter the lymphatics and bloodstream and disseminate to other body sites.

Flash animation showing spirochetes using motility to enter a blood vessel.

html5 version of animation for iPad showing spirochetes using motility to enter a blood vessel.

Movie of motile *Borrelia bergdorferi*, the spirochete that causes Lyme disease. Note corkscrewing motility.
From You Tube, courtesy of CytoVivo.

Electron micrograph of *Treponema pallidum* invading a host cell.

This will be discussed in more detail under Bacterial Pathogenesis in Unit 3.

For More Information: The Ability to Contact Host Cells from Unit 3

For More Information: The Ability to Invade Host Cells from Unit 3

Concept map for Bacterial Flagella

Summary

1. Many bacteria are motile and use flagella to swim through liquid environments.
2. The basal body of a bacterial flagellum functions as a rotary molecular motor, enabling the flagellum to rotate and propel the bacterium through the surrounding fluid.
3. Bacterial flagella appear in several arrangements, each unique to a particular organism.
4. Motility serves to keep bacteria in an optimum environment via taxis.
5. Taxis refers to a motile response to an environmental stimulus enabling the net movement of bacteria towards some beneficial attractant or away from some harmful repellent.
6. Most bacterial flagella can rotate both clockwise and counterclockwise enabling to stop and change direction.
7. The protein flagellin that forms the filament of bacterial flagella functions as a pathogen-associated molecular pattern or PAMP that binds to pattern-recognition receptors or PRRs on a variety of defense cells of the body to trigger innate immune defenses.
8. Motility and chemotaxis probably help some intestinal pathogens to move through the mucous layer so they can attach to the epithelial cells of the mucous membranes and colonize the intestines.
9. Motility enables some spirochetes to penetrate deeper in tissue and enter the lymphatics and bloodstream and disseminate

to other body sites.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ a single flagellum at both ends (ans)
   A. monotrichous
   B. amphitrichous
   C. lophotrichous
   D. peritrichous
   E. axial filaments
2. State how bacterial flagella may play a role in the initiation of innate immune defenses. *(ans)*
3. Briefly describe how bacterial flagella and chemotaxis may play a role in the pathogenocity of some bacteria. *(ans)*
4. Multiple Choice *(ans)*

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2.5C: Fimbriae and Pili

Learning Objectives

1. State the chemical composition, structure, and function of the short adhesion pili of bacteria.
2. State the function of a bacterial conjugation (sex) pilus.
3. Define bacterial conjugation.
4. State how the ability to change the shape of the adhesive tip of its pili could be an advantage to a bacterium.
5. Briefly describe twitching motility induced by type IV pili.

Highlighted Bacterium

1. Read the description of *Neisseria gonorrhoeae* and match the bacterium with the description of the organism and the infection it causes.

Structure and Composition

Fimbriae and pili are thin, protein tubes originating from the cytoplasmic membrane of many bacteria. Both are able to stick bacteria to surfaces, but pili are typically longer and fewer in number than fimbriae. They are found in virtually all Gram-negative bacteria but not in many Gram-positive bacteria. The fimbriae and pili have a shaft composed of a protein called pilin. At the end of the shaft is the adhesive tip structure having a shape corresponding to that of specific glycoprotein or glycolipid receptors on a host cell (Figure $2.5C.1$). There are two basic types of pili: **short attachment pili** and l**ong conjugation pili**.

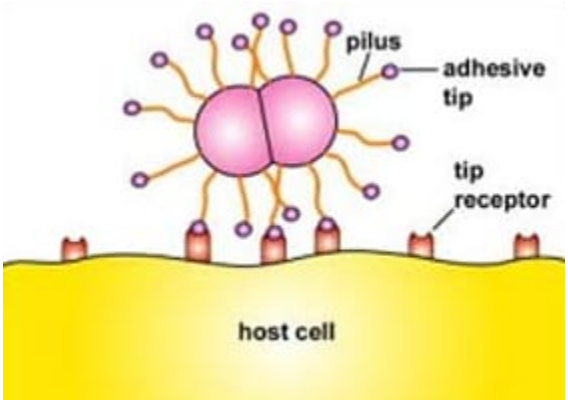


Figure $2.5C.1$: Adhesive Tip of Bacterial Pili Binding to Host Cell Receptors

Short attachment pili, also known as *fimbriae*, are usually short and quite numerous (Figure $2.5C.1$) and enable bacteria to colonize environmental surfaces or cells and resist flushing.

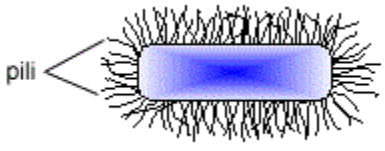


Figure $2.5C.2$: Bacterial Pili.

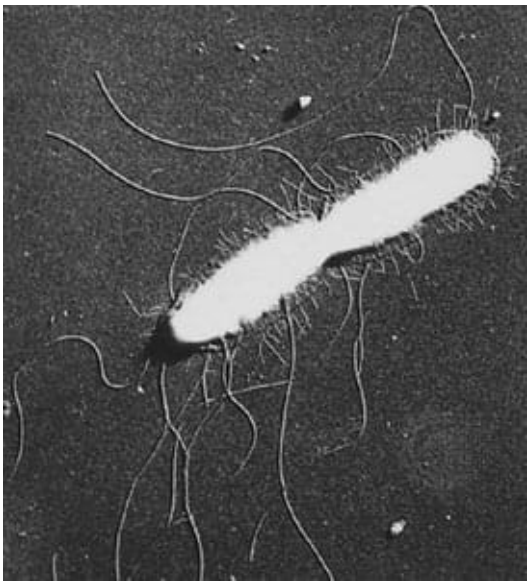


Figure $2.5C.3$: Electron micrograph of S*almonella* showing both flagella and pili from the Wiki Biodiversityserene.

Long conjugation pili, also called "F" or sex pili (Figure $2.5C.4$), that are longer and very few in number. The conjugation pilus enables conjugation. As will be seen later in this unit, conjugation is the transfer of DNA from one bacterium to another by cell-to-cell contact. In gram-negative bacteria it is typically the transfer of DNA from a donor or "male bacterium" with a sex pilus to a recipient or "female bacterium" to enable genetic recombination.

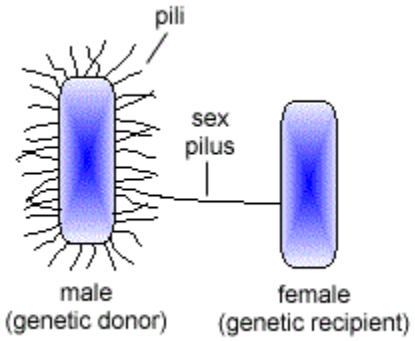


Figure $2.5C.4$: Conjugation (Sex) Pilus

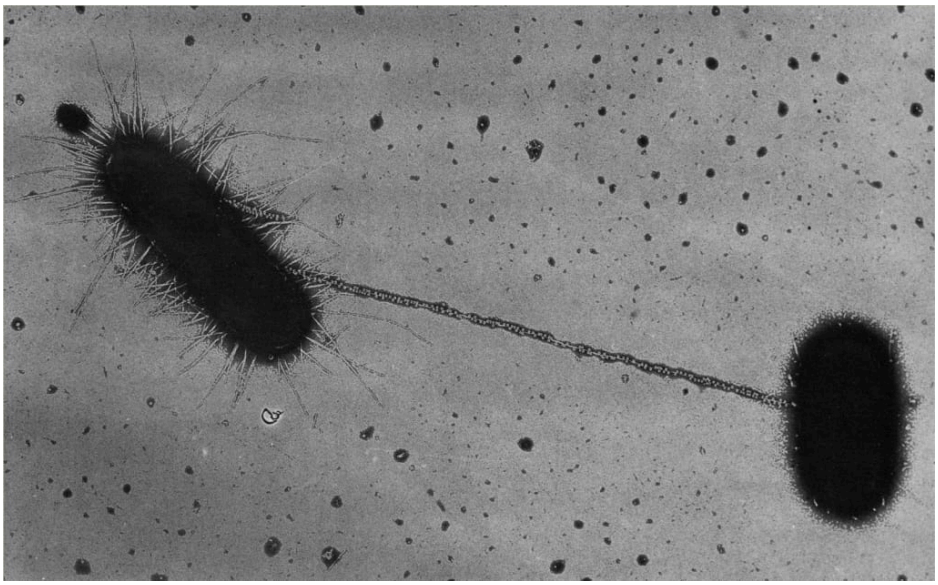


Figure $2.5C.5$: Scanning electron micrograph of E.coli bacteria exchanging genes. Courtesy of Charles C. Brinton Jr. (NIH)

Significance of Pili to Bacterial Pathogenicity

The short attachment pili or fimbriae are organelles of adhesion allowing bacteria to colonize environmental surfaces or cells and resist flushing. The pilus has a shaft composed of a protein called *pilin*. At the end of the shaft is the adhesive tip structure having a shape corresponding to that of specific glycoprotein or glycolipid receptors on a host cell (Figure $2.5C.1$). Because both the bacteria and the host cells have a negative charge, pili may enable the bacteria to bind to host cells without initially having to get close enough to be pushed away by electrostatic repulsion. Once attached to the host cell, the pili can depolymerize and enable adhesions in the bacterial cell wall to make more intimate contact.

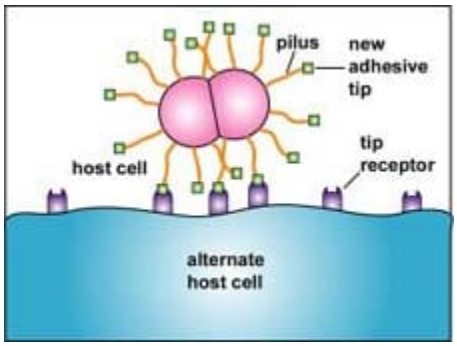


Figure $2.5C.6$: Bacteria Altering the Adhesive Tips of Their Pili. By genetically altering the adhesive tips of their pili, certain bacteria are able to: 1) adhere to and colonize different cell types with different receptors, and 2) evade antibodies made against the previous pili.

Bacteria are constantly losing and reforming pili as they grow in the body and the same bacterium may switch the adhesive tips of the pili in order to adhere to different types of cells and evade immune defenses (Figure $2.5C.6$). This will be discussed in detail later in Unit 3 under Bacterial Pathogenesis. Bacteria that use pili to initially colonize host cells include *Neisseria gonorrhoeae*, *Neisseria meningitidis (inf)*, uropathogenic strains of *Escherichia coli*, and *Pseudomonas aeruginosa (inf)*.

Highlighted Bacterium: *Neisseria gonorrhoeae*

Click on this link, read the description of *Neisseria gonorrhoeae*, and be able to match the bacterium with its description on an exam.

Flash animation showing bacteria lacking pili being flushed out of the urethra.

Flash animation showing how bacteria with pili may resist being flushed out of the urethra.

html5 version of animation for iPad showing bacteria lacking pili being flushed out of the urethra.

html5 version of animation for iPad showing how bacteria with pili may resist being flushed out of the urethra.

One class of pili, known as type IV pili , not only allow for attachment but also enable a twitching motility. They are located at the poles of bacilli and allow for a gliding motility along a solid surface such as a host cell. Extension and retraction of these pili allows the bacterium to drag itself along the solid surface (see Figure $2.5C.5$). In addition, bacteria can use their type IV pili to "slingshot" the bacterium over a cellular surface. In this case, as the pili contract they are thought to become taut like a stretched rubber band. When an anchoring pilus detaches, the taut pili "slingshot" the bacterium in the opposite direction (see Figure $2.5C.6$). This motion typically alternates with the twitching motility and enables a more rapid motion and direction change than with the twitching motility because the rapid slingshotting motion reduces the viscosity of the surrounding biofilm.

This enables bacteria with these types of pili within a biofilm to move around a cellular surface and find an optimum area on that cell for attachment and growth once they have initially bound. Bacteria with type IV pili include *Pseudomonas aeruginosa, Neisseria gonorrhoeae, Neisseria meningitidis*, and *Vibrio cholerae*.

- Electron micrograph of type IV pili of *Neisseria gonorrhoeae* from Magdalene So, University of Arizona

Flash animation showing a bacterium using type IV pili to drag itself (twitching motility) along a surface.

html5 version of animation for iPad showing a bacterium using type IV pili to drag itself (twitching motility) along a surface.

Flash animation showing a bacterium using type IV pili to "slingshot" itself along a surface.

html5 version of animation for iPad showing a bacterium using type IV pili to "slingshot" itself along a surface.

You Tube movie showing twitching motility in *Pseudomonas* due to type IV pili
Courtesy of Dr. Lori Burrows You Tube videos

You Tube movie showing *Pseudomonas* using type IV pili to "walk" on end following binary fission.
Courtesy of Gerard Wong, UCLA Bioengineering, CNSI

Movie of twitching motility of *Pseudomonas*
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

Retraction of pili of *Pseudomonas* used in twitching motility
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

You Tube movie showing a *Pseudomonas* using pili to hop or slingshot itself over a surface.

Exercise: Think-Pair-Share Questions

Neisseria gonorrhoeae is a gram-negative diplococcus that has multiple alleles coding for different and distinct pili adhesive tips as well as different and distinct cell wall adhesins called Opa proteins.

The gonococcus is able to colonize and infect a numerous sites in the body, including the urethra, the rectum, the throat, the conjunctiva of the eye, and the fallopian tubes. It can also colonize sperm.

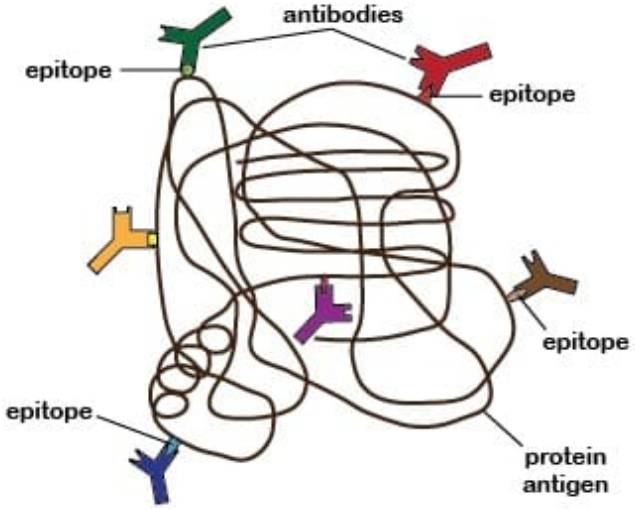
1. Considering the locations in the body where it colonizes, why doesn't the body simply flush the bacterium out of the body?
2. Why is *N. gonorrhoeae* able to colonize so many different sites in the body?

3. We recognize pili adhesive tips and cell wall adhesins as foreign and, during adaptive immunity, make antibodies that bind to these microbial molecules. State how this might help to protect the body.

Significance of Fimbriae and Pili in the Initiation of Body Defense

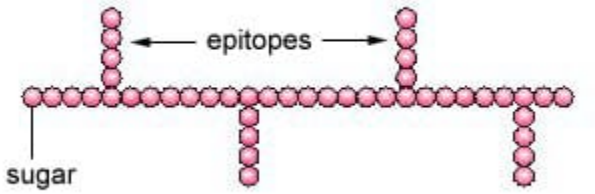
Initiation of Adaptive Immunity

Proteins associated with bacterial fimbriae and pili function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.



Epitopes of an Antigen (Polysaccharide). Proteins have many epitopes of different specificities. During humoral immunity, antibodies are made to fit each epitope of each antigen.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes . An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.



Epitopes of an Antigen (Polysaccharide)

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against pili antigens can stick bacteria to phagocytes, a process called *opsonization*. Antibodies made against the adhesive tips of pili can prevent bacteria from adhering to and colonizing host cells.

2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Medscape article on infections associated with organisms mentioned in this Learning Object. Registration to access this website is free.

- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Vibrio cholerae*

Summary

1. Fimbriae and pili are thin, protein tubes originating from the cytoplasmic membrane found in virtually all Gram-negative bacteria but not in many Gram-positive bacteria. Pili are typically longer and fewer in number than fimbriae.
2. The short attachment pili or fimbriae are organelles of adhesion allowing bacteria to colonize environmental surfaces or cells and resist flushing.
3. The long conjugation pilus enables conjugation in Gram-negative bacteria.
4. The pilus has a shaft composed of a protein called pilin with an adhesive tip structure at the end having a shape corresponding to that of specific receptors on a host cell.
5. The same bacterium may switch the adhesive tips of the pili in order to adhere to different types of cells and evade immune defenses.
6. Type IV pili not only allow for attachment but also enable a twitching motility that enables bacteria to “crawl” or “walk” over the surfaces to which they have attached by extending and retracting their type IV pili.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State the function of the short adhesion pili of bacteria. *(ans)*
2. Define bacterial conjugation. *(ans)*
3. State how the ability to change the shape of the adhesive tip of its pili could be an advantage to a bacterium. *(ans)*
4. Multiple Choice *(ans)*

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2.E: The Prokaryotic Cell: Bacteria (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

Fundamental Statements for this Learning Object:

1. Physical control includes such methods of control as high or low temperature, desiccation, osmotic pressure, radiation, and filtration.
2. Chemical control refers to the use of disinfectants, antiseptics, antibiotics, and chemotherapeutic antimicrobial chemicals.
3. Sterilization is the process of destroying all living organisms and viruses.
4. Disinfection is the elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces.
5. Decontamination is the treatment of an object or inanimate surface to make it safe to handle.
6. A disinfectant is an agents used to disinfect inanimate objects but generally to toxic to use on human tissues.
7. An antiseptic is an agent that kills or inhibits growth of microbes but is safe to use on human tissue.
8. A sanitizer is an agent that reduces microbial numbers to a safe level.
9. An antibiotic is a metabolic product produced by one microorganism that inhibits or kills other microorganisms.
10. Synthetic chemicals that can be used therapeutically.
11. An agent that is cidal in action kills microorganisms.
12. An agent that is static in action inhibits the growth of microorganisms.
13. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host.
14. A broad spectrum agent is one generally effective against a variety of Gram-positive and Gram-negative bacteria.
15. A narrow spectrum agent generally works against just Gram-positives, Gram-negatives, or only a few bacteria.

2.1: Sizes, Shapes, and Arrangements of Bacteria

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following descriptions with the **best** answer.

   _____ Division in one plane; cocci arranged in pairs

   _____ Division in one plane; cocci arranged in chains

   _____ Division in two planes; cocci arranged in a square of four

   _____ Division in one plane; rods completely separate after division.

   _____ Division in one plane; rods arranged in chains.

   _____ A comma shaped bacterium.

   _____ A thin, flexible spiral.

   _____ A thick, rigid spiral.

   A. bacillus
   B. streptobacillus
   C. spirochete
   D. spirillum
   E. vibrio

F. streptococcus
G. staphylococcus
H. diplococcus
I. tetrad
J. sarcina

2. A Gram stain of discharge from an abcess shows cocci in irregular, grape-like clusters. What is the most likely genus of this bacterium?
3. State the diameter of an average-sized coccus-shaped bacterium.
4. Multiple Choice

2.2: Cell Anatomy for the Domain Bacteria: An Overview

1. Match the following descriptions with the **best** answer.

____ Proteins that, in the presence of energy, transport two substances simultaneously across the membrane in opposite directions.

____ Proteins that, in the presence of energy, transport two substances simultaneously across the membrane in the same directions.

____ The movement of water across a membrane from an area of higher water concentration (lower solute concentration) to lower water concentration (higher solute concentration).

____ The net movement of gases or small uncharge polar molecules across a phospholipid bilayer membrane from an area of higher concentration to an area of lower concentration. No metabolic energy is required.

____ A transport where the cell uses transport proteins such as antiporters or symporters and metabolic energy to transport substances across the membrane against the concentration gradient.

____ If the net flow of water is out of a cell, the cell is in _____ environment.

____ If the net flow of water is into a cell, the cell is in _____ environment.

A. uniporters
B. symporters
C. antiporters
D. active transport
E. group translocation
F. passive diffusion
G. osmosis
H. a hypotonic
I. a hypertonic
J. an isotonic

2. Even though there is a lower concentration of a particular nutrient outside a bacterium than inside, the bacterium is still able to transport that nutrient into its cytoplasm. Explain how this might occur and what is required for this transport.

3. A bacterium is placed in a new environment and subsequently water flows out of the bacterium. Is this new environment isotonic, hypotonic, or hypertonic to the bacterium? Is the solute concentration higher inside the bacterium or outside?

4. Bacteria normally do not grow in jams and jellies. In terms of osmosis, what might explain this?

5. Define the following:

a. binary fission

b. geometric progression

6. State the functions of the following in bacterial cell division:

a. Par proteins

b. divisome

c. FtsZ proteins

6. A monomer of peptidoglycan consists of _____, _____, and _____.

7. State the function of peptidoglycan in bacteria.

8. State the role of the following enzymes in peptidoglycan synthesis:

a. autolysins

b. bactoprenols

c. transpeptidases

d. transglycosylase

9. A penicillin is used to treat a bacterial infection. Describe the mechanism by which this antibiotic eventually kills the bacteria.

10. Gram-positive bacteria stain _____ after Gram staining while Gram-negative bacteria stain _____ .

11. Bacteria normally live in a hypotonic environment. Since water flows into a cell in an environment that is hypotonic, why don't the bacteria burst from osmotic pressure?

12. Matching:

____ Enzymes that are secreted and function outside the bacterium.

____ Enzymes that function within the bacterium.

____ All of the chemical reactions carried out by a bacterium.

____ Chemical reactions in which more complex molecules are synthesized.

____ Chemical reactions in which more complex molecules are broken down into smaller, more simple molecules.

A. Metabolism
B. Catabolic reactions
C. Anabolic reactions
D. Exoenzymes
E. Endoenzymes

13. State the primary function of bacterial cytoplasm.

14. The sum of an organism's genetic material is called its_____.

15. Bacterial enzymes involved in in the unwinding, replication, and rewinding of the circular, supercoiled bacterial DNA called _____.

16. Describe the general composition of the chromosome in most bacteria.

17. Briefly describe the process of DNA replication.

18. State what enzyme carries out the following functions during DNA replication.

a. Unwinds the helical DNA by breaking the hydrogen bonds between complementary bases.
b. Synthesizes a short RNA primer at the beginning of each origin of replication.
c. Adds DNA nucleotides to the RNA primer.

d. Digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides.
e. Links the DNA fragments of the lagging strand together.

19. State the overall function of DNA.

20. Define transcription.

21. Define translation.

22. Ciprofloxacin (*Cipro*) is used to treat a variety of bacterial infections. How does it stop bacteria from growing?

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UNIT 2: BACTERIAL GENETICS AND THE CHEMICAL CONTROL OF BACTERIA

3: Bacterial Genetics

3.1: Horizontal Gene Transfer in Bacteria

3.2: Bacterial Quorum Sensing, Pathogenicity Islands, and Secretion Systems (Injectosomes)

3.3: Enzyme Regulation

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4.3: Ways in which Bacteria May Resist Chemical Control Agents

4.E: Using Antibiotics and Chemical Agents to Control Bacteria (Exercises)

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3: BACTERIAL GENETICS

Bacterial genetics is the subfield of genetics devoted to the study of bacteria. Bacterial genetics are subtly different from eukaryotic genetics, however bacteria still serve as a good model for animal genetic studies. One of the major distinctions between bacterial and eukaryotic genetics stems from the bacteria's lack of membrane-bound organelles (this is true of all prokaryotes. While it is a fact that there are prokaryotic organelles, they are never bound by a lipid membrane, but by a shell of proteins), necessitating protein synthesis occur in the cytoplasm.

3.1: Horizontal Gene Transfer in Bacteria

3.2: Bacterial Quorum Sensing, Pathogenicity Islands, and Secretion Systems (Injectosomes)

3.3: Enzyme Regulation

3.E: Bacterial Genetics (Exercises)

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3.1: Horizontal Gene Transfer in Bacteria

Learning Objectives

After completing this section you should be able to perform the following objectives.

1. Compare and contrast mutation and horizontal gene transfer as methods of enabling bacteria to respond to selective pressures and adapt to new environments.
2. Define horizontal gene transfer and state the most common form of horizontal gene transfer in bacteria.
3. Briefly describe the mechanisms for transformation in bacteria.
4. Briefly describe the following mechanisms of horizontal gene transfer in bacteria:
   a. generalized transduction
   b. specialized transduction
5. Briefly describe the following mechanisms of horizontal gene transfer in bacteria:
   a. Transfer of conjugative plasmids, conjugative transposons, and mobilizable plasmids in Gram-negative bacteria
   b. F^+ conjugation
   c. Hfr conjugation
6. Describe R-plasmids and the significance of R-plasmids to medical microbiology.

Bacteria are able to respond to selective pressures and adapt to new environments by acquiring new genetic traits as a result of mutation, a modification of gene function within a bacterium, and as a result of horizontal gene transfer, the acquisition of new genes from other bacteria. Mutation occurs relatively slowly. The normal mutation rate in nature is in the range of 10^{-6} to 10^{-9} per nucleotide per bacterial generation, although when bacterial populations are under stress, they can greatly increase their mutation rate. Furthermore, most mutations are harmful to the bacterium. Horizontal gene transfer, on the other hand, enables bacteria to respond and adapt to their environment much more rapidly by acquiring large DNA sequences from another bacterium in a single transfer.

Horizontal gene transfer, also known as lateral gene transfer, is a process in which an organism transfers genetic material to another organism that is not its offspring. The ability of *Bacteria* and *Archaea* to adapt to new environments as a part of bacterial evolution most frequently results from the acquisition of new genes through horizontal gene transfer rather than by the alteration of gene functions through mutations. (It is estimated that as much as 20% of the genome of *Escherichia coli* originated from horizontal gene transfer.)

Horizontal gene transfer is able to cause rather large-scale changes in a bacterial genome. For example, certain bacteria contain multiple virulence genes called pathogenicity islands that are located on large, unstable regions of the bacterial genome. These pathogenicity islands can be transmitted to other bacteria by horizontal gene transfer. However, if these transferred genes provide no selective advantage to the bacteria that acquire them, they are usually lost by deletion. In this way the size of the bacterium's genome can remain approximately the same size over time.

There are three mechanisms of horizontal gene transfer in bacteria: transformation, transduction, and conjugation. The most common mechanism for horizontal gene transmission among bacteria, especially from a donor bacterial species to different recipient species, is conjugation. Although bacteria can acquire new genes through transformation and transduction, this is usually a more rare transfer among bacteria of the same species or closely related species.

Transformation

Transformation is a form of genetic recombination in which a DNA fragment from a dead, degraded bacterium enters a competent recipient bacterium and is exchanged for a piece of DNA of the recipient. Transformation usually involves only homologous recombination, a recombination of homologous DNA regions having nearly the same nucleotide sequences. Typically this involves similar bacterial strains or strains of the same bacterial species.

A few bacteria, such as *Neisseria gonorrhoeae, Neisseria meningitidis, Hemophilus influenzae, Legionella pneomophila, Streptococcus pneumoniae*, and *Helicobacter pylori* tend to be naturally competent and transformable. Competent bacteria are

able to bind much more DNA than noncompetent bacteria. Some of these genera also undergo autolysis that then provides DNA for homologous recombination. In addition, some competent bacteria kill noncompetent cells to release DNA for transformation.

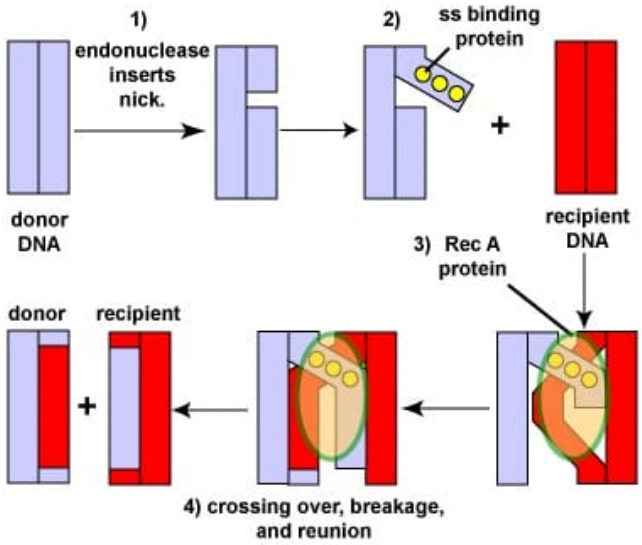
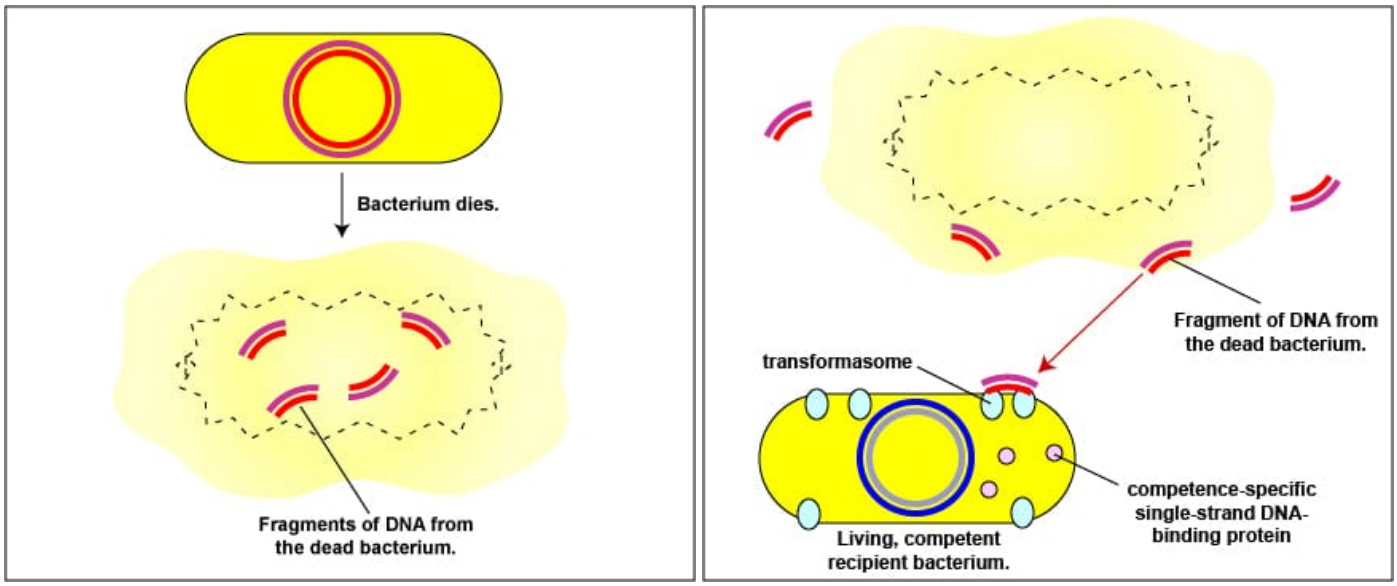


Figure 3.1.1: Pairing of Homologous DNA molecules and Exchange of DNA Segments by way of Rec A Protein. 1) A DNA endonuclease inserts a nick in one strand of the donor DNA. 2) The nicked strand is separated from its partner strand by proteins functioning as a helicase. Molecules of single-stranded binding protein (yellow) then bind. 3) Rec A protein then binds to the single-strand fragment and promotes base pairing of the donor DNA with the recipient DNA (crossing over). 4) The linked molecules are separated by resolvases, enzymes that cut and rejoin the cross-linked DNA molecules.

During transformation, DNA fragments (usually about 10 genes long) are released from a dead degraded bacterium and bind to DNA binding proteins on the surface of a competent living recipient bacterium. Depending on the bacterium, either both strands of DNA penetrate the recipient, or a nuclease degrades one strand of the fragment and the remaining DNA strand enters the recipient. This DNA fragment from the donor is then exchanged for a piece of the recipient's DNA by means of RecA proteins and other molecules and involves breakage and reunion of the paired DNA segments as seen in (Figure 3.1.1). Transformation is summarized in Figure 3.1.2.



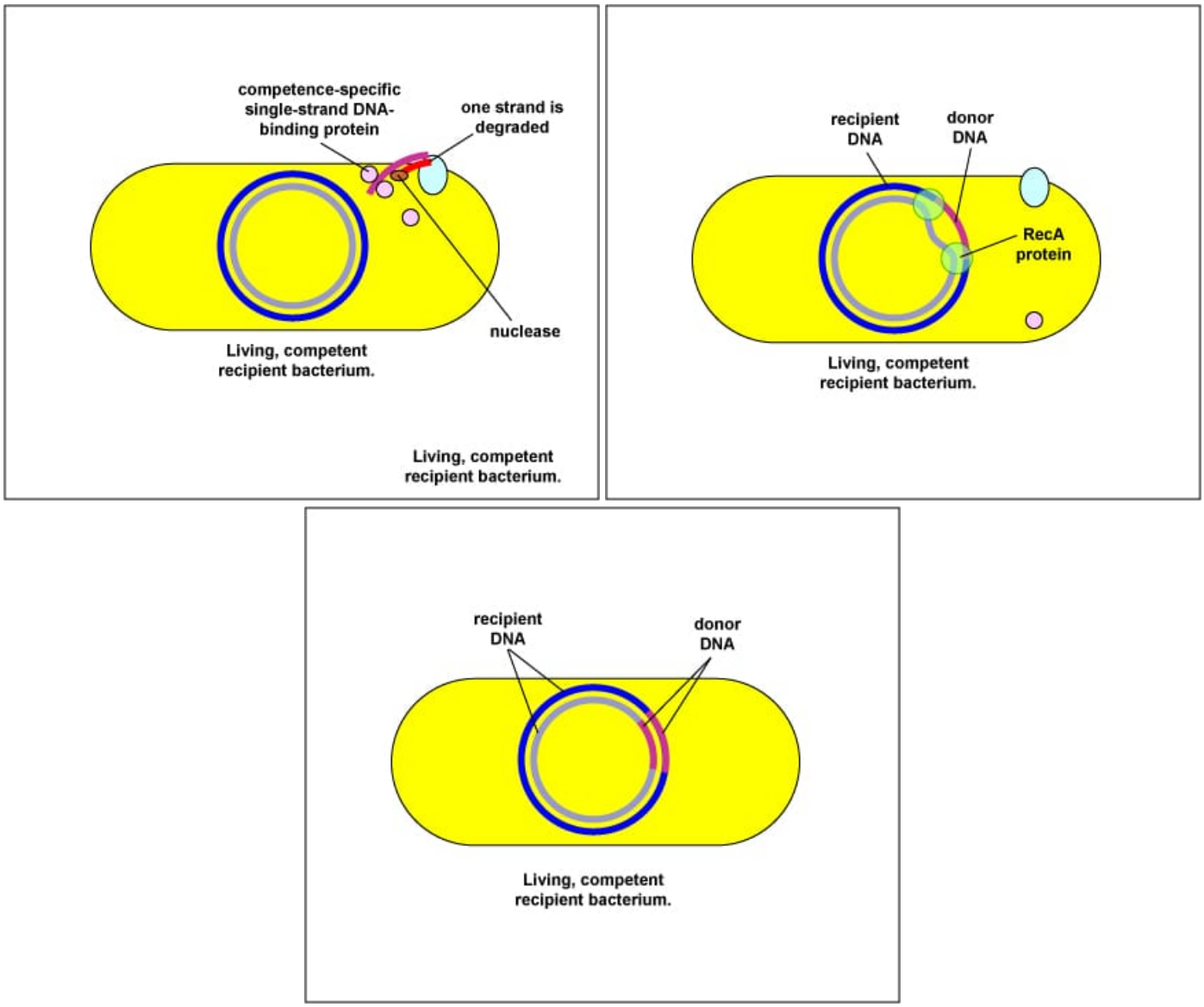


Figure 3.1.2*: Transformation: Step 1: A donor bacterium dies and is degraded.Step 2: DNA fragments, typically around 10 genes long, from the dead donor bacterium bind to transformasomes on the cell wall of a competent, living recipient bacterium.Step 3: In this example, a nuclease degrades one strand of the donor fragment and the remaining DNA strand enters the recipient. Competence-specific single-stranded DNA-binding proteins bind to the donor DNA strand to prevent it from being degraded in the cytoplasm. Step 4: RecA proteins promotes genetic exchange between a fragment of the donor's DNA and the recipient's DNA (see Figure* 3.1.1 *for the functions of RecA proteins). This involves breakage and reunion of paired DNA segments. Step 5: Transformation is complete.*

Transduction

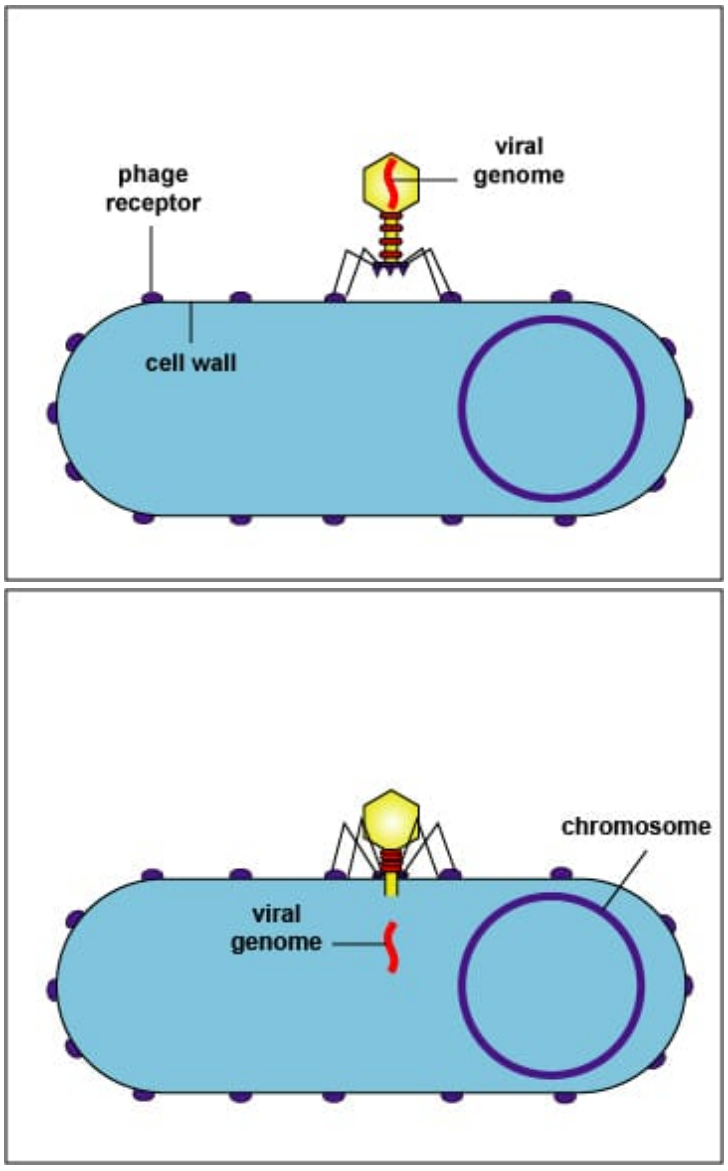
Transduction involves the transfer of a DNA fragment from one bacterium to another by a bacteriophage. There are two forms of transduction: *generalized transduction* and *specialized transduction*.

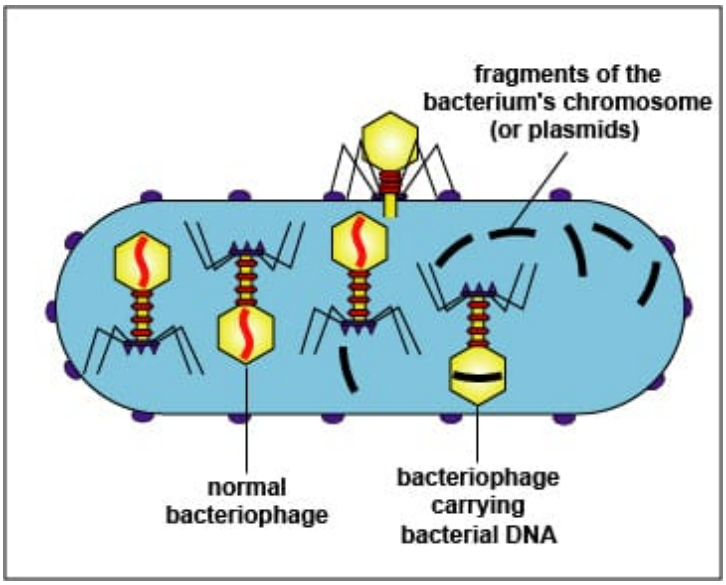
During the replication of *lytic bacteriophages* and *temperate bacteriophages*, occasionally the phage capsid accidently assembles around a small fragment of bacterial DNA. When this bacteriophage, called a transducing particle, infects another bacterium, it injects the fragment of donor bacterial DNA it is carrying into the recipient where it can subsequently be exchanged for a piece of the recipient's DNA by homologous recombination. Generalized transduction is summarized in Figure 3.1.3.

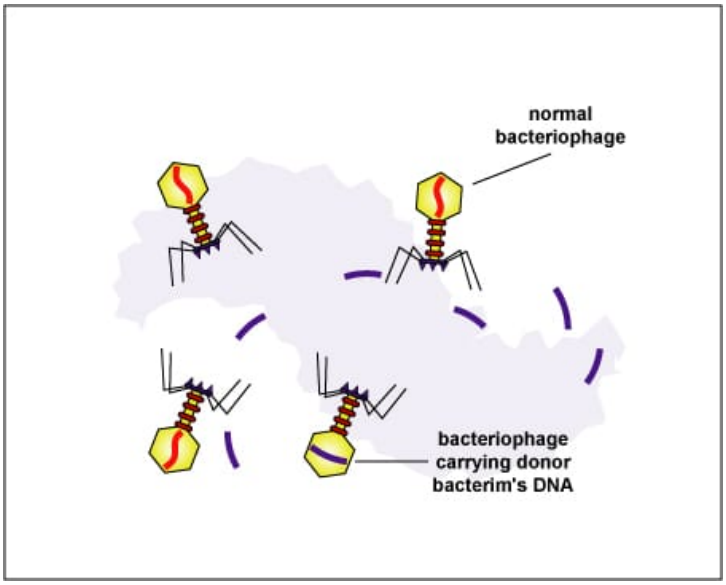
- **Step 1**: A bacteriophage adsorbs to a susceptible bacterium.

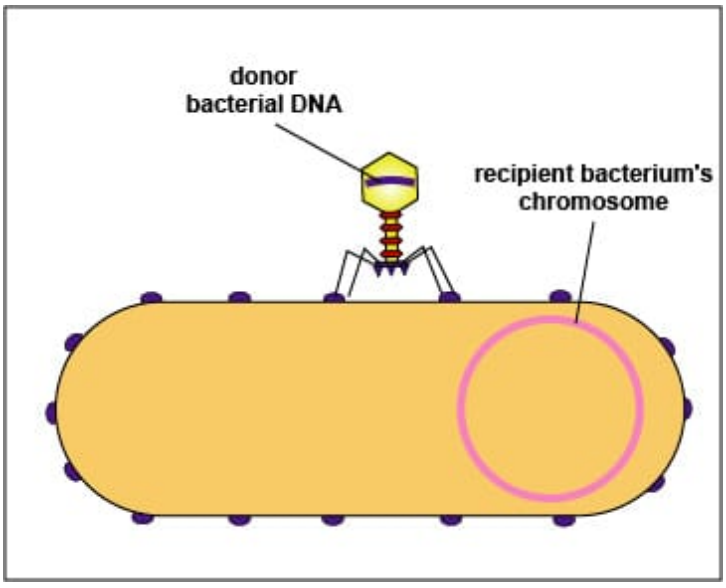
- **Step 2**: The bacteriophage genome enters the bacterium. The genome directs the bacterium's metabolic machinery to manufacture bacteriophage components and enzymes. Bacteriophage-coded enzymes will also breakup the bacterial chromosome.
- **Step 3:** Occasionally, a bacteriophage capsid mistakenly assembles around either a fragment of the donor bacterium's chromosome or around a plasmid instead of around a phage genome.
- **Step 4**: The bacteriophages are released as the bacterium is lysed. Note that one bacteriophage is carrying a fragment of the donor bacterium's DNA rather than a bacteriophage genome.
- **Step 5:** The bacteriophage carrying the donor bacterium's DNA adsorbs to a recipient bacterium.
- **Step 6:** The bacteriophage inserts the donor bacterium's DNA it is carrying into the recipient bacterium.
- **Step 7:** Homologous recombination occurs and the donor bacterium's DNA is exchanged for some of the recipient's DNA. (Figure 3.1.1 shows the functions of the RecA proteins involved in homologous recombination.)

Generalized transduction occurs in a variety of bacteria, including *Staphylococcus, Escherichia, Salmonella*, and *Pseudomonas*.




fragments of the
bacterium's chromosome
(or plasmids)
normal
bacteriophage
bacteriophage
carrying
bacterial DNA


normal
bacteriophage
bacteriophage
carrying donor
bacterim's DNA


donor
bacterial DNA
recipient bacterium's
chromosome

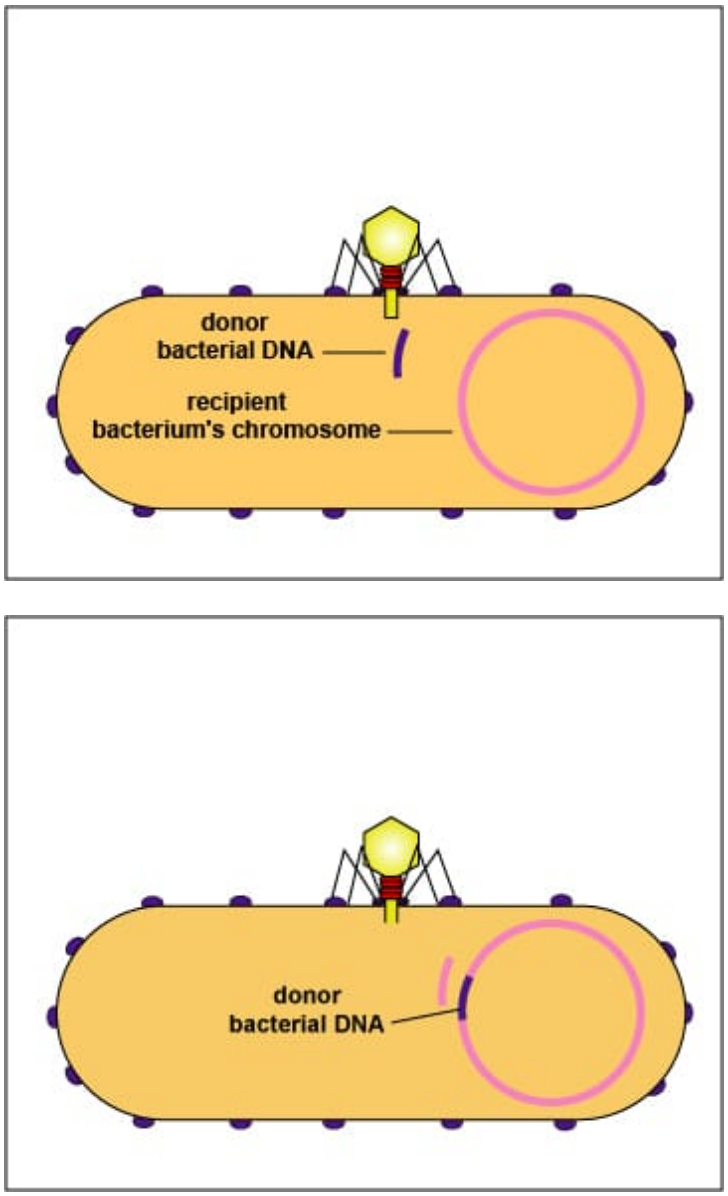


Figure 3.1.3: Generalized Transduction by Lytic Bacteriophage,

Plasmids, such as the penicillinase plasmid of *Staphylococcus aureus*, may also be carried from one bacterium to another by generalized transduction.

Specialized transduction: This may occur occasionally during the lysogenic life cycle of a temperate bacteriophage. During spontaneous induction, a small piece of bacterial DNA may sometimes be exchanged for a piece of the bacteriophage genome, which remains in the bacterial nucleoid. This piece of bacterial DNA replicates as a part of the bacteriophage genome and is put into each phage capsid. The bacteriophages are released, adsorb to recipient bacteria, and inject the donor bacterium DNA/phage DNA complex into the recipient bacterium where it inserts into the bacterial chromosome (Figure 3.1.4).

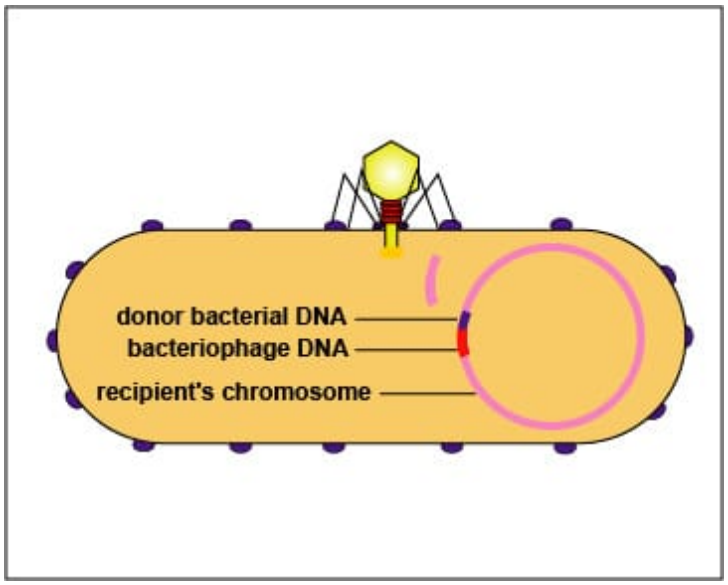


Figure 3.1.4: Specialized Transduction by Temperate Bacteriophage. Step 1: A temperate bacteriophage adsorbs to a susceptible bacterium and injects its genome. Step 2: The bacteriophage inserts its genome into the bacterium's chromosome to become a prophage. Step 3: Occasionally during spontaneous induction, the DNA is excised incorrectly and a small piece of the donor bacterium's DNA is picked up as part of the bacteriophage's genome in place of some of the bacteriophage DNA that remains in the bacterium's chromosome. Step 4: As the bacteriophage replicates, the segment of bacterial DNA replicates as part of the bacteriophage's genome. Every bacteriophage now carries that segment of bacterial DNA. Step 5: The bacteriophage adsorbs to a recipient bacterium and injects its genome. Step 6: The bacteriophage genome carrying the donor bacterial DNA inserts into the recipient bacterium's chromosome.

Conjugation

Genetic recombination in which there is a transfer of DNA from a living donor bacterium to a living recipient bacterium by cell-to-cell contact. In Gram-negative bacteria it typically involves a *conjugation* or *sex pilus*.

Conjugation is encoded by plasmids or transposons. It involves a donor bacterium that contains a conjugative plasmid and a recipient cell that does not. A conjugative plasmid is self-transmissible, in that it possesses all the necessary genes for that plasmid to transmit itself to another bacterium by conjugation. Conjugation genes known as *tra* genes enable the bacterium to form a mating pair with another organism, while *oriT* (origin of transfer) sequences determine where on the plasmid DNA transfer is initiated by serving as the replication start site where DNA replication enzymes will nick the DNA to initiate DNA replication and transfer. In addition, mobilizable plasmids that lack the *tra* genes for self-transmissibility but possess the *oriT* sequences for initiation of DNA transfer may also be transferred by conjugation if the bacterium containing them also possesses a conjugative plasmid. The *tra* genes of the conjugative plasmid enable a mating pair to form, while the *oriT* of the mobilizable plasmid enable the DNA to moves through the conjugative bridge (Figure 3.1.5).

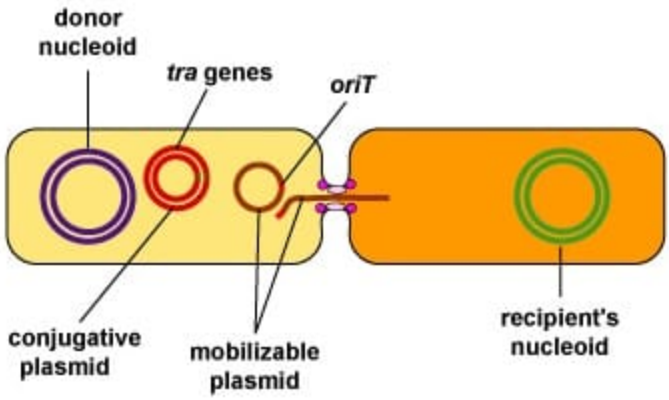


Figure 3.1.5: Transfer of Mobilizable Plasmids During Conjugation. Mobilizable plasmids, that lack the tra genes for self-transmissibility but possess the oriT sequences for initiation of DNA transfer, may also be transferred by conjugation if the bacterium containing them also possesses a conjugative plasmid. The tra genes of the conjugative plasmid enable a mating pair to form while the oriT quences of the mobilizable plasmid enables the DNA to move through the conjugative bridge.

Transposons ("jumping genes") are small pieces of DNA that encode enzymes that enable the transposon to move from one DNA location to another, either on the same molecule of DNA or on a different molecule. Transposons may be found as part of a bacterium's chromosome (conjugative transposons) or in plasmids and are usually between one and twelve genes long. A transposon contains a number of genes, such as those coding for antibiotic resistance or other traits, flanked at both ends by insertion sequences coding for an enzyme called transpoase. Transpoase is the enzyme that catalyzes the cutting and resealing of the DNA during transposition.

Conjugative transposons, like conjugative plasmids, carry the genes that enable mating pairs to form for conjugation. Therefore, conjugative transposons also enable mobilizable plasmids and nonconjugative transposons to be transferred to a recipient bacterium during conjugation.

Many conjugative plasmids and conjugative transposons possess rather promiscuous transfer systems that enables them to transfer DNA not only to like species, but also to unrelated species. The ability of bacteria to adapt to new environments as a part of bacterial evolution most frequently results from the acquisition of large DNA sequences from another bacterium by conjugation.

a. General mechanism of transfer of conjugative plasmids by conjugation in Gram-negative bacteria

In Gram-negative bacteria, the first step in conjugation involves a conjugation pilus (sex pilus or F pilus) on the donor bacterium binding to a recipient bacterium lacking a conjugation pilus. Typically the conjugation pilus retracts or depolymerizes pulling the two bacteria together. A series of membrane proteins coded for by the conjugative plasmid then forms a bridge and an opening between the two bacteria, now called a mating pair.

Using the rolling circle model of DNA replication, a nuclease breaks one strand of the plasmid DNA at the origin of transfer site (*oriT*) of the plasmid and that nicked strand enters the recipient bacterium. The other strand remains behind in the donor cell. Both the donor and the recipient plasmid strands then make a complementary copy of themselves. Both bacteria now possess the conjugative plasmid. This process is summarized in Figure 3.1.6).

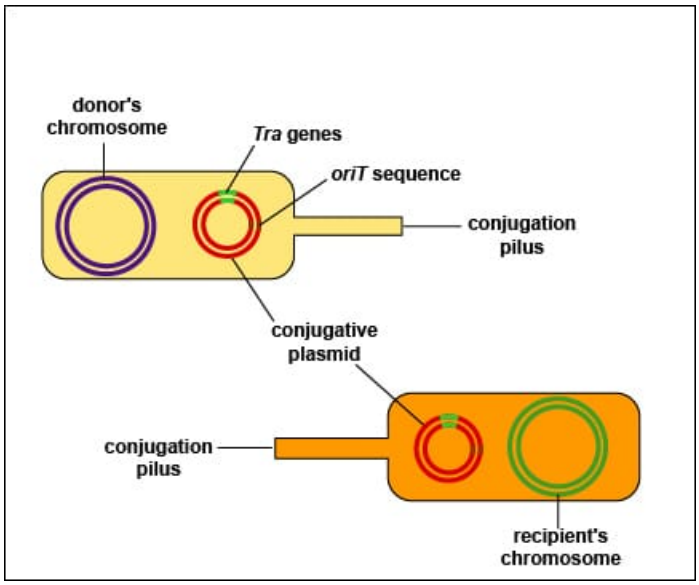


Figure 3.1.6: *Transfer of Conjugative Plasmids. Step 1: In Gram-negative bacteria, the first step in conjugation involves a conjugation pilus (sex pilus or F pilus) on the donor bacterium binding to a recipient bacterium lacking a conjugation pilus. Step 2: Typically the conjugation pilus retracts or depolymerizes pulling the two bacteria together. A series of membrane proteins coded for by the conjugative plasmid then forms a bridge and an opening between the two bacteria, now called a mating pair. Step 3: Using the rolling circle model of DNA replication, a nuclease breaks one strand of the plasmid DNA at the origin of transfer site (oriT) of the plasmid. The nuclease also has helicase activity and unwinds the strand that is going to be transferred. Step 4: The nicked plasmid strand enters the recipient bacterium. The other strand remains behind in the donor cell. Step 5: Both the donor and the recipient plasmid strands then make a complementary copy of themselves. Step 6: Both bacteria now possess the conjugative plasmid and can make a conjugation pilus.*

This is the mechanism by which resistance plasmids (R-plasmids), coding for multiple antibiotic resistance and conjugation pilus formation, are transferred from a donor bacterium to a recipient. This is a big problem in treating opportunistic Gram-negative infections such as urinary tract infections, wound infections, pneumonia, and septicemia by such organisms as *E. coli, Proteus, Klebsiella, Enterobacter, Serratia*, and *Pseudomonas,* as well as with intestinal infections by organisms like *Salmonella* and *Shigella*.

There is also evidence that the conjugation pilus may also serve as a direct channel through which single-stranded DNA may be transferred during conjugation.

b. F^+ conjugation

This results in the transfer of an F^+ plasmid possessing *tra* genes coding only for a conjugation pilus and mating pair formation from a donor bacterium to a recipient bacterium. One strand of the F^+ plasmid is broken with a nuclease at the origin of transfer (*oriT*) sequence that determines where on the plasmid DNA transfer is initiated by serving as the replication start site where DNA replication enzymes will nick the DNA to initiate DNA replication and transfer. The nicked strand enters the recipient bacterium while the other plasmid strand remains in the donor. Each strand then makes a complementary copy. The recipient then becomes an F^+ male and can make a sex pilus (see 7A through 7D).

In addition, mobilizable plasmids that lack the *tra* genes for self-transmissibility but possess the *oriT* sequences for initiation of DNA transfer, may also be transferred by conjugation. The *tra* genes of the F^+ plasmid enable a mating pair to form and the *oriT* sequences of the mobilizable plasmid enable the DNA to moves through the conjugative bridge (Figure 3.1.5).

c. Hfr (high frequency recombinant) conjugation

Hfr conjugation begins when an F^+ plasmid with *tra* genes coding for mating pair formation inserts or integrates into the chromosome to form an Hfr bacterium. (A plasmid that is able to integrate into the host nucleoid is called an *episome*.) A nuclease then breaks one strand of the donor's DNA at the origin of transfer (*oriT*) location of the inserted F^+ plasmid and the nicked strand of the donor DNA begins to enter the recipient bacterium. The remaining non-nicked DNA strand remains in the donor and makes

a complementary copy of itself.

The bacterial connection usually breaks before the transfer of the entire chromosome is completed so the remainder of the F^+ plasmid seldom enters the recipient. As a result, there is a transfer of some chromosomal DNA, which may be exchanged for a piece of the recipient's DNA through homologous recombination, but not the ability to form a conjugation pilus and mating pairs (see Figure 3.1.8A through 8E).

Exercise: Think-Pair-Share Questions

1. A strain of living *Streptococcus pneumoniae* that cannot make a capsule is injected into mice and has no adverse effect. This strain is then mixed with a culture of heat-killed *Streptococcus pneumoniae* that when alive was able to make a capsule and kill mice. After a period of time, this mixture is injected into mice and kills them. In terms of horizontal gene transfer, describe what might account for this.
2. A gram-negative bacterium that was susceptible to most common antibiotics suddenly becomes resistant to several of them. It also appears to be spreading this resistance to others of its kind. Describe the mechanism that most likely accounts for this.

Summary

1. Mutation is a modification of gene function within a bacterium and while it enables bacteria to adapt to new environments, it occurs relatively slowly.
2. Horizontal gene transfer enables bacteria to respond and adapt to their environment much more rapidly by acquiring large DNA sequences from another bacterium in a single transfer.
3. Horizontal gene transfer is a process in which an organism transfers genetic material to another organism that is not its offspring.
4. Mechanisms of bacterial horizontal gene transfer include transformation, transduction, and conjugation.
5. During transformation, a DNA fragment from a dead, degraded bacterium enters a competent recipient bacterium and is exchanged for a piece of DNA of the recipient. Typically this involves similar bacterial strains or strains of the same bacterial species.
6. Transduction involves the transfer of either a chromosomal DNA fragment or a plasmid from one bacterium to another by a bacteriophage.
7. Conjugation is a transfer of DNA from a living donor bacterium to a living recipient bacterium by cell-to-cell contact. In Gram-negative bacteria it involves a conjugation pilus.
8. A conjugative plasmid is self-transmissible, that is, it possesses conjugation genes known as tra genes enable the bacterium to form a mating pair with another organism, and oriT (origin of transfer) sequences that determine where on the plasmid DNA transfer is initiated.
9. Mobilizable plasmids that lack the tra genes for self-transmissibility can be co-transfered in a bacterium possessing a conjugative plasmid.
10. Transposons ("jumping genes") are small pieces of DNA that encode enzymes that enable the transposon to move from one DNA location to another, either on the same molecule of DNA or on a different molecule.
11. Conjugative transposons carry the genes that enable mating pairs to form for conjugation.
12. F^+ conjugation is the transfer of an F^+ plasmid possessing tra genes coding only for a conjugation pilus and mating pair formation from a donor bacterium to a recipient bacterium. Mobilizable plasmids may be co-transfered during F^+ conjugation.
13. During Hfr conjugation, an F^+ plasmid with tra genes coding for mating pair formation inserts into the bacterial chromosome to form an Hfr bacterium. This results in a transfer of some chromosomal DNA from the donor to the recipient which may be exchanged for a piece of the recipient's DNA through homologous recombination.

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3.2: Bacterial Quorum Sensing, Pathogenicity Islands, and Secretion Systems (Injectosomes)

Learning Objectives

1. Define the following:
   a. pathogenicity
   b. virulence
2. Even though a microorganism may be considered pathogenic, it still may not be able to cause disease upon entering the body. Discuss why.
3. Define and briefly describe the overall process of quorum sensing in bacteria and how it may enable bacteria to behave as a multicellular population.
4. State at least two possible advantages of individual bacterial behavior.
5. State at least two possible advantages of multicellular bacterial behavior.
6. State what is meant by intraspecies, interspecies, and interkingdom communication.
7. State the function of bacterial secretions systems (injectisomes) such as the type 3 and type 6 secretion systems in bacterial pathogenicity.

In this Learning Object we are going to look at several aspects of bacterial genetics that are directly related to bacterial pathogenicity, namely, quorum sensing, pathogenicity islands, and secretion systems. Pathogenicity and virulence are terms that refer to an organism's ability to cause disease. Pathogenicity is the ability of a microbe to cause disease and inflict damage upon its host, whereas virulence is the degree of pathogenicity within a group or species of microbes as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism, that is its ability to cause disease, is determined by its virulence factors .

Many of the virulence factors that enable bacteria to colonize the body and/or harm the body are the products of quorum sensing genes. Many bacteria are able to sense their own population density, communicate with each other by way of secreted chemical factors, and behave as a population rather than as individual bacteria . This plays an important role in pathogenicity and survival for many bacteria.

Bacterial Quorum Sensing

Bacteria can behave either as individual single-celled organisms or as multicellular populations. Bacteria exhibit these behaviors by chemically "talking" to one another through a process called quorum sensing. Quorum sensing involves the production, release, and community-wide sensing of molecules called autoinducers that modulate gene expression, and ultimately bacterial behavior, in response to the density of a bacterial population.

To initiate the process of quorum sensing, bacterial genes code for the production of signaling molecules called autoinducers that are released into the bacterium's surrounding environment. These signaling molecules then bind to signaling receptors either on the bacterial surface or in the cytoplasm. When these autoinducers reach a critical, threshold level, they activate bacterial quorum sensing genes that enable the bacteria to behave as a multicellular population rather than as individual single-celled organisms (Figure 3.2.3.2.2). The autoinducer/receptor complex is able to bind to DNA promoters and activate the transcription of quorum sensing-controlled genes in the bacterium. In this way, individual bacteria within a group are able to benefit from the activity of the entire group.

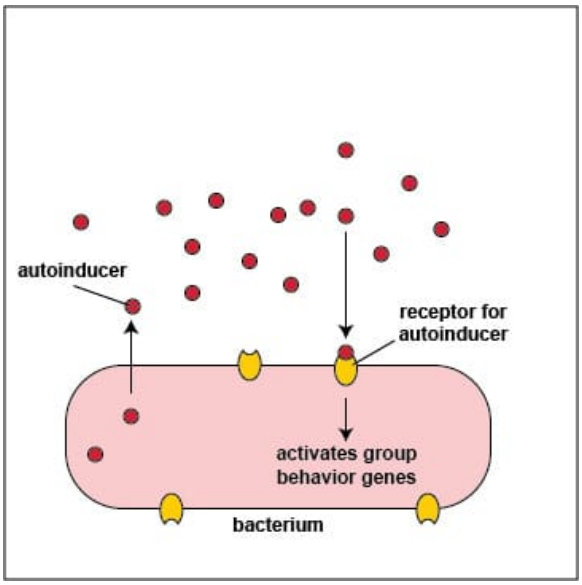


Figure 3.2.3.2.1: Mechanism for Quorum Sensing. Bacteria "talk" to one another through a process called quorum sensing. Bacterial genes code for the production of signaling molecules called autoinducers that are released into the surrounding environment. These signaling molecules then bind to signaling receptors either on the bacterial surface or in the cytoplasm, in this case, on the surface. When these autoinducers reach a critical, threshold level, they activate bacterial quorum sensing genes that enable the bacteria to behave as a multicellular population rather than as individual single-celled organism. The autoinducer/receptor complex is able to bind to DNA promoters and activate the transcription of quorum sensing-controlled genes in the bacterium. In this way, individual bacteria within a group are able to benefit from the activity of the entire group.

1. In Gram-negative bacteria, the autoinducers are typically molecules called acyl-homoserine lactones or AHL. AHLs diffuse readily out of and into bacterial cells where they bind to AHL receptors in the cytoplasm of the bacteria. When a critical level of AHL is reached, the cytoplasmic autoinducer/receptor complex functions as a DNA-binding transcriptional activator.
2. In Gram-positive bacteria, the autoinducers are oligopeptides, short peptides typically 8-10 amino acids long. Oligopeptides cannot diffuse in and out of bacteria like AHLs, but rather leave bacteria via specific exporters. They then bind to autoinducer receptors on the surface of the bacterium. When a critical level of oligopeptide is reached, the binding of the oligopeptide to its receptor starts a phosphorylation cascade that activates DNA-binding transcriptional regulatory proteins called response regulators.

The outcomes of bacteria-host interaction are often related to bacterial population density. Bacterial virulence, that is its ability to cause disease, is largely based on the bacterium's ability to produce gene products called virulence factors that enable that bacterium to colonize the host, resist body defenses, and harm the body.

At a low density of bacteria, the autoinducers diffuse away from the bacteria (Figure 3.2.3.2.2). Sufficient quantities of these molecules are unable to bind to the signaling receptors on the bacterial surface and the quorum sensing genes that enable the bacteria to act as a population are not activated. This enables the bacteria to behave as individual, single-celled organisms.

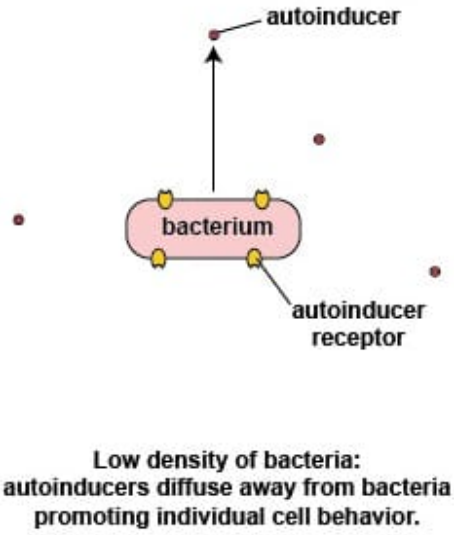


Figure 3.2.3.2.2: Quorum Sensing with a Low Density of Bacterial Cells At a low density of bacteria, the signaling molecules (autoinducers) diffuse away from the bacteria. Sufficient quantities of these molecules are unavailable for binding to the signaling receptors on the bacterial surface (Gram-positive bacteria) or in the cytoplasm (Gram-negative bacteria), and the quorum sensing genes that enable the bacteria to act as a population are not activated. The bacterium then utilizes genes that enable the bacterium to act as an indiviual organism rather than as a multicellular population. Acting as individual organisms may better enable that low density of bacteria to gain a better foothold in their new environment.

Possible advantages of individual bacterial behavior seen at low bacterial density

If a relatively small number of a specific bacterium were to enter the body and immediately start producing their virulence factors, chances are the body's immune systems would have sufficient time to recognize and counter those virulence factors and remove the bacteria before there was sufficient quantity to cause harm. The bacterium instead utilizes genes that enable it to act as an individual organism rather than as part of a multicellular population.

Acting as individual organisms may better enable that low density of bacteria to gain a better foothold in their new environment in the following ways:

1. Many bacteria are capable of motility and motility serves to keep bacteria in an optimum environment via taxis .

Motility and chemotaxis probably help some intestinal and urinary pathogens to move through the mucous layer so they can attach to the epithelial cells of the mucous membranes. In fact, many bacteria that can colonize the mucous membranes of the bladder and the intestines are motile. Motility probably helps these bacteria move through the mucus in places where it is less viscous.

2. One of the body's innate defenses is the ability to physically remove bacteria from the body through such means as the constant shedding of surface epithelial cells from the skin and mucous membranes, the removal of bacteria by such means as coughing, sneezing, vomiting, and diarrhea, and bacterial removal by bodily fluids such as saliva, blood, mucous, and urine. Bacteria may resist this physical removal by producing pili (see Figure 3.2.3), cell wall adhesin proteins (Figure 3.2.3.2.4), and/or biofilm-producing capsules . Some pili, called type IV pili also allow some bacteria to "walk" or "crawl" along surfaces to spread out and eventually form microcolonies.

Figure 3.2.3.2.3: Adhesive Tip of Bacterial Pili Binding to Host Cell Receptors

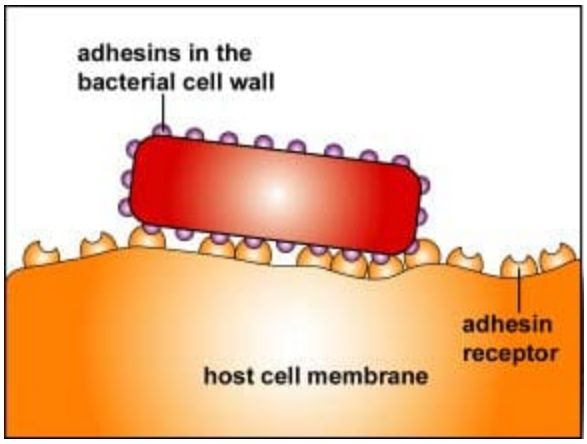


Figure 3.2.3.2.4: Bacterial Adhesins. Surface proteins called adhesins in the bacterial cell wall bind to receptor molecules on the surface of a susceptible host cell enabling the bacterium to make intimate contact with the host cell, adhere, colonize, and resist flushing.

3. Many bacteria secrete an extracellular polysaccharide or polypeptide matrix called a *capsule* or *glycocalyx* that enables the bacteria to adhere to host cells, resist phagocytosis, and form microcolonies. As the bacteria geometrically increase in number by binary fission, so does the amount of their secreted autoinducers, and production of high levels of autoinducers then enables the population of bacteria to communicate with one another by quorum sensing. At a high density of bacteria, large quantities of autoinducers are produced (Figure 3.2.3.2.5) and are able to bind to the signaling receptors on the bacterial surface in sufficient quantity so as to activate the quorum sensing genes that enable the bacteria to behave as a multicellular population (Figure 3.2.3 .2.1).

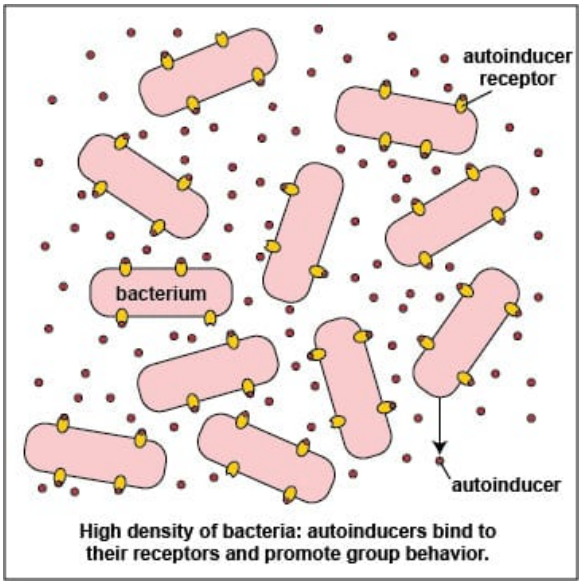


Figure 3.2.3.2.5: Quorum Sensing with a High Density of Bacterial Cells. At a high density of bacteria, sufficient quantities of signaling molecules (autoinducers) are available for binding to the signaling receptors on the bacterial surface (Gram-positive bacteria) or in the cytoplasm (Gram-negative bacteria), and the quorum sensing genes that enable the bacteria to act as a population become activated. The outcomes of bacteria-host interaction are often related to bacterial population density. Bacterial virulence, that is its ability to cause disease, is largely based on the bacterium's ability to produce gene products called virulence factors that enable that bacterium to colonize the host, resist body defenses, and harm the body.

Advantages of Multicellular Behavior seen at High Bacterial Density

1. By behaving as a multicellular population, individual bacteria within a group are able to benefit from the activity of the entire group. As the entire population of bacteria simultaneously turn on their virulence genes, the body's immune systems are much less likely to have enough time to counter those virulence factors before harm is done.
2. This triggers production of an extracellular adhesive matrix (glycocalyx) enabling the bacteria to form microcolonies and irreversibly attachment to the mucous membranes . Biofilm formation begins.

3. Virulence factors such as exoenzymes and toxins can damage host cells enabling the bacteria in the biofilm to obtain nutrients. The biofilm continues to develop and mature.
4. As the area becomes over-populated with bacteria, quorum sensing enables some of the bacteria to escape the biofilm, often by again producing flagella, and return to individual single-celled organism behavior in order to find a new sight to colonize.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is an example of a quorum sensing bacterium. *P. aeruginosa* causes severe hospital-acquired infections, chronic infections in people with cystic fibrosis, and potentially fatal infections in those who are immunocompromised.

1. When *P. aeruginosa* first enters the body, they are at a low density of bacteria. The autoinducers diffuse away from the bacteria (Figure 3.2.3.2.2), sufficient quantities of these molecules are unable to bind to the signaling receptors, and the quorum sensing genes that enable the bacteria to act as a population are not activated. The *P. aeruginosa* continue to function as individual bacteria. Motility genes (coding for flagella) and adhesin genes (coding for pili and cell wall adhesins) are expressed. The flagella enable the initial bacteria to swim through mucus towards host tissues such as mucous membranes. Pili then enable the bacteria to reversibly attach to host cells in order to resist flushing and begin colonization (Figure 3.2.3.2.6; left). Type IV pili, which enable a twitching motility in some bacteria, then enable the bacteria as they replicate to crawl along and spread out over the mucous membranes (Figure 3.2.3.2.6; middle). The pili subsequently retract and bacterial cell wall adhesins enable a more intimate attachment of the bacterium to the mucous membranes (Figure 3.2.3 .2.6; right).

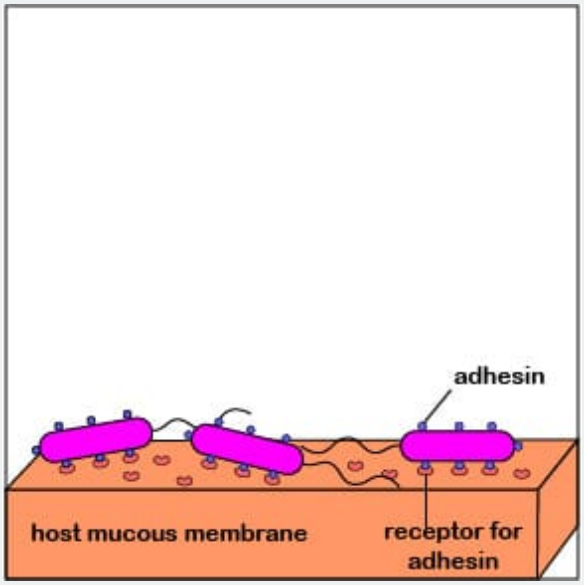


Figure 3.2.3.2.6: Development of a Biofilm by Pseudomonas aeruginosa. Step 1 (left): Planktonic Pseudomonas aeruginosa use their polar flagella and chemotaxis to swim towards host mucous membranes. Pili then bind to host cell receptors for initial but reversible bacterial attachment. Step 2 (middle): As the bacteria begin to replicate, type IV pili enable the bacteria, by way of twitching motility, to crawl along the surface of the mucous membranes and spread out. Step 3 (right): The pili retract and bacterial cell wall adhesins enable a more intimate attachment of the bacterium

2. Once *P. aeruginosa* has colonized, it is able to replicate geometrically and achieve a high population density. Quorum sensing genes are activated and the bacteria function as a population. This triggers production of an extracellular polysaccharide called *alginate* to form microcolonies and enables irreversible attachment to the mucous membranes (Figure 3.2.7; left). Biofilm formation begins.

3. Quorum sensing genes coding for enzymes and toxins that damage host cells are produced. These are injected into the host cells by way of an injectosome. This releases nutrients for the bacteria in the biofilm. The bacteria continue to replicate as the biofilm continues to develop, mushroom up, and mature (Figure 3.2. 7; middle).

4. As the bacteria replicate, the biofilm continues to mature (Figure 3.2.7; right). Water channels form within the biofilm to deliver water, oxygen, and nutrients to the growing population of *P. aeruginosa*. The high density of bacteria bacteria are now acting as a multicellular population rather than as individual bacteria.

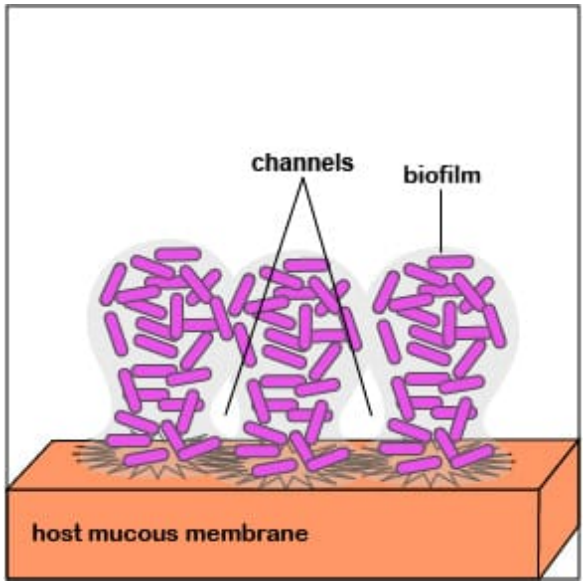


Figure 3.2.3.2.7: Development of a Biofilm by Pseudomonas aeruginosa: Step 4 (left): As the bacteria replicate, quorum sensing genes trigger production of an extracellular polysaccharide called alginate to form microcolonies and enable irreversible attachment to the mucous membranes. Biofilm formation begins. Step 5 (middle): Quorum sensing genes coding for enzymes and toxins that damage host cells are produced. This releases nutrients for the bacteria in the biofilm. The bacteria continue to replicate as the biofilm continues to develop, mushroom up, and mature. Step 6 (right): As the bacteria replicate, the biofilm continues to mature. Water channels form within the biofilm to deliver water, oxygen, and nutrients to the growing population of P. aeruginosa.

The biofilm enables bacteria to:

- resist attack by antibiotics;
- trap nutrients for bacterial growth and remain in a favorable niche;
- adhere to environmental surfaces and resist flushing;
- live in close association and communicate with other bacteria in the biofilm; and
- resist phagocytosis and attack by the body's complement pathways.

5. When the population of *P. aeruginosa* begins to outgrow their local environment, quorum sensing enables them to turn off adhesin genes and turn on flagella genes that allow some of the bacteria to spread out of the biofilm to new location within that environment via motility (Figure 3.2.3.2.8).

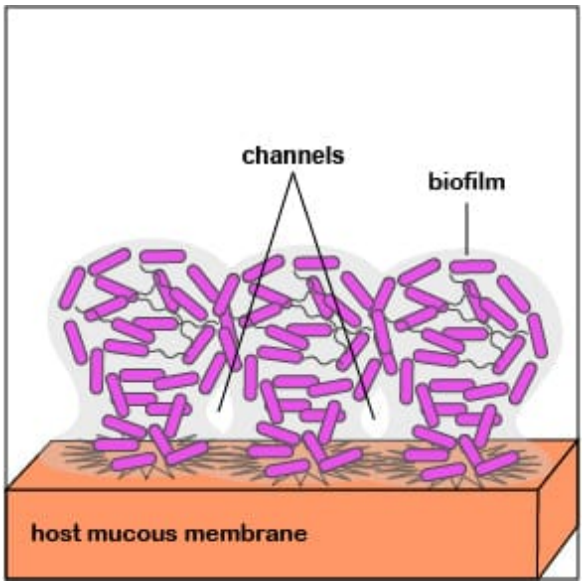


Figure 3.2.3.2.8: Development of a Biofilm by Pseudomonas aeruginosa: Step 7 (left): As the population begins to overgrow the area and nutrients become limited, quorum sensing genes trigger some of the P. aeruginosa in the biofilm to again produce flagella. Step 8 (right): Planktonic P. aeruginosa leave the biofilm and move to a new location to begin new biofilms.

It turns out that bacteria are multilingual. They use quorum sensing not only to "talk" to members their own species (intraspecies communication), but also to "talk" to bacteria that are not of their genus and species (interspecies communication). Intraspecies autoinducers and receptors enable bacteria to communicate with others of their own species while interspecies autoinducers and receptors enable bacteria to communicate with bacteria of a different species or genus (Figure 3.2.3.2.9). The autoinducers for interspecies communications are referred to as AI-2 family autoinducers and are different from the intraspecies (AI-1) autoinducers. In some cases bacteria use interspeciecies communication to work cooperatively with various other bacteria in their biofilm to the benefit all involved; in other cases, bacteria may use interspecies communication in such a way that one group benefits at the expense of another.

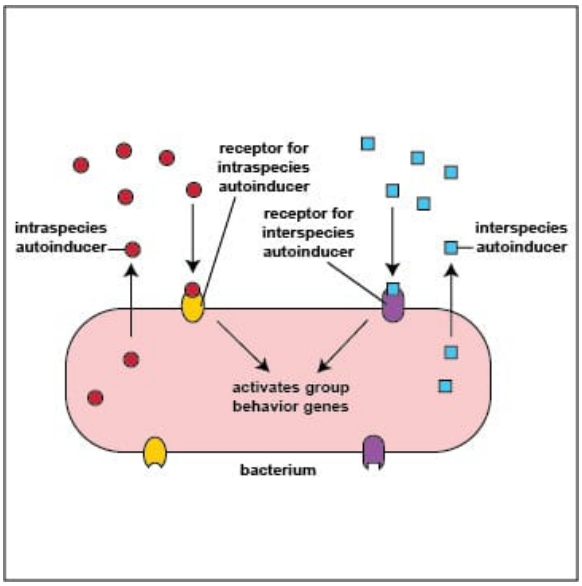


Figure 3.2.3.2.9: Intraspecies and Interspecies Communication. Intraspecies autoinducers and receptors enable bacteria to communicate with others of their own species while interspecies autoinducers and receptors enable bacteria to communicate with bacteria of a different species or genus.

Furthermore, bacteria are capable of interkingdom communication, communication between bacteria and their animal or plant host. Increasing numbers of bacteria are being found that have signaling receptors that recognize human hormones. For example, a number of bacteria that are pathogens of the human intestinal tract have a sensing molecule called QseC that binds the human hormones adrenaline and noradrenaline. This, in turn, activates various virulence genes of the bacteria. On the other hand, some

bacterial autoinducers can enter human host cells and regulate human cellular function. For example, at low concentration some bacterial autoinducers suppress host immune responses thus better enabling those bacteria to better establish themselves in the body. At high concentrations, however, they stimulate an inflammatory response in the host to help the bacteria to spread from the initial infection site. One bacterial autoinducer has been found to initiate apoptosis (cell suicide) in phagocytes such as neutrophils and macrophages.

Bacterial Pathogenicity Islands

The genomes of pathogenic bacteria, when compared with those of similar nonpathogenic species or strains, often show extra genes coding for virulence factors , that is, molecules expressed and secreted by the bacterium that enable them to colonize the host, evade or inhibit the immune responses of the host, enter into or out of a host cell, and/or obtain nutrition from the host. These include virulence factors such as capsules, adhesins, type 3 secretion systems, invasins, and toxins.

Most genes coding for virulence factors in bacteria are located in pathogenicity islands or PAIs and are usually acquired by horizontal gene transfer . These PAIs may be located in the bacterial chromosome, in plasmids, or even in bacteriophage genomes that have entered the bacterium. The genomes of most pathogenic bacteria typically contain multiple PAIs that can account for up to 10 transpoases ,- 20% of the bacterium's genome. PAIs carry genes such as integrases , or insertion sequences that enable them to insert into host bacterial DNA. Transfer RNA (tRNA) genes are often the target site for integration of PAIs. Conjugative plasmids are the most frequent means of transfer of PAIs from one bacterium to another and the transfer of PAIs can then confer virulence to a previously nonpathogenic bacterium.

Type 3 Secretion Systems (T3SS or Injectisomes) and Type 6 Secretion Systems (T6SS)

Many bacteria involved in infection have the ability to co-opt the functions of host cells for the bacterium’s own benefit. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication to the benefit of the bacteria.

The most common type is the type 3 secretion system or T3SS (Figure 3.2.3.2.10). A secretion apparatus in the cytoplasmic membrane and cell wall of the bacterium polymerizes a hollow needle that is lowered to the cytoplasmic membrane of the host cell and a *translocon* protein is then delivered to anchor the needle to the host cell. Effector proteins in the bacterium can now be injected into the cytoplasm of the host cell. The delivery system is sometimes called an *injectisome*. (A type 4 secretion system can transfer effector proteins and/or DNA into the host cell because it is similar to the conjugation transfer system initiated by *tra* genes discussed under horizontal gene transfer.)

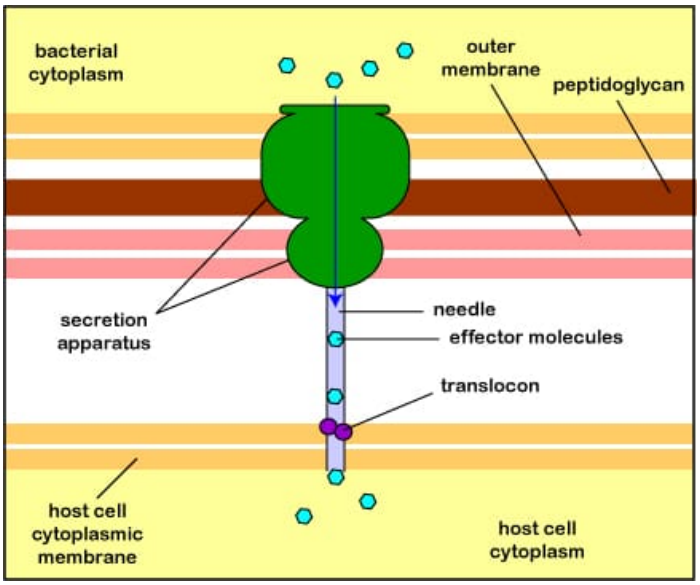
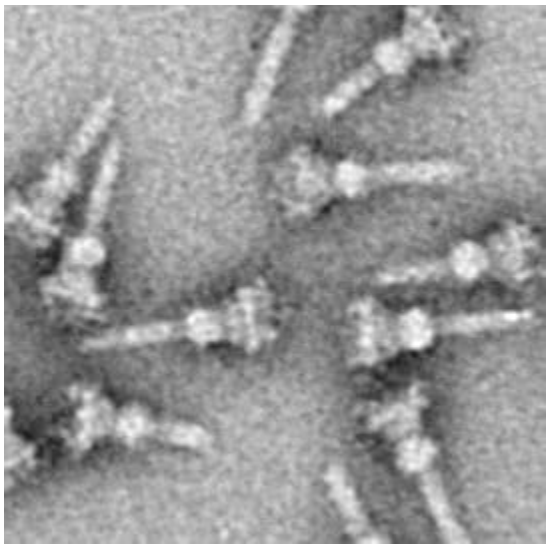


Figure 3.2.3.2.10: The Bacterial Type 3 Secretion System. Many bacteria involved in infection have the ability to co-opt the functions of the host cell for the bacterium's own benefit. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication. The most common type is the type 3 secretion system. A secretion apparatus in the cytoplasmic membrane and cell wall of the bacterium polymerizes a hollow needle that is lowered to the cytoplasmic membrane of the host cell and a translocon protein is then delivered to anchor the needle to the host cell. Effector proteins in the bacterium can now be injected into the cytoplasm of the host cell. The delivery system is sometimes called an injectisome.



Electron micrograph of an injectisome. A transmission electron-microscope image of isolated T3SS needle complexes from Salmonella typhimurium. (CC BY-SA 2.5; Schraidt O, Lefebre MD, Brunner MJ, Schmied WH, Schmidt A, Radics J, Mechtler K, Galán JE, Marlovits TC - Cropped image from Schraidt et al. (2010), Topology and Organization of the Salmonella typhimurium Type III Secretion Needle Complex Components. PLoS Pathog 6(4): e1000824.doi:10.1371/journal.ppat.1000824)

Some bacteria, such as *Pseudomonas aeruginosa* and *Vibrio cholerae*, produce a type 6 secretion system, or T6SS, that consists of a protein tube surrounded by a contractile sheath, similar to the tail of T4-bacteriophages (a bacteriophage is a virus that only infects bacteria.) The type 6 secretion system not only injects effector molecules into eukaryotic cells, but also is able to inject antibacterial effector molecules into other bacteria in order to kill those bacteria. Predator bacteria can use their T6SS to kill prey bacteria. In fact, *V. cholerae* and *P. aeruginosa* have been shown to "duel" with one another via their respective T6SSs.

V. cholerae also uses its T6SS to promote horizontal gene transfer by way of transformation. Individual *V. cholerae* cells also use their T6SS to attack one another upon cell-to-cell contact. Most members of the population, however, produce immunity proteins

that protect them from being killed by the effector molecules that are injected. Not all strains of *V. cholerae* in the population, however, produce these immunity proteins and these non-immune cells are subsequently lysed, releasing their DNA into the environment. This DNA can then be taken up by neighboring competent *V. cholerae* via transformation.

Exercise 3.2.1: Think-Pair-Share Questions

Briefly describe how bacterial quorum sensing may play a role in pathogenicity by:

a. Promoting colonization of a new host by bacteria that have just entered the body.
b. Enabling the bacterium to persist within that host once they have colonized.
c. Allowing some of the bacteria to spread to a new location within a host or to a new host.

Exercise 3.2.2: Think-Pair-Share Questions

Briefly describe how the ability to produce a type 3 secretion system might play a role in a pathogen colonizing the body and causing an infection.

Summary

1. Pathogenicity is the ability of a microbe to cause disease and inflict damage upon its host; virulence is the degree of pathogenicity within a group or species of microbes.
2. The pathogenicity of an organism is determined by its virulence factors.
3. Virulence factors enable that bacterium to colonize the host, resist body defenses, and harm the body.
4. Most of the virulence factors are the products of quorum sensing genes.
5. Quorum sensing involves the production, release, and community-wide sensing of molecules called autoinducers that modulate gene expression, and ultimately bacterial behavior, in response to the density of a bacterial population.
6. The outcomes of bacteria-host interaction are often related to bacterial population density.
7. At a low density of bacteria, the autoinducers diffuse away from the bacteria and there are insufficient quantities of these molecules to activate the quorum sensing genes that enable the bacteria to act as a population. As a result the bacteria behave as individual, single-celled organisms.
8. Acting as individual organisms may enable a low density of bacteria to gain a better foothold in their new environment by enabling bacteria to use motility and taxis to contact host cells, use pili to initially adhere to and crawl over host cell surfaces, use adhesins to adhere to host cells and resist flushing, and secrete a glycocalyx to form microcolonies.
9. As the bacteria increase in numbers geometrically as a result of binary fission and reach high density, large quantities of autoinducers are produced and are able to bind to the signaling receptors on the bacterial surface in sufficient quantity so as to activate the quorum sensing genes that enable the bacteria to now behave as a multicellular population.
10. By behaving as a multicellular population, individual bacteria within a group are able to benefit from the activity of the entire group.
11. As the entire population of bacteria simultaneously turn on their virulence genes, the body's immune systems are much less likely to have enough time to counter those virulence factors before harm is done. Virulence factors such as exoenzymes and toxins can damage host cells enabling the bacteria in the biofilm to obtain nutrients.
12. As the area becomes over-populated with bacteria, quorum sensing enables some of the bacteria to escape the biofilm and return to individual single-celled organism behavior in order to find a new sight to colonize.
13. Quorum sensing enables bacteria to communicate with members of their own species, with other species of bacteria, and with their eukaryotic host cells.
14. Most genes coding for virulence factors in bacteria are located in pathogenicity islands or PAIs and are usually acquired by horizontal gene transfer.
15. Many bacteria involved in infection have the ability to co-opt the functions of the host cell for the bacterium's own benefit by producing secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter the host cell's cellular machinery, cellular function, or cellular communication.

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3.3: Enzyme Regulation

Learning Objectives

1. Compare and contrast the genetic control of enzyme activity (enzyme synthesis) in bacteria with the control of enzyme activity through feedback inhibition.
2. Compare and contrast an inducible operon with a repressible operon and give an example of each.
3. Compare how the presense or absence of tryptophan affects the *trp* operon.
4. Compare how the presense or absence of lactose affects the *lac* operon.
5. Compare how the presense or absence of an inducer affects activators.
6. Briefly describe how small RNAs can regulate enzyme activity.
7. Define the following:
   a. repressor
   b. inducer
   c. activator
   d. enhancer
   e. small RNAs
8. Compare and contrast competitive inhibition with noncompetitive inhibition.

In living cells, there are hundreds of different enzymes working together in a coordinated manner. Living cells neither synthesize nor break down more material than is required for normal metabolism and growth. All of this necessitates precise control mechanisms for turning metabolic reactions on and off. There is tremendous diversity in the mechanisms bacteria use to regulate enzyme synthesis and enzyme activity. For pretty much every step between the activation of a gene and the final enzyme reaction from that gene product there is some bacterial mechanism for regulation that step. Here we will look at several well studied examples.

Genetic Control of Enzyme Synthesis through Repression, Induction, or Enhancement of Transcription

Genetic control of enzyme activity refers to controlling transcription of the mRNA needed for an enzyme's synthesis. In prokaryotic cells, this involves the induction, repression, or enhancement of enzyme synthesis by regulatory proteins that can bind to DNA and either induce, block, or enhance the function of RNA polymerase , the enzyme required for transcription. The regulatory proteins are often part of either an operon or a regulon. An operon is a set of genes transcribed as a polycistronic message that is collectively controlled by a regulatory protein. A regulon is a set of related genes controlled by the same regulatory protein but transcribed as monocistronic units. Regulatory proteins may function either as repressors, activators, or enhancers.

a. Repressors

Repressors are regulatory proteins that block transcription of mRNA. They do this by binding to a portion of DNA called the operator (operators are often called boxes now) that lies downstream of a promoter. The binding of the regulatory protein to the operator prevents RNA polymerase from binding to the promoter and transcribing the coding sequence for the enzymes. This is called negative control and is mostly n in biosynthetic reactions where a bacterium only makes a molecule like a particular amino acid when that amino acid is not present in the cell.

Repressors are allosteric proteins that have a binding site for a specific molecule. Binding of that molecule to the allosteric site of the repressor can alter the repressor's shape that, in turn affects its ability to bind to DNA. This can work in one of two ways:

1. Some repressors are synthesized in a form that cannot by itself bind to the operator. This is referred to as a repressible system. The binding of a molecule called a corepressor, however, alters the shape of the regulatory protein to a form that can bind to the operator and subsequently block transcription. An example of this type of **repressible system** is the *trp* operon in *Escherichia coli* that encodes the five enzymes in the pathway for the biosynthesis of the amino acid tryptophan. In this case, the repressor protein coded for by the *trp* regulatory gene, normally does not bind to the operator region of the *trp* operon and the five enzymes

needed to synthesize the amino acid tryptophan are made (Figure 3.3.1A and Figure 3.3.1B).

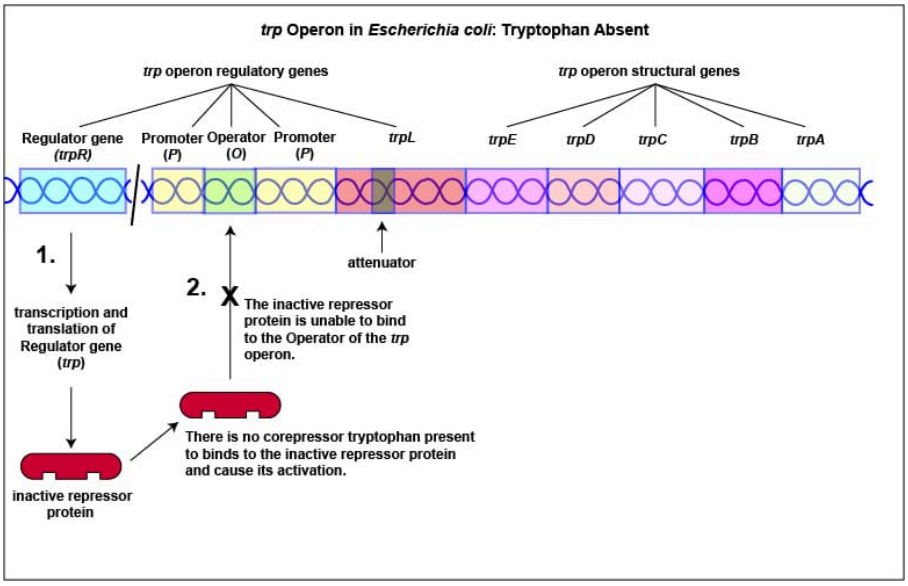


Figure 3.3.1A: A Repressible Operon in the Absence of a Corepressor (The Tryptophan Operon). Step 1: The Regulator gene codes for an inactive repressor protein. Step 2: The inactive repressor protein is unable to bind to the Operator region of the trp operon.

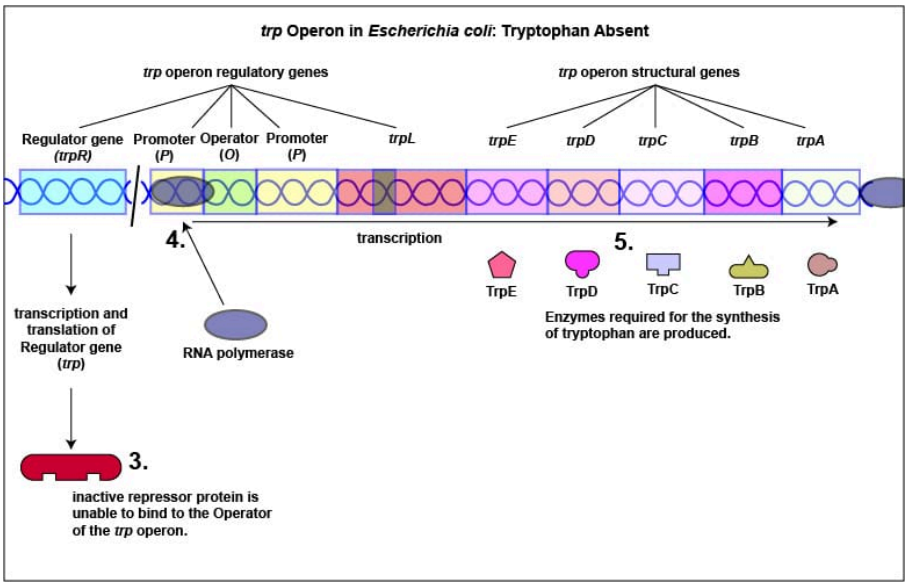


Figure 3.3.1B: A Repressible Operon in the Absence of a Corepressor (The Tryptophan Operon). Step 3: Since the inactive repressor protein is unable to bind to the Operator region, RNA polymerase (the enzyme responsible for the transcription of genes) is able to bind to the Promoter region of the trp operon. Step 4: RNA polymerase is now able to transcribe the five trp operon structural genes (trpE, trpD, trpC, trpB, and trpA) into mRNA. Step 5: With the transcription of these genes, the five enzymes needed for the bacterium to synthesize the amino acid tryptophan are now made. TrpE and TrpD are the two subunits for making anthranilate synthetase, the enzyme that catalyzes the first two reactions in the tryptophan pathway. TrpC is is indole glycerolphosphate synthetase, the enzyme that catalyzes the next two steps in the pathway. TrpB and TrpA are subunits for making tryptophan synthetase. the enzyme that catalizes the synthesis of tryptophan from indole-glycerol phosphate and serine.

Tryptophan, the end product of these enzyme reactions, however, functions as a corepressor. Once sufficient tryptophan has been synthesized, the cell needs to terminate its synthesis. The tryptophan is able to bind to a site on the allosteric repressor protein, changing its shape and enabling it to interact with the *trp* operator region. Once the repressor binds to the operator, RNA polymerase is unable to bind to the promoter and transcribe the genes for tryptophan biosynthesis. Therefore, when sufficient tryptophan is present, transcription of the enzymes that allows for its biosynthesis are turned off (Figure 3.3.2A and Figure 3.3.2 B).

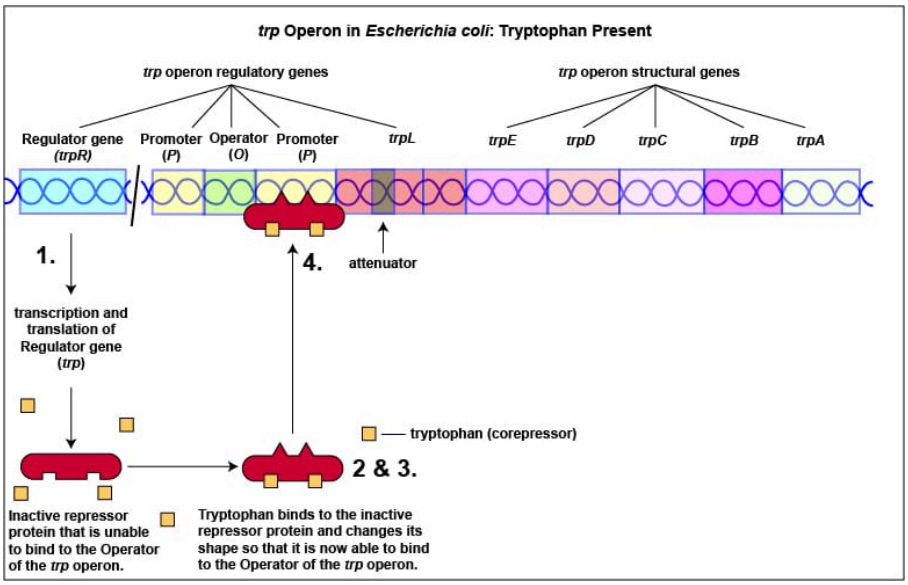


Figure 3.3.2A: A Repressible Operon in the Presence of a Corepressor (The Tryptophan Operon). Step 1: The Regulator gene codes for an inactive repressor protein. Step 2: If the corepressor tryptophan is present, it binds to to the inactive repressor protein.Step 3: The binding of the corepressor causes inactive repressor protein to change shape and become activated. Step 4: The activated repressor protein then binds to the Operator region of the trp operon.

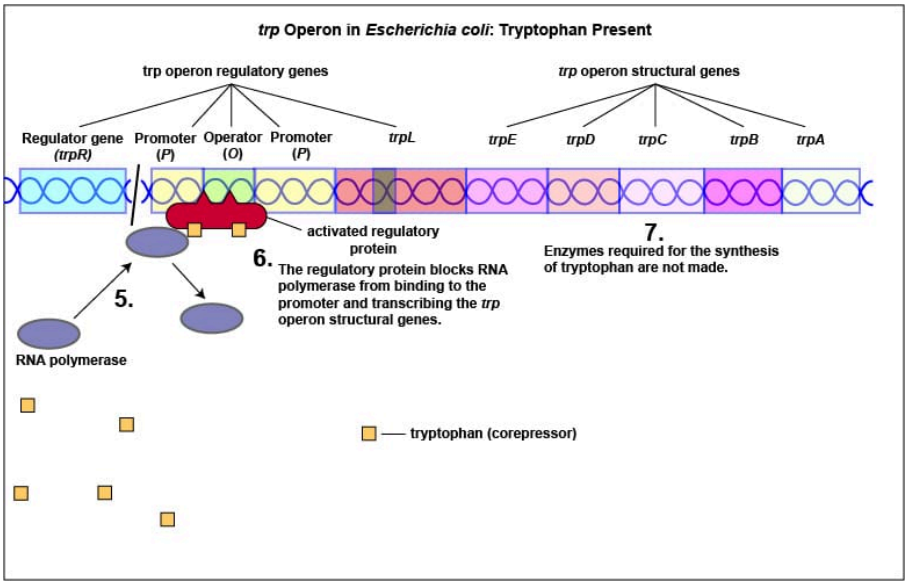


Figure 3.3.2B: A Repressible Operon in the Presence of a Corepressor (The Tryptophan Operon). Step 5: With the active repressor protein bound to the Operator region, RNA polymerase (the enzyme responsible for the transcription of genes) is unable to bind to the Promoter region of the trp operon. Step 6: If RNA polymerase does not bind to the Promoter region, the five trp operon structural genes are not transcribed into mRNA. Step 7: Without the transcription of the five genes, the five enzymes needed for the bacterium to synthesize the amino acid tryptophan are not made.

In addition to repression, the expression of the *trp* operon is also regulated by attenuation. The *trpL* gene codes for a mRNA leader sequence that controls operon expression through attenuation. This leader sequence mRNA consists of domains 1, 2, 3, and 4. Domain 3 can base pair with either domain 2 or domain 4.

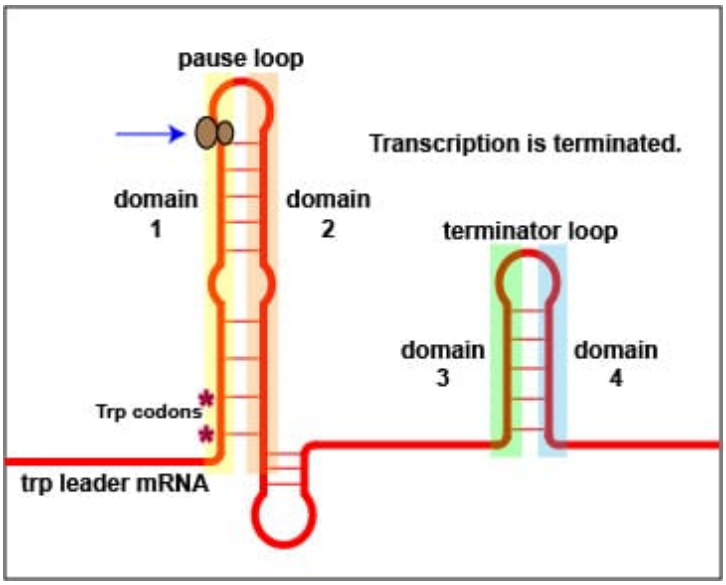


Figure 3.3.3A: Attenuation in the Trp Operon of Escherichia coli: Excess Tryptophan. When excess tryptophan is available, there is a rapid translation of the early trp leader mRNA enabling domain 2 to pair with domain 1 and form a pause loop. The ribosome pauses at a stop codon (arrow) causing domain 3 to pair with domain 4 and form a terminator loop. Transcription of the remainder of the trp operon is terminated. Rapid initial translation is able to occur with excess tryptophan present because there is a sufficient quantity of Trp tRNA available to translate the two Trp codons (asterisks).

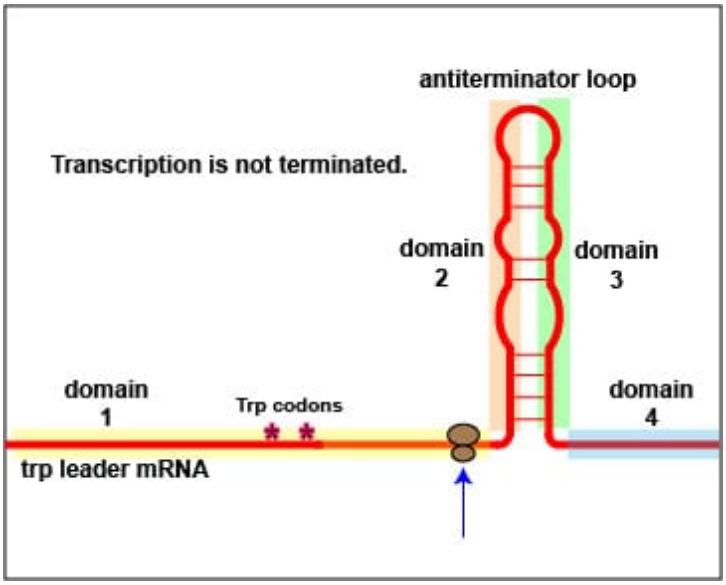


Figure 3.3.3B: Attenuation in the Trp Operon of Escherichia coli: Low Levels of Tryptophan. When tryptophan is limited, there is a slow translation of the early trp leader mRNA which enables domain 2 to pair with domain 3 and form an antiterminator loop. Transcription of the remainder of the trp operon continues and the enzymes required for tryptophan synthesis are made. Slow initial translation is able to occur with low levels of tryptophan present because there is limited Trp tRNA available to translate the two Trp codons (asterisks) causing the ribosome to stall at the Trp codons and enabling domain 2 to pair with domain 3 rather than domain 1.

At high tryptophan concentrations, domains 3 and 4 pair in such a way as to form stem and loop structures that block the transcription of the remainder of the leader sequence mRNA and subsequently, the transcription of the structural genes for tryptophan biosynthesis (Figure 3.3.3A). However, at low concentrations of tryptophan, domains 3 and 2 pair. This pairing allows for the full transcription of the leader sequence mRNA, as well as that of the structural genes for tryptophan biosynthesis (Figure 3.3.3B).

2. Other repressors are synthesized in a form that readily binds to the operator and blocks transcription. However, the binding of a molecule called an inducer alters the shape of the regulatory protein in a way that now blocks its binding to the operator and thus permits transcription. This is referred to as an **inducible system**.

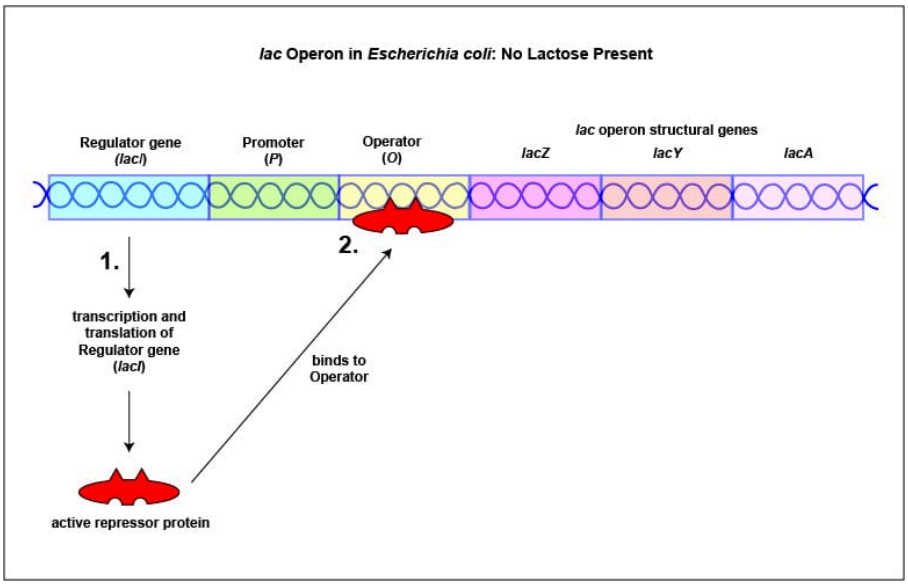


Figure 3.3.4A: An Inducible Operon in the Absence of an Inducer (The Lactose Operon of Escherichia coli). Step 1: The Regulator gene (lacI) codes for an active repressor protein. Step 2: The repressor protein then binds to the Operator region of the lac operon.

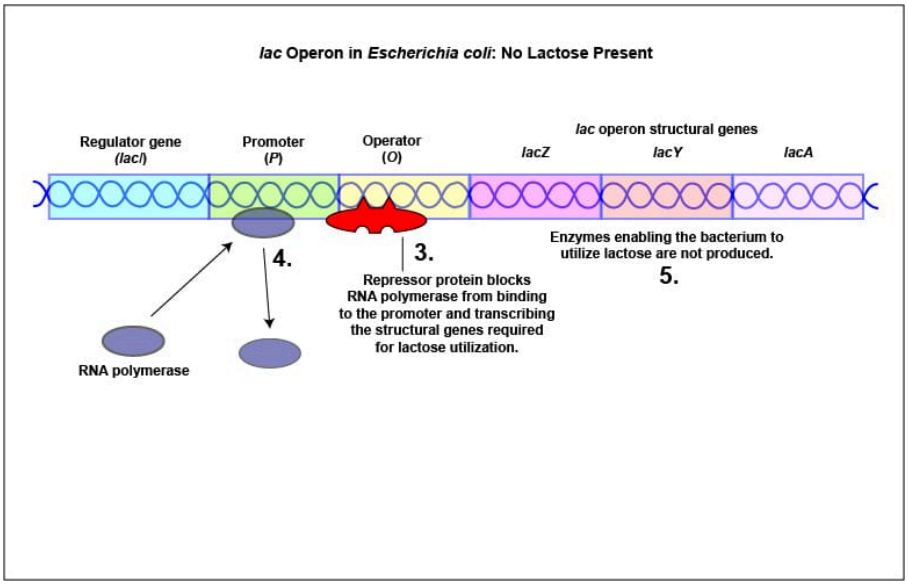


Figure 3.3.4B: An Inducible Operon in the Absence of an Inducer (The Lactose Operon of Escherichia coli). Step 3: With the active repressor protein bound to the Operator region, RNA polymerase (the enzyme responsible for the transcription of genes) is unable to bind to the Promoter region of the operon. Step 4: If RNA polymerase does not bind to the Promoter region, the 3 lac operon structural genes (lacZ, lac Y, and lacA) are not transcribed into mRNA. Step 5: Without the transcription of these genes, the enzymes needed for the utilization of the sugar lactose by the bacterium are not synthesized.

An example of an inducible system is the *lac* operon that encodes for the three enzymes needed for the degradation of lactose by *E. coli*. *E. coli* will only synthesize the enzymes it requires to utilize lactose if that sugar is present in the surrounding environment. In this case, lactose functions as an inducer . In the absence of lactose, the active repressor protein binds to the operator and RNA polymerase is unable to bind to the promoter and transcribe the genes for utilization of lactose. As a result, the enzymes needed for the utilization of lactose are not synthesized (Figure 3.3.4A and Figure 3.3.4B). When lactose, the inducer, is present, a metabolite of lactose called allolactose binds to the allosteric repressor protein and causes it to change shape in such a way that it is no longer able to bind to the operator. Now RNA polymerase is able to transcribe the three *lac* operon structural genes and the bacterium is able to synthesize the enzymes required for the utilization of lactose (Figure 3.3.5A and Figure 3.3.5B).

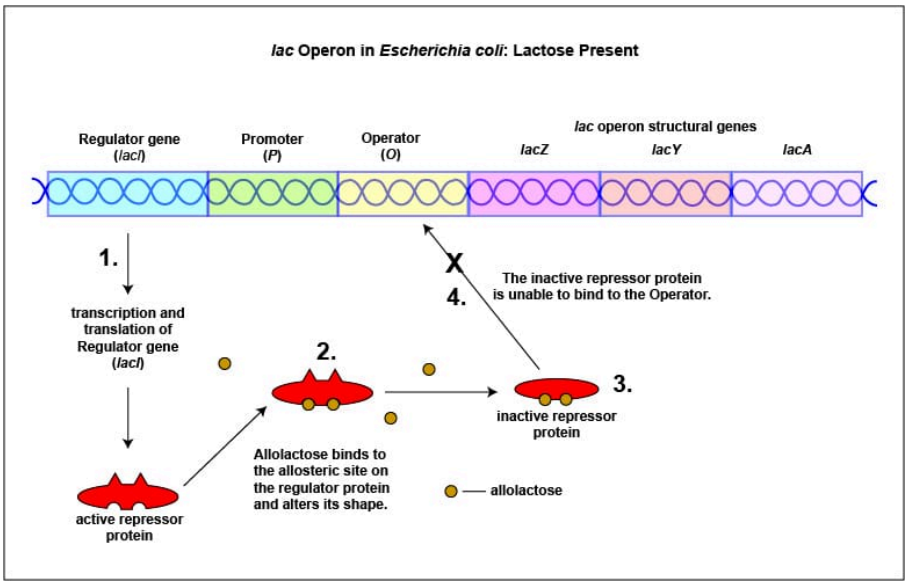


Figure 3.3.5A: An Inducible Operon in the Presence of an Inducer(The Escherichia coli Lactose Operon)Step 1: The Regulator gene codes for an active repressor protein. Step 2: Allolactose (consisting of glucose and galactose), a metebolite of the inducer molecule lactose, binds to the active repressor protein. Step 3: The binding of the inducer alters the shape of the repressor protein making it inactive. Step 4: The inactive repressor protein is no longer able to bind to the Operator region of the lac operon.

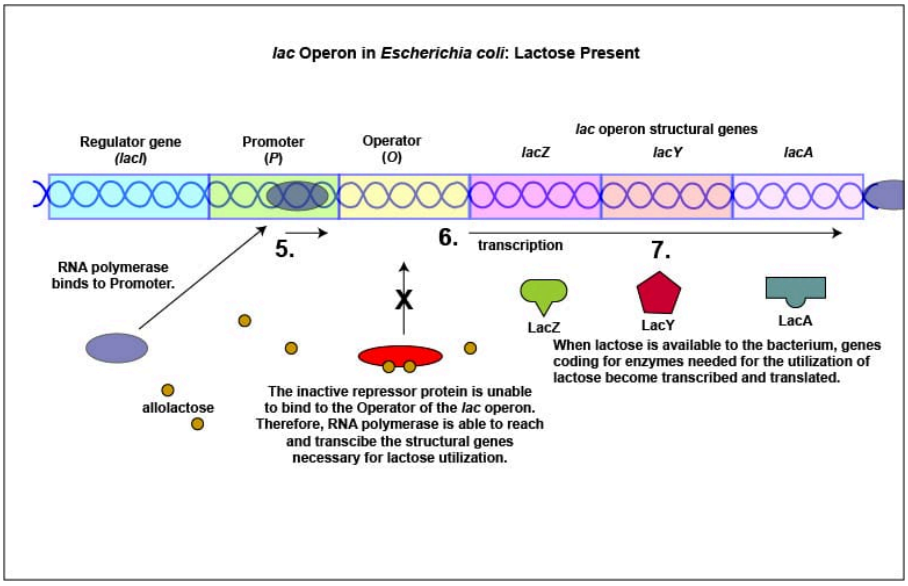


Figure 3.3.5B: An Inducible Operon in the Presence of an Inducer (The Escherichia coli Lactose Operon) Step 5: Since the inactive repressor protein is unable to bind to the Operator region, RNA polymerase (the enzyme responsible for the transcription of genes) is now able to bind to the Promoter region of the lac operon. Step 6: RNA polymerase is now able to transcribe the three lac operon structural genes (lacZ, lacY, and lacA) into mRNA. Step 7: With the transcription of these genes, the enzymes needed for the bacterium to utilize the sugar lactose are now synthesized. The lacZ gene codes for LacZ (beta-galactosidase), an enzyme that breaks down lactose into glucose and galactose. The lacY gene codes for LacY (beta-galactosidase permease), an enzyme which transports lactose into the bacterium. The lacA gene codes for LacA (transacetylase), of uncertain function in lactose catabolism.

b. Activators

Activators are **regulatory proteins** that promote transcription of mRNA. Activators control genes that have a promotor to which RNA polymerase cannot bind. The promotor lies adjacent to a segment of DNA called the activator-binding site. The activator is an allosteric protein synthesized in a form that cannot normally bind to the activator-binding site. As a result, RNA polymerase is unable to bind to the promoter and transcribe the genes (Figure 3.3.6). However, binding of a molecule called an inducer to the activator alters the shape of the activator in a way that now allows it to bind to the activator-binding site. The binding of the activator to the activator-binding site, in turn, enables RNA polymerase to bind to the promotor and initiate transcription (Figure

3.3.7A and Figure 3.3.7B). This is called positive control and is mostly n in catabolic reactions where a bacterium only makes enzymes for the catabolism of a substrate when that substrate is available to the cell.

c. Enhancers

Enhancers are regulatory proteins that bind to DNA located some distance from the operon they control by working with DNA-bending proteins. The DNA-binding proteins bend the DNA in a way that now allows the enhancer to interact with the promoter in such a way that RNA polymerase can now bind and initiate transcription (Figure 3.3.8).

2. Genetic Control of Enzyme Synthesis through Promoter Recognition and through DNA Supercoiling

a. Promoter Recognition: The specific sigma factors that bind to RNA polymerase determine which operon will be transcribed.

b. DNA Supercoiling: DNA supercoiling can change the tertiary shape of a DNA molecule from its normal form to one that has a left-handed twist called Z-DNA. The activities of some promoters are decreased with Z-DNA while others are increased.

3. Genetic Control of Enzyme Synthesis through the Translational Control of Enzyme Synthesis

a. RNA interference (RNAi)

RNA interference (RNAi) is a process whereby small non-coding regulatory RNAs (ncRNAs) such as microRNAs (miRNAs) regulate gene expression. These ncRNAs are regulatory molecules that are complementary to an early portion of the 5' end of the mRNA coding for the enzyme. When the small RNA binds to the mRNA by complementary base pairing , ribosomes cannot attach to the mRNA blocking its translation. As a result, the enzyme is not made (Figure 3.3.9). In bacteria these ncRNAs are often called small RNAs (sRNAs); in animal cells, plant cells, and viruses they are often called microRNAs (miRNA).

b. Ribosomal Proteins (r-proteins)

Ribosomal proteins bind to rRNA to form ribosomal subunits. Because the nucleotide base sequence for the mRNA coding for the r-proteins has similarities to that of the rRNA to which that r-protein binds during subunit formation, r-proteins not yet incorporated into ribosomal subunits can bind to that mRNA and block translation

4. Controlling the Enzyme's Activity (Feedback Inhibition).

Enzyme activity can be controlled by competitive inhibition and non-competitive inhibition.

a. With what is termed non-competitive inhibition , the inhibitor is the end product of a metabolic pathway that is able to bind to a second site (the allosteric site) on the enzyme. Binding of the inhibitor to the allosteric site alters the shape of the enzyme's active site thus preventing binding of the first substrate in the metabolic pathway. In this way, the pathway is turned off (Figure 3.3.10).

b. In the case of what is called competitive inhibition , the inhibitor is the end product of an enzymatic reaction. That end product is also capable of reacting with the enzyme's active site and prevents the enzyme from binding its normal substrate. As a result, the end product is no longer synthesized (Figure 3.3.11).

Summary

1. In living cells there are hundreds of different enzymes working together in a coordinated manner, and since cells neither synthesize nor break down more material than is required for normal metabolism and growth, precise enzyme regulation is required for turning metabolic reactions on and off.
2. There is tremendous diversity in the mechanisms bacteria use to regulate enzyme synthesis and enzyme activity.
3. Ways in which enzymes can be controlled or regulated include controlling the synthesis of the enzyme (genetic control) and

controlling the activity of the enzyme (feedback inhibition).

4. In prokaryotes, genetic control of enzyme activity includes the induction or repression of enzyme synthesis by regulatory proteins that can bind to DNA and either block or enhance the function of RNA polymerase, the enzyme required for transcription.
5. An operon is a set of genes collectively controlled by a regulatory protein.
6. Regulatory proteins may function either as repressors or activators.
7. Repressors are regulatory proteins that block transcription of mRNA by preventing RNA polymerase from transcribing the coding sequence for the enzymes.
8. Some repressors, as in the case of the trp operon, are synthesized in a form that cannot by itself bind to the operator. This is referred to as a repressible system. The binding of a molecule called a corepressor, however, alters the shape of the regulatory protein to a form that can bind to the operator and subsequently block transcription.
9. Some repressors, as in the case of the lac operon, are synthesized in a form that readily binds to the operator and blocks transcription. However, the binding of a molecule called an inducer alters the shape of the regulatory protein in a way that now blocks its binding to the operator and thus permits transcription. This is referred to as an inducible system.
10. Activators are regulatory proteins that promote transcription of mRNA by enabling RNA polymerase to transcribing the coding sequence for the enzymes.
11. Enhancers are regulatory proteins that bind to DNA located some distance from the operon they control by working with DNA-bending proteins. The DNA-bending proteins bend the DNA in a way that now allows the enhancer to interact with the promoter in such a way that RNA polymerase can now bind and initiate transcription
12. Bacteria also use translational control of enzyme synthesis. One method is for the bacteria to produce noncoding RNA (ncRNA) molecules that are complementary to the mRNA coding for the enzyme, and when the small RNA binds to the mRNA by complementary base pairing, ribosomes cannot attach to the mRNA, the mRNA is not transcribed and translated into protein, and the enzyme is not made. In bacteria, these ncRNAs are often called small RNAs (sRNAs).
13. Feedback inhibition controls the activity of the enzyme rather than its synthesis and can be noncompetitive or competitive.
14. In the case of non-competitive inhibition, the inhibitor is the end product of a metabolic pathway that is able to bind the allosteric site on the enzyme. Binding of the inhibitor to the allosteric site alters the shape of the enzyme's active site thus preventing binding of the first substrate in the metabolic pathway. In this way, the pathway is turned off.
15. In the case of what is called competitive inhibition, the inhibitor is the end product of an enzymatic reaction. That end product is also capable of reacting with the enzyme's active site and prevents the enzyme from binding its normal substrate. As a result, the end product is no longer synthesized.

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3.E: Bacterial Genetics (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

3.1: Horizontal Gene Transfer in Bacteria

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define horizontal gene transfer.
2. State three mechanisms of horizontal gene transfer in bacteria.
3. Briefly describe the mechanisms for transformation in bacteria.
4. Briefly describe the mechanism of generalized transduction in bacteria.
5. Briefly describe the following mechanisms of horizontal gene transfer in bacteria:
    a. Transfer of conjugative plasmids in gram-negative bacteria
    b. F+ conjugation
6. Describe R-plasmids, R-plasmid conjugation, and the significance of R-plasmids to medical microbiology.
7. Multiple Choice

3.2: Bacterial Quorum Sensing, Pathogenicity Islands, and Secretion Systems (Injectosomes)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define pathogenicity.
2. Define virulence.
3. Even though a microorganism may be considered pathogenic, it still may not be able to cause disease upon entering the body. Discuss why.
4. Define and briefly describe the overall process of quorum sensing in bacteria and how it may enable bacteria to behave as a multicellular population.
5. Multiple Choice

3.3: Enzyme Regulation

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching

    _____ Regulatory proteins that block transcription of mRNA by binding to a portion of DNA called the operator that lies downstream of a promoter.

    _____ A molecule that alters the shape of the regulatory protein in a way that blocks its binding to the operator and thus permits transcription.

    _____ Regulatory proteins that promote transcription of mRNA.

    _____ A molecule that alters the shape of the regulatory protein to a form that can bind to the operator and block transcription.

_____ Producing antisense RNA that is complementary to the mRNA coding for the enzyme. When the antisense RNA binds to the mRNA by complementary base pairing, the mRNA cannot be translated into protein and the enzyme is not made.

_____ The induction or repression of enzyme synthesis by regulatory proteins that can bind to DNA and either block or enhance the function of RNA polymerase.

_____ The inhibitor is the end product of a metabolic pathway that is able to bind to a second site (the allosteric site) on an enzyme. Binding of the inhibitor to the allosteric site alters the shape of the enzyme's active site thus preventing binding of the first substrate in the metabolic pathway.

_____ The inhibitor is the end product of an enzymatic reaction. That end product is also capable of reacting with the enzyme's active site and prevents the enzyme from binding its normal substrate.

____Regulatory proteins that bind to DNA located some distance from the operon they control by working with DNA-bending proteins that enable RNA polymerase can to bind to a promoter and initiate transcription.

A. activators
B. competitive inhibition
C. corepressors
D. genetic control
E. inducer
F. non-competitive inhibition
G. repressors
H. translational control
I. enhancers

2. Describe how the *lac* operon in *E. coli* functions as an inducible operon.

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4.1: An Overview to Control of Microorganisms

selective toxicity

- broad spectrum antibiotic
- narrow spectrum antibiotic
- antibiotic
- chemotherapeutic synthetic drug
- cidal
- static
- sterilization
- disinfection
- disinfectant
- antiseptic
- physical agent

Control of microorganisms is essential in order to prevent the transmission of diseases and infection, stop decomposition and spoilage, and prevent unwanted microbial contamination. Microorganisms are controlled by means of physical agents and chemical agents. Physical agents include such methods of control as high or low temperature, desiccation, osmotic pressure, radiation, and filtration. Control by chemical agents refers to the use of disinfectants, antiseptics, antibiotics, and chemotherapeutic antimicrobial chemicals.

In this unit we will concentrate on the chemical control of microbial growth with a special emphasis on the antibiotics and chemotherapeutic antimicrobial chemicals used in treating bacterial infections. Control of microorganisms by means of physical agents will be covered in Lab 18 and control by means of disinfectants, antiseptics, and sanitizers will be discussed in Lab 19.

The basis of chemotherapeutic control of bacteria is selective toxicity. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host. A broad spectrum agent is one generally effective against a variety of Gram-positive and Gram-negative bacteria; a narrow spectrum agent generally works against just Gram-positives, Gram-negatives, or only a few bacteria. As mentioned above, such agents may be cidal or static in their action. A cidal agent kills the organism while a static agent inhibits the organism's growth long enough for body defenses to remove it.

There are two categories of antimicrobial chemotherapeutic agents: antibiotics and synthetic drugs. Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Chemotherapeutic synthetic drugs are antimicrobial drugs synthesized by chemical procedures in the laboratory. Many of today's antibiotics are now actually semi-synthetic and some are even made synthetically.

Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Why then do bacteria produce antibiotics? There is growing support for multiple actions for microbial antibiotic production:

- If produced in large enough amounts, antibiotics may be used as a weapon to inhibit or kill other microbes in the vicinity to reduce competition for food.
- Antibiotics produced in sublethal quantities may function as interspecies quorum sensing molecules enabling a number of different bacteria to form within a common biofilm where metabolic end products of one organism may serve as a substrate for another. All the organisms are protected within the same biofilm.
- Antibiotics produced in sublethal quantities may function as interspecies quorum sensing molecules enabling some bacteria to manipulate others to become motile and swim away thus reducing the competition for food.
- Antibiotics action may result in the degradation of bacterial cell walls or DNA and these products can act as cues that trigger other bacteria to produce a protective biofilm.
- Antibiotics produced in sublethal quantities may trigger intraspecies quorum sensing. Exposure to low concentrations of an antibiotic may trigger bacteria to produce quorum sensing molecules that trigger the population to produce a protective biofilm. The biofilm then protects the population from greater concentrations of the antibiotic.

Summary

1. Physical control includes such methods of control as high or low temperature, desiccation, osmotic pressure, radiation, and filtration.
2. Chemical control refers to the use of disinfectants, antiseptics, antibiotics, and chemotherapeutic antimicrobial chemicals.
3. Sterilization is the process of destroying all living organisms and viruses.
4. Disinfection is the elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces.
5. Decontamination is the treatment of an object or inanimate surface to make it safe to handle.
6. A disinfectant is an agents used to disinfect inanimate objects but generally to toxic to use on human tissues.
7. An antiseptic is an agent that kills or inhibits growth of microbes but is safe to use on human tissue.
8. A sanitizer is an agent that reduces microbial numbers to a safe level.
9. An antibiotic is a metabolic product produced by one microorganism that inhibits or kills other microorganisms.
10. Synthetic chemicals that can be used therapeutically.
11. An agent that is cidal in action kills microorganisms.
12. An agent that is static in action inhibits the growth of microorganisms.
13. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host.
14. A broad spectrum agent is one generally effective against a variety of Gram-positive and Gram-negative bacteria.
15. A narrow spectrum agent generally works against just Gram-positives, Gram-negatives, or only a few bacteria.

Glossary

Basic terms used in discussing the control of microorganisms include:

1. **Sterilization**
Sterilization is the process of destroying all living organisms and viruses. A sterile object is one free of all life forms, including bacterial endospores, as well as viruses.

2. **Disinfection**
Disinfection is the elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces.

3. **Decontamination**
Decontamination is the treatment of an object or inanimate surface to make it safe to handle.

4. **Disinfectant**
A disinfectant is an agents used to disinfect inanimate objects but generally to toxic to use on human tissues.

5. **Antiseptic**
An antiseptic is an agent that kills or inhibits growth of microbes but is safe to use on human tissue.

6. **Sanitizer**
A sanitizer is an agent that reduces microbial numbers to a safe level.

7. **Antibiotic**
An antibiotic is a metabolic product produced by one microorganism that inhibits or kills other microorganisms.

8. **Chemotherapeutic synthetic drugs**
Synthetic chemicals that can be used therapeutically.

9. **Cidal**
An agent that is cidal in action will kill microorganisms and viruses.

10. **Static**
An agent that is static in action will inhibit the growth of microorganisms.

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4.2: Ways in which Chemical Control Agents Affect Bacteria

Learning Objectives

- Describe six different ways antibiotics or disinfectants may affect bacterial structures or macromolecules and state how each ultimately causes harm to the cell.
- State which of the following groups of antibiotics: 1) inhibit peptidoglycan synthesis; 2) inhibit nucleic acid synthesis; 3) alter bacterial 30S ribosomal subunits blocking translation; or 4) alter bacterial 50S ribosomal subunits blocking translation.
  a. macrolides(erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc.), oxazolidinones (linezolid), and streptogramins
  b. penicillins, monobactams, carbapenems, cephalosporins, and vancomycin
  c. fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.), sulfonamides and trimethoprim, and metronidazole
  d. aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc.) and tetracyclines (tetracycline, doxycycline, demeclocycline, minocycline, etc.)
- State two modes of action for disinfectants, antiseptics, and sanitizers.

The basis of chemotherapeutic control of bacteria is selective toxicity. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host. A broad spectrum agent is one generally effective against a variety of Gram-positive and Gram-negative bacteria; a narrow spectrum agent generally works against just Gram-positives, Gram-negatives, or only a few bacteria. Such agents may be cidal or static in their action. A cidal agent kills the organism while a static agent inhibits the organism's growth long enough for body defenses to remove it. There are two categories of antimicrobial chemotherapeutic agents: antibiotics and synthetic drugs. Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Synthetic drugs are antimicrobial drugs synthesized by chemical procedures in the laboratory. Many of today's antibiotics are now actually semisynthetic and some are even made synthetically. We will now look at the various ways in which our control agents affect bacteria altering their structures or interfering with their cellular functions.

- Describe one way an antibiotic can inhibit peptidoglycan synthesis, state how that ultimately kills the bacterium, and give an example of such an antibiotic.
- Describe one way an antibiotic can alter bacterial ribosomes, state how that ultimately inhibits or kills the bacterium, and give an example of such an antibiotic.
- Describe one way an antibiotic can interfere with bacterial DNA synthesis, state how that ultimately kills the bacterium, and give an example of such an antibiotic

Many Antibiotics inhibit Synthesis of Peptidoglycan and cause Osmotic Lysis

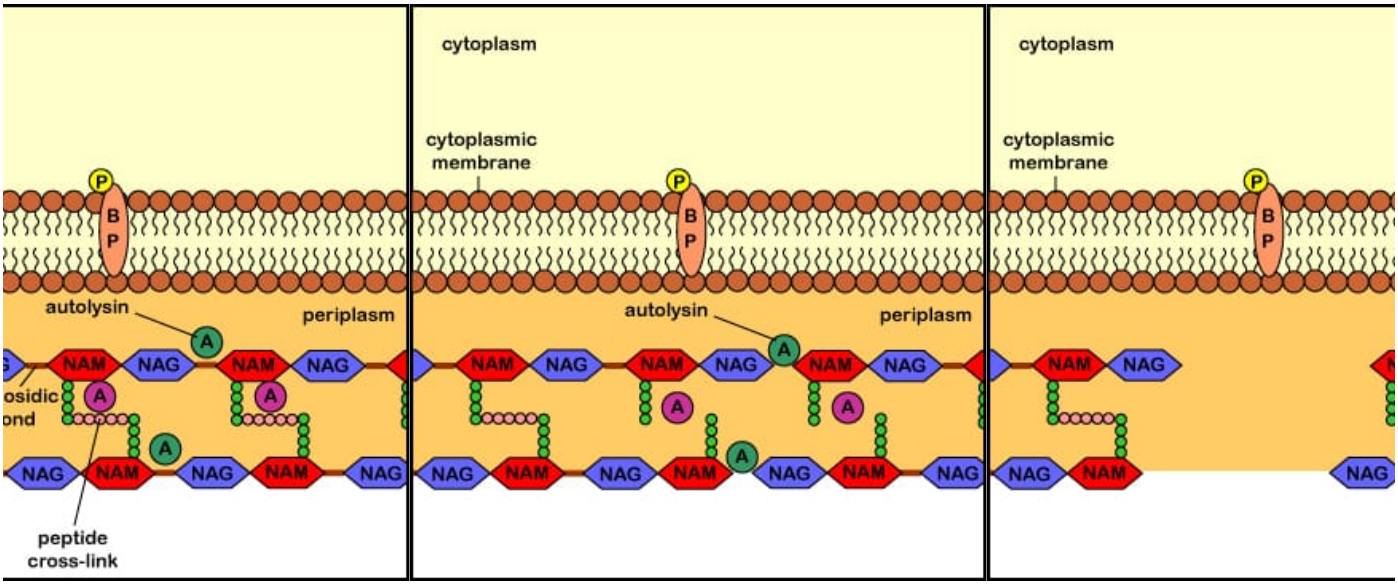


Figure 4.2.4.2.4: Action of Transpeptidase in Peptidoglycan Synthesis. (Step 1) Finally, transpeptidase enzymes reform the peptide cross-links between the rows and layers of peptidoglycan to make the wall strong.

Interference with this process results in the formation of a weak cell wall and osmotic lysis of the bacterium. Agents that inhibit peptidoglycan synthesis include the penicillins (penicillin G, methicillin, oxacillin, ampicillin, amoxicillin, ticarcillin, etc.), the cephalosporins (cephalothin, cefazolin, cefoxitin, cefotaxime, cefaclor, cefoperazone, cefixime, ceftriaxone, cefuroxime, etc.), the carbapenems (imipenem, metropenem), the monobactems (aztreonem), and the carbacephems (loracarbef). Penicillins, monobactams, carbapenems, and cephalosporins are known chemically as beta-lactam antibiotics because they all share a molecular structure called a beta-lactam ring (see Figure 4.2.5). The glycopeptides (vancomycin, teichoplanin) and lipopeptides (daptomycin) also inhibit peptidoglycan synthesis.

a. Beta lactam antibiotics such as penicillins and cephalosporins

Penicillins, cephalosporins, as well as other beta-lactam antibiotics (see Common Antibiotics), bind to the transpeptidase enzymes (also called penicillin-binding proteins) responsible for reforming the peptide cross-links between rows and layers of peptidoglycan of the cell wall as new peptidoglycan monomers are added during bacterial cell growth. This binding blocks the transpeptidase enzymes from cross-linking the sugar chains and results in a weak cell wall. In addition, these antibiotics appear to interfere with the bacterial controls that keep autolysins in check, with resulting degradation of the peptidoglycan and osmotic lysis of the bacterium (Figure 4.2.6).

Flash animation illustrating how penicillins inhibit peptidoglycan synthesis.

html5 version of animation for iPad showing how penicillins inhibit the synthesis of peptidoglycan.

Flash animation showing how penicillins inhibit peptidoglycan synthesis.
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YouTube movie showing lysis of *E. coli* after exposure to a penicillin #1

YouTube movie showing lysis of *E. coli* after exposure to a penicillin #2

b. Glycopeptides

Glycopeptides such as vancomycin (see Common Antibiotics) and the lipoglycopeptide teichoplanin bind to the D-Ala-D-Ala portion of the pentapeptides of the peptidoglycan monomers and block the formation of gycosidic bonds between the sugars by the transgycosidase enzymes, as well as the formation of the peptide cross-links by the transpeptidase enzymes. This results in a weak cell wall and subsequent osmotic lysis of the bacterium (see Figure 4.2.7).

Flash animation illustrating how vancomycins inhibit peptidoglycan synthesis.

html5 version of animation for iPad illustrating how vancomycins inhibit peptidoglycan synthesis.

Flash animation showing how vancomycin inhibit peptidoglycan synthesis.
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c. Bacitracin

Bacitracin (see Common Antibiotics) binds to the transport protein bactoprenol after it inserts a peptidoglycan monomer into the growing cell wall. It subsequently prevents the dephosphorylation of the bactoprenol after it releases the monomer it has transported across the membrane. Bactoprenol molecules that have not lost the second phosphate group cannot assemble new monomers and transport them across the cytoplasmic membrane. As a result, no new monomers are inserted into the growing cell wall. As the autolysins continue to break the peptide cross-links and new cross-links fail to form, the bacterium bursts from osmotic lysis (see Figure 4.2.8).

Flash animation illustrating how bacitracin inhibit peptidoglycan synthesis.

html5 version of animation for iPad illustrating how bacitracin inhibit peptidoglycan synthesis.

Flash animation showing how bacitracin inhibit peptidoglycan synthesis.
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Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

A few antimicrobial chemotherapeutic agents inhibit normal synthesis of the acid-fast cell wall

A few antimicrobial chemotherapeutic agents inhibit normal synthesis of the acid-fast cell wall of the genus *Mycobacterium* (see Common Antibiotics).. INH(isoniazid) appears to block the synthesis of mycolic acid, a key component of the acid-fast cell wall of mycobacteria (see Figure 4.2.9). Ethambutol interferes with the synthesis of the outer membrane of acid-fast cell walls (see Figure 4.2.9).

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

A very few antibiotics alter the bacterial cytoplasmic membrane causing leakage of molecules and enzymes needed for normal bacterial metabolism.

A very few antibiotics, such as polymyxins, colistins, and daptomycin (Common Antibiotics), as well as many disinfectants and antiseptics, such as orthophenylphenol, chlorhexidine, hexachlorophene, zephiran, alcohol, and triclosans, alter the bacterial cytoplasmic membrane causing leakage of molecules and enzymes needed for normal bacterial metabolism.

a. Polymyxins and colistins act as detergents and alter membrane permeability in Gram-negative bacteria. They cannot effectively diffuse through the thick peptidoglycan layer in gram-positives.
b. Daptomycin disrupts the bacteria cytoplasmic membrane function by apparently binding to the membrane and causing rapid depolarization. This results on a loss of membrane potential and leads to inhibition of protein, DNA and RNA synthesis, resulting in bacterial cell death.
c. Pyrazinamide inhibits fatty acid synthesis in the membranes of *Mycobacterium tuberculosis*.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

Some antimicrobial chemotherapeutic agents inhibit normal nucleic acid replication in bacteria (see Common Antibiotics).

a. Fluoroquinolones

Fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, gatifloxacin, etc., (Common Antibiotics)) work by inhibiting one or more of a group of enzymes called topoisomerase, enzymes needed for supercoiling, replication, and separation of circular bacterial DNA (see Figure 4.2.10). For example, DNA gyrase (topoisomerase II) catalyzes the negative supercoiling of the circular DNA found in bacteria. It is critical in bacterial DNA replication, DNA repair, transcription of DNA into RNA, and genetic recombination. Topoisomerase IV, on the other hand, is involved in the relaxation of the supercoiled circular DNA, enabling the separation of the interlinked daughter chromosomes at the end of bacterial DNA replication.

In Gram-negative bacteria, the main target for fluoroquinolones is DNA gyrase (topoisomerase II), an enzyme responsible for supercoiling of bacterial DNA during DNA replication; in Gram-positive bacteria, the primary target is topoisomerase IV, an enzyme responsible for relaxation of supercoiled circular DNA and separation of the inter-linked daughter chromosomes.

Flash animation illustrating a normal bacterial enzyme reaction.

html5 version of animation for iPad illustrating a normal bacterial enzyme reaction.

Flash animation illustrating antimicrobial agents may inactivate a bacterial enzyme.

html5 version of animation for iPad illustrating antimicrobial agents may inactivate a bacterial enzyme.

For More Information: The Nucleoid from Unit 1.

b. Sulfonamides

Sulfonamides (sulfamethoxazole, sulfanilamide) and diaminopyrimidines (trimethoprim) (see Common Antibiotics) block enzymes in the bacteria pathway required for the synthesis of tetrahydrofolic acid, a cofactor needed for bacteria to make the nucleotide bases thymine, guanine, uracil, and adenine (see Figure 4.2.11).

This is done through a process called competitive antagonism whereby a drug chemically resembles a substrate in a metabolic pathway. Because of their similarity, either the drug or the substrate can bind to the substrate's enzyme. While the enzyme is bound to the drug, it is unable to bind to its natural substrate and that blocks that step in the metabolic pathway (see Figure 4.2.12). Typically, a sulfonamide and a diaminopyrimidine are combined. Co-trimoxazole, for example, is a combination of sulfamethoxazole and trimethoprim.

Flash animation showing competitive antagonism.

html5 version of animation for iPad showing competitive antagonism.

Sulfonamides such as sulfamethoxazole tie up the first enzyme in the pathway, the conversion of para-aminobenzoic acid to dihydropteroic acid (see Figure 4.2.11). Trimethoprim binds to the third enzyme in the pathway, an enzyme that is responsible for converting dihydrofolic acid to tetrahydrofolic acid (see Figure 4.2.11). Without the tetrahydrofolic acid, the bacteria cannot synthesize DNA or RNA.

c. Metronidazole

Metronidazole (see Common Antibiotics) is a drug that is activated by the microbial proteins flavodoxin and feredoxin found in microaerophilc and anaerobic bacteria and certain protozoans. Once activated, the metronidazole puts nicks in the microbial DNA strands.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

d. Rifampin

Rifampin (rifamycin) (see Common Antibiotics) blocks transcription by inhibiting bacterial RNA polymerase, the enzyme responsible for transcription of DNA to mRNA.

For More Information: Transcription from Unit 7

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Alter Prokaryotic Ribosomal Subunits, Inhibit RNA Polymerase, and Denature Enzymes

Many antibiotics alter bacterial ribosomes, interfering with translation of mRNA into proteins and thereby causing faulty protein synthesis (see Common Antibiotics).

To learn more detail about the specific steps involved in translation during bacterial protein synthesis, see the animation that follows. Protein synthesis is discussed in greater detail in Unit 6.

For More Information: Ribosomes from Unit 1

For More Information: Translation from Unit 7

Flash animation illustrating the early stages of translation during bacterial protein synthesis.

html5 version of animation for iPad illustrating the early stages of translation during bacterial protein synthesis.

a. Aminoglycosides

The aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc. (see Common Antibiotics)) bind irreversibly to the 16S rRNA in the 30S subunit of bacterial ribosomes. Although the exact mechanism of action is still uncertain, there is evidence that some prevent the transfer of the peptidyl tRNA from the A-site to the P-site, thus preventing the elongation of the polypeptide chain. Some aminoglycosides also appear to interfere with the proofreading process that helps assure the accuracy of translation (see Figure 4.2.13). Possibly the antibiotics reduce the rejection rate for tRNAs that are near matches for the codon. This leads to misreading of the codons or premature termination of protein synthesis (see Figure 4.2.14). Aminoglycosides may also interfere directly or indirectly with the function of the bacterial cytoplasmic membrane. Because of their toxicity, aminoglycosides are generally used only when other first line antibiotics are not effective.

Flash animation illustrating aminoglycosides preventing the translocation of tRNA from the A-site to the P-site of bacterial ribosomes.

html5 version of animation for iPad illustrating aminoglycosides preventing the translocation of tRNA from the A-site to the P-site of bacterial ribosomes.

Flash animation illustrating aminoglycosides causing a misreading of codons.

html5 version of animation for iPad illustrating aminoglycosides causing a misreading of codons.

b. Tetracyclines

The tetracyclines (tetracycline, doxycycline, demeclocycline, minocycline, etc. (see Common Antibiotics)) bind reversibly to the 16S rRNA in the 30S ribosomal subunit, distorting it in such a way that the anticodons of charged tRNAs cannot align properly with the codons of the mRNA (see Figure 4.2.15).

Flash animation illustrating how tetracyclines bind to the 30S ribosomal subunit and block translation.

html5 version of animation for iPad illustrating how tetracyclines bind to the 30S ribosomal subunit and block translation.

c. Macrolides

The macrolides (erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc. (see Common Antibiotics)) bind reversibly to the 23S rRNA in the 50S subunit of bacterial ribosomes. They appear to inhibit elongation of the protein by preventing the enzyme peptidyltransferase from forming peptide bonds between the amino acids (see Figure 4.2.16). They may also prevent the transfer of the peptidyl tRNA from the A-site to the P-site (see Figure 4.2.17) as the beginning peptide chain on the peptidyl tRNA adheres to the ribosome, creates friction, and blocks the exit tunnel of the 50S ribosomal subunit.

Flash animation illustrating how macrolides bind to the 50S ribosomal subunit and block translation by blocking peptidyltransferase.

Flash animation illustrating how macrolides bind to the 50S ribosomal subunit and block translation by preventing the transfer of the peptidyl tRNA from the A-site to the P-site.

html5 version of animation for iPad illustrating how macrolides bind to the 50S ribosomal subunit and block translation by blocking peptidyltransferase.

html5 version of animation for iPad illustrating how macrolides bind to the 50S ribosomal subunit and block translation by preventing the transfer of the peptidyl tRNA from the A-site to the P-site.

d. Oxazolidinones

The oxazolidinones (linezolid, sivextro) (see Common Antibiotics), following the first cycle of protein synthesis, interfere with

translation sometime before the initiation phases. They appear to bind to the 50S ribosomal subunit and interfere with its binding to the initiation complex (see Figure 4.2.18).

Flash animation illustrating how oxazolidinones block the binding of the 50S ribosomal subunit to the initiation complex.

html5 version of animation for iPad illustrating how oxazolidinones block the binding of the 50S ribosomal subunit to the initiation complex.

e. Streptogramins

The streptogramins (synercid, a combination of quinupristin and dalfopristin (see Common Antibiotics)) bind to two different locations on the 23S rRNA in the 50S ribosomal subunit and work synergistically to block translation. There are reports that the streptogramins may inhibit the attachment of the charged tRNA to the A-site or may block the peptide exit tunnel of the 50S ribosomal subunit.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Alter Prokaryotic Ribosomal Subunits, Inhibit RNA Polymerase, and Denature Enzymes

For a more detailed description of any specific antimicrobial agent, see the website of RxList - The Internet Drug Index.

Modes of action for disinfectants, antiseptics, and sanitizers

Disinfection is the elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces, whereas decontamination is the treatment of an object or inanimate surface to make it safe to handle. Sterilization is the process of destroying all living organisms and viruses. A sterile object is one free of all life forms, including bacterial endospores, as well as viruses.

The term disinfectant is used for an agent used to disinfect inanimate objects or surfaces but is generally too toxic to use on human tissues. An antiseptic refers to an agent that kills or inhibits growth of microbes but is safe to use on human tissue. A sanitizer describes an agent that reduces microbial numbers to a safe level. Because disinfectants and antiseptics often work slowly on some viruses - such as the hepatitis viruses, bacteria with an acid-fast cell wall such as *Mycobacterium tuberculosis*, and especially bacterial endospores, produced by the genus *Bacillus* and the genus *Clostridium*, they are usually unreliable for sterilization - the destruction of all life forms.

There are a number of factors which influence the antimicrobial action of disinfectants and antiseptics, including:

1. The concentration of the chemical agent.
2. The temperature at which the agent is being used. Generally, the lower the temperature, the longer it takes to disinfect or decontaminate.
3. The kinds of microorganisms present. Endospore producers such as *Bacillus* species, *Clostridium* species, and acid-fast bacteria like *Mycobacterium tuberculosis* are harder to eliminate.
4. The number of microorganisms present. The more microorganisms present, the harder it is to disinfect or decontaminate.
5. The nature of the material bearing the microorganisms. Organic material such as dirt and excreta interferes with some agents.

The best results are generally obtained when the initial microbial numbers are low and when the surface to be disinfected is clean and free of possible interfering substances.

Concept map for Lab 19 - Using disinfectants, antisepticics, and sanitizers to control microorganisms

There are 2 common antimicrobial modes of action for disinfectants, antiseptics, and sanitizers:

1. They may damage the lipids and/or proteins of the semipermeable cytoplasmic membrane of microorganisms resulting in leakage of cellular materials needed to sustain life.

2. They may denature microbial enzymes and other proteins, usually by disrupting the hydrogen and disulfide bonds that give the protein its three-dimensional functional shape. This blocks metabolism.

A large number of such chemical agents are in common use. Some of the more common groups are listed below:

1. Phenol and phenol derivatives: Phenol (5-10%) was the first disinfectant commonly used. However, because of its toxicity and odor, phenol derivatives (phenolics) are now generally used. The most common phenolic is orthophenylphenol, the agent found in O-syl®, Staphene®, and Amphyl®. Bisphenols contain two phenolic groups and typically have chlorine as a part of their structure. They include hexachlorophene and triclosan. Hexachlorophene in a 3% solution is combined with detergent and is found in PhisoHex®. Triclosan is an antiseptic very common in antimicrobial soaps and other products. Biguanides include chlorhexadine and alexidine. A 4% solution of chlorhexidine in isopropyl alcohol and combined with detergent (Hibiclens® and Hibitane®) is a common hand washing agent and surgical handscrub. These agents kill most bacteria, most fungi, and some viruses, but are usually ineffective against endospores. Chloroxylenol (4-chloro-3,5-dimethylphenol) is a broad spectrum antimicrobial chemical compound used to control bacteria, algae, fungi and virus and is often used in antimicrobial soaps and antiseptics. Phenol and phenolics alter membrane permeability and denature proteins. Bisphenols, biguanides, and chloroxylenol alter membrane permeability.

2. Soaps and detergents: Soaps are only mildly microbicidal. Their use aids in the mechanical removal of microorganisms by breaking up the oily film on the skin (emulsification) and reducing the surface tension of water so it spreads and penetrates more readily. Some cosmetic soaps contain added antiseptics to increase antimicrobial activity.

Detergents may be anionic or cationic. Anionic (negatively charged) detergents, such as laundry powders, mechanically remove microorganisms and other materials but are not very microbicidal. Cationic (positively charged) detergents alter membrane permeability and denature proteins. They are effective against many vegetative bacteria, some fungi, and some viruses. However, bacterial endospores and certain bacteria such as *Mycobacterium tuberculosis and Pseudomonas* species are usually resistant. Soaps and organic materials like excreta also inactivate them. Cationic detergents include the quaternary ammonium compounds such as benzalkonium chloride, zephiran®, diaprene, roccal, ceepryn, and phemerol. Household Lysol® contains alkyl dimethyl benzyl ammonium chloride and alcohols.

3. Alcohols

70% solutions of ethyl or isopropyl alcohol are effective in killing vegetative bacteria, enveloped viruses, and fungi. However, they are usually ineffective against endospores and non-enveloped viruses. Once they evaporate, their cidal activity will cease. Alcohols denature membranes and proteins and are often combined with other disinfectants, such as iodine, mercurials, and cationic detergents for increased effectiveness.

4. Acids and alkalies

Acids and alkalies alter membrane permeability and denature proteins and other molecules. Salts of organic acids, such as calcium propionate, potassium sorbate, and methylparaben, are commonly used as food preservatives. Undecylenic acid (Desenex®) is used for dermatophyte infections of the skin. An example of an alkali is lye (sodium hydroxide).

5. Heavy metals

Heavy metals, such as mercury, silver, and copper, denature proteins. Mercury compounds (mercurochrome, metaphen, merthiolate) are only bacteriostatic and are not effective against endospores. Silver nitrate (1%) is sometimes put in the eyes of newborns to prevent gonococcal ophthalmia. Copper sulfate is used to combat fungal diseases of plants and is also a common algicide. Selinium sulfide kills fungi and their spores.

6. Chlorine

Chlorine gas reacts with water to form hypochlorite ions, which in turn denature microbial enzymes. Chlorine is used in the chlorination of drinking water, swimming pools, and sewage. Sodium hypochlorite is the active agent in household bleach. Calcium hypochlorite, sodium hypochlorite, and chloramines (chlorine plus ammonia) are used to sanitize glassware, eating utensils, dairy and food processing equipment, hemodialysis systems, and treating water supplies.

7. Iodine and iodophores

Iodine also denatures microbial proteins. Iodine tincture contains a 2% solution of iodine and sodium iodide in 70% alcohol. Aqueous iodine solutions containing 2% iodine and 2.4% sodium iodide are commonly used as a topical antiseptic.

Iodophores are a combination of iodine and an inert polymer such as polyvinylpyrrolidone that reduces surface tension and slowly releases the iodine. Iodophores are less irritating than iodine and do not stain. They are generally effective against vegetative bacteria, *Mycobacterium tuberculosis*, fungi, some viruses, and some endospores. Examples include Wescodyne®, Ioprep®, Ioclide®, Betadine®, and Isodine®.

8. Aldehydes

Aldehydes, such as formaldehyde and glutaraldehyde, denature microbial proteins. Formalin (37% aqueous solution of formaldehyde gas) is extremely active and kills most forms of microbial life. It is used in embalming, preserving biological specimens, and in preparing vaccines. Alkaline glutaraldehyde (Cidex®), acid glutaraldehyde (Sonacide®), and glutaraldehyde phenate solutions (Sporocidin®) kill vegetative bacteria in 10-30 minutes and endospores in about 4 hours. A 10 hour exposure to a 2% glutaraldehyde solution can be used for cold sterilization of materials. *Ortho*-phthalaldehyde (OPA) is dialdehyde used as a high-level disinfectant for medical instruments.

9. Peroxygens

Peroxygens are oxidizing agents that include hydrogen peroxide and peracetic acid. Hydrogen peroxide is broken down into water and oxygen by the enzyme catalase in human cells and is not that good of an antiseptic for open wounds but is useful for disinfecting inanimate objects. The high concentrations of hydrogen peroxide overwhelm the catalase found in microbes. Peracetic acid is a disinfectant that kills microorganisms by oxidation and subsequent disruption of their cytoplasmic membrane. It is widely used in health care, food processing, and water treatment.

10. Ethylene oxide gas

Ethylene oxide is one of the very few chemicals that can be relied upon for sterilization (after 4-12 hours exposure). Since it is explosive, it is usually mixed with inert gases such as freon or carbon dioxide. Gaseous chemosterilizers, using ethylene oxide, are commonly used to sterilize heat-sensitive items such as plastic syringes, petri plates, textiles, sutures, artificial heart valves, heart-lung machines, and mattresses. Ethylene oxide has very high penetrating power and denatures microbial proteins. Vapors are toxic to the skin, eyes, and mucous membranes and are also carcinogenic. Another gas that is used as a sterilant is chlorine dioxide which denatures proteins in vegetative bacteria, bacterial endospores, viruses, and fungi.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function:
Agents that Alter Prokaryotic Ribosomal Subunits,
Inhibit RNA Polymerase, and Denature Enzymes

Summary

1. Many antibiotics (penicillins, cephalosporins, vancomycin, bacitracin) inhibit normal synthesis of peptidoglycan by bacteria and cause osmotic lysis. They do this by inactivating the enzymes or the transporters involved in peptidoglycan synthesis.
2. A few antimicrobial chemotherapeutic agents (INH, ethambutol) inhibit normal synthesis of the acid-fast cell wall.
3. A very few antibiotics (polymyxin, colistin, daptomycin) alter the bacterial cytoplasmic membrane causing leakage of molecules and enzymes needed for normal bacterial metabolism.
4. Some antimicrobial chemotherapeutic agents (fluoroquinolones, sulfonamides, trimethoprim) inhibit normal nucleic acid replication in bacteria.
5. Many antibiotics (tetracyclines, macrolides, oxazolidinones, streptogramins) alter bacterial ribosomes, interfering with translation of mRNA into proteins and thereby causing faulty protein synthesis.
6. There are 2 common antimicrobial modes of action for disinfectants, antiseptics, and sanitizers: damaging the lipids and/or proteins of the semipermeable cytoplasmic membrane of microorganisms resulting in leakage of cellular materials; and denaturing microbial enzymes and other proteins.
7. A number of factors which influence the antimicrobial action of disinfectants and antiseptics, including the concentration of the chemical agent, the temperature at which the agent is being used, the kinds of microorganisms present, the number of microorganisms present, and the nature of the material bearing the microorganisms.
8. Endospore producers such as Bacillus species, Clostridium species, and acid-fast bacteria like Mycobacterium tuberculosis are harder to eliminate.

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4: USING ANTIBIOTICS AND CHEMICAL AGENTS TO CONTROL BACTERIA

4.1: An Overview to Control of Microorganisms
4.2: Ways in which Chemical Control Agents Affect Bacteria
4.3: Ways in which Bacteria May Resist Chemical Control Agents
4.E: Using Antibiotics and Chemical Agents to Control Bacteria (Exercises)

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4.3: Ways in which Bacteria May Resist Chemical Control Agents

Name two bacteria that have low-permeability membrane barriers and are thereby intrinsically resistant to many antibiotics.

- Briefly describe 4 different mechanisms as a result of genetic changes in a bacterium that may enable that bacterium to resist an antibiotic.
- Describe R (Resistance) plasmids and state their significance to medical microbiology.
- State what the following stand for: MRSA, VRE,CRE, and XDR TB.
- Define antibiotic tolerance.

The basis of chemotherapeutic control of bacteria is selective toxicity. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host. A broad spectrum agent is one generally effective against a variety of gram-positive and gram-negative bacteria; a narrow spectrum agent generally works against just gram-positives, gram-negatives, or only a few bacteria. Such agents may be cidal or static in their action. A cidal agent kills the organism while a static agent inhibits the organism's growth long enough for body defenses to remove it. There are two categories of antimicrobial chemotherapeutic agents: antibiotics and synthetic drugs. Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Synthetic drugs are antimicrobial drugs synthesized by chemical procedures in the laboratory. Many of today's antibiotics are now actually semisynthetic and some are even made synthetically.

We will now look at the two sides of the story with regards to controlling bacteria by means of chemicals:

1. Ways in which Our Control Agents Affect Bacterial Structures or Function
2. Ways in which Bacteria May Resist Our Control Agents

We will now look at the various ways in which bacteria become resistant to our control agents.

Some opportunistic pathogens, such as *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, and *Enterococcus* species, have low-permeability membrane barriers and are thereby intrinsically resistant to many antibiotics. Most bacteria, however, become resistant to antibiotics as a result of mutation or horizontal gene transfer. Mutation in bacterial DNA can alter the order of nucleotide bases in a gene and alter that gene product. Horizontal gene transfer can alter or add bacterial genes, again altering the bacterium's gene products. See function of DNA.

Most bacteria, become resistant to antibiotics by way of one or more of the following mechanisms that are coded for by genes in the bacterial chromosomeor in plasmids:

1. Producing an enzyme capable of inactivating the antibiotic;
2. Altering the target site receptor for the antibiotic to reduce or block its binding;
3. Preventing the entry of the antibiotic into the bacterium and/or using an efflux pump to transport the antibiotic out of the bacterium; and/or
4. Modulating gene expression to produce more of the bacterial enzyme that is being tied up or altered by the antibiotic.

Nice summary of antibiotic resistant cases and associated deaths; from the CDC.
Improving antibiotic use among hospitalized patients; from CDC.
Estimates of Healthcare-Associated Infections (HCIs) 2011; from CDC.
Getting Smart About Antibiotics; from CDC.

We will now look at each of these mechanisms of resistance.

Producing to inactivate the antibiotic

(see Figure 4.3.1).

Bacteria may acquire new genes that code for an enzyme that inactivates a particular antibiotic or group of antibiotics. For example:

a. Bacteria typically become resistant to penicillins, monobactams, carbapenems, and cephalosporins are known chemically as beta-lactam antibiotics (see Figure 4.3.2) and many bacteria become resistant to these antibiotics by producing various beta-lactamases that are able to inactivate some forms of these drugs. Beta-lactamases break the beta-lactam ring of the antibiotic, thus inactivating the drug. (Penicillinase is a beta-lactamase that inactivates certain penicillins.) To overcome this mechanism of resistance, sometimes beta-lactam antibiotics such as amoxicillin, ticarcillin, imipenem, or ampicillin are combined with beta-lactamase inhibitors such as clavulanate, tazobactam, or sulbactam (see Common Antibiotics) - chemicals that resemble beta-lactam antibiotic (see Figure 4.3.2). These agents bind to the bacterial beta-lactamases and neutralize them.

b. Bacteria may become resistant to aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc.) and streptogramins by enzymatically adding new chemical groups to these antibiotics, thus inactivating the drug.

Flash animation showing a bacterium producing an enzyme capable of destroying the antibiotic.

html5 version of animation for iPad showing a bacterium producing an enzyme capable of destroying the antibiotic.

Altering the target site receptor for the antibiotic in the bacterium to reduce or block its binding.

Antibiotics work by binding to some bacterial target site, such as a 50S ribosomal subunit, a 30S ribosomal subunit, or a particular bacterial enzyme such as a transpeptidases or a DNA topoisomerase. Bacteria may acquire new genes that alter the molecular shape of the portion of the ribosomal subunit or the enzyme to which the drug normally binds. For example:

a. Bacteria may become resistant to to macrolides (erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc.) by producing a slightly altered 50S ribosomal subunit that still functions but to which the antibiotic can no longer bind (see Figure 4.3.3).

b. Bacteria may become resistant to beta-lactam antibiotics (penicillins, monobactams, carbapenems, and cephalosporins) by producing altered transpeptidases (penicillin-binding proteins) with greatly reduced affinity for the binding of beta-lactam antibiotics.

c. Bacteria may become resistant to vancomycin by producing altered cross-linking peptides in the peptidoglycan to which the antibiotic no longer bonds.

d. Bacteria may become resistant to fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.) by producing altered DNA gyrase or other topoisomerases to which the drug no longer binds (see Figure 4.3.4).

Flash animation showing a bacterium producing an altered ribosomal subunit to which the antibiotic no longer binds.

html5 version of animation for iPad showing a bacterium producing an altered ribosomal subunit to which the antibiotic no longer binds.

Flash animation showing a bacterium producing an altered enzyme to which the antibiotic no longer binds.

html5 version of animation for iPad showing a bacterium producing an altered enzyme to which the antibiotic no longer binds.

For More Information: Ribosomes from Unit 1

For More Information: Peptidoglycan from Unit 1.

For More Information: The Nucleoid from Unit 1.

Altering the membranes and transport systems to prevent the entry of the antibiotic into the bacterium and/or using an efflux pump to transport the antibiotic out of the bacterium.

Antibiotics that target ribosomes or enzymes within the bacterium must first pass through the porins in the outer membrane of gram-negative and acid-fast bacterial cell walls, and then the cytoplasmic membrane in the case of all bacteria. Subsequently, the antibiotic has to accumulate to a high enough concentration within the bacterium to inhibit or kill the organism.

a. A Gram-negative or an acid-fast bacterium may block the entry of an antmicrobial drug by acquiring genes that alter the porins in the cell wall's outer membrane (see Figure 4.3.5).

b. A bacterium may block the entry of an antmicrobial drug by acquiring genes that alter the carrier (transport) proteins used to transport the drug through the bacterium's cytoplasmic membrane (see Figure 4.3.6). This is generally not a common mechanism of antibiotic resistance.

c. A bacterium may acquire genes coding for an energy-driven efflux pump in its the cytoplasmic membrane that is able to to pump the antibiotic out of the bacterium and preventing it from accumulating to a high enough concentration to inhibit or kill the organism (see Figure 4.3.7). This is the most common method bacteria use to prevent toxic levels of antimicrobial drugs from accumulating within the cytoplasm.

Flash animation showing a bacterium producing altered porins to block transport of the drug across the outer membrane.

Flash animation showing a bacterium producing an altered carrier protein to block transport of the drug across the cytoplasmic membrane.

Flash animation showing a bacterium producing new transporter protein able to pump the drug out of the bacterium.

html5 version of animation for iPad showing a bacterium producing altered porins to block transport of the drug across the outer membrane.

html5 version of animation for iPad showing a bacterium producing an altered carrier protein to block transport of the drug across the cytoplasmic membrane.

html5 version of animation for iPad showing a bacterium producing new transporter protein able to pump the drug out of the bacterium.

For More Information: The Cytoplasmic Membrane from Unit 1.

Modulating gene expression to produce more of the bacterial enzyme that is being tied up or altered by the antibiotic.

Remember that enzymes function as catalysts and are present in cells in small amounts because they are not altered as they carry out their specific biochemical reactions. As mentioned in the previous section, numerous antimicrobial drugs work by inactivating bacterial enzymes and blocking metabolic reactions. Making a particular enzyme and the amount of enzyme that is made is under genetic control.

Genetic control of enzyme activity refers to controlling transcription of the mRNA needed for an enzyme's synthesis. In prokaryotic cells, this involves the induction or repression of enzyme synthesis by regulatory proteins that can bind to DNA and either block or enhance the function of RNA polymerase, the enzyme required for transcription.

Bacteria also use translational control of enzyme synthesis. In this case, the bacteria produce noncoding RNAs (ncRNAs) or antisense RNAa such as microRNAs (miRNAs) that are complementary to an early portion of the mRNA coding for the enzyme. When the noncoding RNA binds to the mRNA by complementary base pairing, ribosomes cannot attach, the mRNA cannot be translated into protein, and the enzyme is not made (See Figure 4.3.8).

For More Information: Enzyme Regulation from Unit 2.

Mutations or horizontal gene transfer may result in a modulation of gene expression or translational events that favor increased production of the enzyme being tied up or altered by the antimicrobial agent (see Figure 4.3.9). Since enzymes are normally produced in limited amounts, production of excessive amounts of enzyme may allow for the metabolic activity being blocked by the agent to still occur.

Flash animation showing competitive antagonism.

html5 version of animation for iPad showing competitie antagonism.

Flash animation showing a bacterium producing more of a limited enzyme.

html5 version of animation for iPad showing a bacterium producing more of a limited enzyme.

GIF animation showing antisense RNA.

Many pathogenic bacteria, as well as normal flora, form complex bacterial communities as biofilms.

Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. By living as a community of bacteria as a biofilm, these bacteria are:

- better able to resist attack by antibiotics, and
- are better able to resist the host immune system.

Why bacterium within a biofilm are more antibiotic resistant isn't completely understood but various mechanisms have been preposed. The extracellular polysaccharide may make it more difficult for the antibiotic to reach all of the bacteria. Bacteria within a biofilm are generally in a metabolically more inert state and this could slow down antibacterial action of the drug. Many antibiotics are static, not cidal in action; the body depends on phagocytes to remove the inhibited bacteria. The biofilm structure

makes engulfment by phagocytes pretty much impossible.

Exposure to antibiotics doesn't "cause" bacteria to become drug resistant. The above changes in the bacterium that enable it to resist the antibiotic occur naturally as a result of mutation or as a result of horizontal gene transfer. For example, when under stress from antibiotics, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium 10,000 times as fast as the mutation rate that occurs during normal binary fission. This causes a sort of hyperevolution where mutation acts as a self defense mechanism for the bacterial population by increasing the chance of forming an antibiotic-resistant mutant that is able to survive at the expense of the majority of the population. (Remember that most mutations are harmful to a cell.)

For More Information: Mutation from Unit 7.

In addition, horizontal gene transfer as a result of transformation, transduction, and conjugation can transfer antibiotic resistance from one bacterium to another. Horizontal gene transfer enables bacteria to respond and adapt to their environment much more rapidly than mutation by acquiring large DNA sequences from another bacterium in a single transfer.

For More Information: Horizontal Gene Transfer from Unit 2

Concept map for Ways in Which Bacteria Resist Antibiotics and Chemical Agents

Briefly describe 3 different mechanisms, as a result of mutation or horizontal gene transfer in a bacterium, that may enable that bacterium to resist an antibiotic

- State at least 4 medical dangers associated with the improper use of antibiotics and list 3 common examples of antibiotic misuse.

Exposure to the antibiotic typically selects for strains of the organism that have become resistant through these natural processes. Misuse of antibiotics, such as prescribing them for non-bacterial infections (colds, influenza, most upper respiratory infections, etc.) or prescribing the "newest" antibiotic on the market when older brands may still be as effective simply inceases the rate at which this natural selection for resistance occurs. According to the Centers for Disease Control and Prevention, as many as one-third (50 million out of 150 million) of antibiotic prescriptions given on an outpatient basis are unneeded. Patient noncompliance with antimicrobial therapy, namely, not taking the prescribed amount of the antibiotic at the proper intervals for the appropriate length of time, also plays a role in selecting for resistant strains of bacteria.

The spread of antibiotic resistance in pathogenic bacteria is due to both direct selection and indirect selection.

- Direct selection refers to the selection of antibiotic resistant pathogens at the site of infection.
- Indirect selection is the selection of antibiotic-resistant normal floras within an individual anytime an antibiotic is given. At a later date, these resistant normal flora may transfer resistance genes to pathogens that enter the body. In addition, these resistant normal flora may be transmitted from person to person through such means as the fecal-oral route or through respiratory secretions.

As an example, many Gram-negative bacteria possess R (Resistance) plasmids that have genes coding for multiple antibiotic resistance through the mechanisms stated above, as well as transfer genes coding for a conjugation (sex) pilus (see Figs. 10A-10F). It is possible for R-plasmids to accumulate transposons to increase bacterial resistance. Such an organism can conjugate with other bacteria and transfer to them an R plasmid. *E. coli, Proteus, Serratia, Enterobacter, Salmonella, Shigella*, and *Pseudomonas* are bacteria that frequently have R-factor plasmids.

Flash animation illustrating R plasmid conjugation.

html5 version of animation for iPad illustrating R plasmid conjugation.

In addition to plasmids, conjugative transposons also frequently transmit antibiotic resistance from one bacterium to another. Conjugative transposons, like conjugative plasmids, carry the genes that enable mating pairs to form for conjugation. Therefore, conjugative transposons also enable mobilizable plasmids and nonconjugative transposons to be transferred to a recipient bacterium during conjugation.

For More Information: Horizontal Gene Transfer from Unit 2

Examples of Antibilotic Resistant Bacteria

Examples of resistant strains of bacteria of ever increasing medical importance include:

- Penicillinase-Producing *Neisseria gonorrhoeae* (PPNG): Most strains of *Neisseria gonorrhoeae* have penicillinase plasmids and are known as PPNG (penicillinase-producing *Neisseria gonorrhoeae*). As a result, penicillin is no longer the drug of choice for gonorrhea.
- Carbapenem-Resistant Enterobacteriaceae (CRE): More recently, carbapenemase-producing *Klebsiella pneumoniae* (KPC) strains are frequently being identified among nosocomial pathogens globally. Carbapenemase is a broad-spectrum beta-lactamase enzyme first found in *K. pneumoniae* isolates that results in resistance to all penicillins, cephalosporins, carbapenems (i.e., imipenem, ertapenem, metropenem), and monobactams (i.e., aztreonam). These broad-spectrum beta-lactamases are also known as extended spectrum beta-lactamases or ESBLs. These ESBLs are now being seen in a variety *Enterobacteriaceae* including *Enterobacter* spp., *E. coli*, *Serratia* spp., and *Salmonella enterica*. These ESBL-producing *Enterobacteriaceae* are known as carbapenem-resistant *Enterobacteriaceae*, or CRE.
- Methicillin-Resistant Staphylococcus aureus (MRSA): *Staphylococcus aureus* resistance to methicillin confers resistance to all penicillins and cephalosporins.
- Vancomycin-Resistant Enterococcus (VRE): Vancomycin-resistant *Enterococcus* (VRE) are intrinsically resistant to most antibiotics and have acquired resistance to the first line drug of choice, vancomycin.
- XDR TB: Extensively drug-resistant tuberculosis (XDR TB), a relatively rare type of multidrug-resistant *Mycobacterium tuberculosis* that is resistant to almost all drugs used to treat TB, including the two best first-line drugs: isoniazid and rifampin. XDR TB is also resistant to the best second-line medications: fluoroquinolones and at least one of three injectable drugs i.e., amikacin, kanamycin, or capreomycin.

Dormant persisters: Another mechanism that protects some bacteria from antibiotics is antibiotic tolerance. In the case of antibiotic tolerance, the tolerant bacterium is not killed but simply stops growing when the antibiotic is present. It then is able to recover once the antibiotic is no longer in the host. For example, *Streptococcus pneumoniae* tolerant to vancomycin appear to repress their autolysins in the presence of the drug and don't undergo osmotic lysis. Antibiotic tolerance is especially significant in terms of bacteria that form biofilms associated with catheters, heart valves, orthopedic devices, and people with cystic fibrosis. These biofilms often contain a small percentage of dormant persisters that, because they are not dividing, tolerate the antibiotics.

Its been found that bacteria simultaneously produce toxins that inhibit their own growth and antitoxins that bind to the toxin and cause its neutralizion. Small numbers of bacteria in the population, however, become persisters because they produce lower levels of antitoxin or the antitoxin is degraded by stress. As a result, the free toxin arrests bacterial growth enabling a persistent state that is able to survive stressors such as antibiotics and starvation.

Bacteria such as *E. coli, Proteus, Enterobacter, Serratia, Pseudomonas, Staphylococcus aureus,* and *Enterococcus* mentioned above, are the leading cause of health care-associated infections. According to the Centers for Disease Control and Prevention (CDC) Healthcare-associated infection's website, "In American hospitals alone, healthcare-associated infections account for an estimated 1.7 million infections and 99,000 associated deaths each year" in the U.S. The CDC also estimates that “more than two million people in the United States get infections that are resistant to antibiotics and at least 23,000 people die as a result.”

Finally, Bacterial endospores, such as those produced by *Bacillus* and *Clostridium*, are also resistant to antibiotics, most disinfectants, and physical agents such as boiling and drying. Although harmless themselves, they are involved in the transmission of some diseases to humans. Examples include anthrax (*Bacillus anthracis*), tetanus (*Clostridium tetani*), botulism (*Clostridium botulinum*), gas gangrene (*Clostridium perfringens*), and pseudomembranous colitis (*Clostridium difficile*).

Summary

1. Most bacteria become resistant to antibiotics by way of one or more mechanisms that are coded for by genes in the bacterial

chromosome and/or in bacterial plasmids.
2. Bacterial genes may code for production of an enzyme that inactivates the antibiotic.
3. Bacterial genes may code for an altered target site receptor (ribosomal subunit, enzyme, etc.) for the antibiotic to reduce or block its binding.
4. Bacterial genes may code for altered membrane components that prevent the entry of the antibiotic into the bacterium and/or using an efflux pump to transport the antibiotic out of the bacterium.
5. Bacterial genes may code for modulated gene expression to produce more of the bacterial enzyme that is being tied up or altered by the antibiotic.
6. When under stress from antibiotics, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium causing a hyperevolution to increase the chance of forming an antibiotic-resistant mutant that is able to survive.
7. Horizontal gene transfer as a result of transformation, transduction, and conjugation can transfer antibiotic resistance from one bacterium to another. Horizontal gene transfer enables bacteria to respond and adapt to their environment much more rapidly than mutation by acquiring large DNA sequences from another bacterium in a single transfer.
8. Another mechanism that protects some bacteria from antibiotics is antibiotic tolerance whereby the tolerant bacterium, called a dormant persister, is not killed but simply stops growing when the antibiotic is present.
9. CDC estimates that “more than two million people in the United States get infections that are resistant to antibiotics and at least 23,000 people die as a result.”

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4.E: Using Antibiotics and Chemical Agents to Control Bacteria (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

4.1: An Overview to Control of Microorganisms

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching:

   _____ An agent that kills the organism.

   _____ An agent that inhibits the organism's growth long enough for body defenses to remove it.

   _____The chemical agent being used should inhibit or kill the intended pathogen without seriously harming the host.

   _____ A chemical agent that generally works against just gram-positives, gram-negatives, or only a few bacteria.

   _____ A chemical agent that is generally effective against a variety of gram-positive and gram-negative bacteria.

   _____ Antimicrobial drugs synthesized by chemical procedures in the laboratory.

   _____ Metabolic products of one microorganism that inhibit or kill other microorganisms.

   ____ The process of destroying all living organisms and viruses.

   ____ The elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces.

   ____ An agent that kills or inhibits growth of microbes but is safe to use on human tissue.

   A. selective toxicity
   B. broad spectrum agent
   C. narrow spectrum agent
   D. cidal
   E. static
   F. sterilization
   G. antibiotic
   H. chemotherapeutic synthetic drug
   I. antiseptic
   J. disinfection
   K. disinfectant

4.2: Ways in which Chemical Control Agents Affect Bacteria

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching:

_____ Alter bacterial 30S ribosomal subunits blocking translation.

_____ Inhibit peptidoglycan synthesis causing osmotic lysis.

_____ Alter bacterial 50S ribosomal subunits blocking translation.

_____ Inhibit nucleic acid synthesis.

A. macrolides(erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc.), oxazolidinones (linezolid), and streptogramins
B. penicillins, monobactams, carbapenems, cephalosporins, and vancomycin
C. fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.), sulfonamides and trimethoprim, and metronidazole
D. aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc.) and tetracyclines (tetracycline, doxycycline, demeclocycline, minocycline, etc.)

2. Describe 4 different ways antibiotics or disinfectants may affect bacterial structures or macromolecules and state how this ultimately causes harm to the cell.
   A.
   B.
   C.
   D.
3. Multiple Choice

4.3: Ways in which Bacteria May Resist Chemical Control Agents

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Name 2 bacteria that have low-permeability membrane barriers and are thereby intrinsically resistant to many antibiotics.
2. Briefly describe 3 different mechanisms as a result of genetic changes in a bacterium that may enable that bacterium to resist an antibiotic.
   A.
   B.
   C.
3. State what the following stand for:
   A. MRSA
   B. VRE
   C. CRE
4. Briefly describe R plasmids and state their significance in our attempts to treat infections with antibiotics.
5. Multiple Choice

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Overview of Microbial Pathogenesis

Learning Objectives

After completing this section you should be able to perform the following objectives.

1. Define the following:
   a. pathogenicity
   b. virulence
   c. virulence factors
   d. infection
   e. disease
   f. etiologic agent
   g. reservoir
   h. zoonosis
   i. vector
   j. portal of entry and portal of exit
2. Compare and contrast sign and symptom.
3. List four requirements for a microorganism to cause infectious disease.
4. Contrast and give examples of direct and indirect transmission of microorganisms.
5. Even though a microorganism may be considered pathogenic, it still may not be able to cause disease upon entering the body. Discuss why.

In this course we are looking at various fundamental concepts of microbiology, with particular emphasis on their relationships to human health. The overall goal is to better understand the total picture of infectious diseases in terms of host-infectious agent interaction. Bacteria are found in almost every environment. Only a relatively few bacteria cause human disease and many benefit humans. For example, many are important decomposers that assure the flow and recycling of nutrients through ecosystems. Others have important industrial and pharmaceutical uses.

While the typical human body contains an estimated 10 trillion human cells, it also contains over 100 trillion bacteria and other microbes. The complex mutually beneficial symbiotic relationship between humans and their natural microbes is critical to good health. It is now recognized that the millions of genes associated with the normal flora or microbiota of the human body -especially in the intestinal tract - aid in the digestion of many foods, the regulation of multiple host metabolic pathways, and the regulation the body's immune defenses. These collective microbial genes are referred to as the human microbiome. There are currently an estimated 3, 000,000 - 5,000,000 genes from over 1000 species that constitute the human microbiome compared to the approximately 23,000 genes that make up the human genome. Some of these same normal microbiota, however, can also cause opportunistic infections when they get into parts of the body where they do not normally live or when the body becomes immunosuppressed. However, in this section we are going to concentrate on bacteria that are potentially harmful to humans and try to understand what factors influence their ability to cause disease.

The Good, the Bad, and the Ugly

Most bacteria are not harmful. In fact, only 10% of bacteria are “bad” or pathogenic, while the other 90% "good" or neutral and are necessary components for human life.

Infection versus Disease

Pathogenicity and virulence are terms that refer to an organism's ability to cause disease. Pathogenicity is the ability of a microbe to cause disease and inflict damage upon its host, whereas virulence is the degree of pathogenicity within a group or species of microbes as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism, that is its ability to cause disease, is determined by its virulence factors.

As learned earlier under Bacterial Genetics, most of the virulence factors that enable bacteria to colonize the body and/or harm the body are the products of quorum sensing genes. Many bacteria use quorum sensing to sense their own population density, communicate with each other by way of secreted chemical factors, and behave as a population rather than as individual bacteria. This plays an important role in pathogenicity and survival for many bacteria.

The genomes of pathogenic bacteria, when compared with those of similar nonpathogenic species or strains, often show extra genes coding for virulence factors, that is, molecules expressed and secreted by the bacterium that enable them to colonize the host, evade or inhibit the immune responses of the host, enter into or out of a host cell, and/or obtain nutrition from the host. These include virulence factors such as capsules, adhesins, type 3 secretion systems, invasins, and toxins.

We also learned that most genes coding for virulence factors in bacteria are located in pathogenicity islands or PAIs and are usually acquired by horizontal gene transfer. These PAIs may be located in the bacterial chromosome, in plasmids, or even in bacteriophage genomes that have entered the bacterium. The genomes of most pathogenic bacteria typically contain multiple PAIs that can account for up to 10 - 20% of the bacterium's genome. PAIs carry genes such as transpoases, integrases, or insertion sequences that enable them to insert into host bacterial DNA. Transfer RNA (tRNA) genes are often the target site for integration of PAIs. Conjugative plasmids are the most frequent means of transfer of PAIs from one bacterium to another and the transfer of PAIs can then confer virulence to a previously nonpathogenic bacterium.

An infection is when a microorganism has established itself in a host - has colonized that host - whether not it causing harm or imparting damage. A disease, on the other hand, is where there is impairment to host function as a result of damage or injury. For example, the microbes that constitute the body's normal flora or microbiota have infected the body, but they seldom cause disease unless they invade a part of the body where they do not normally reside and/or the host becomes immunocompromised. In medicine, the term etiology refers to the causes of diseases or pathologies. In terms of infectious disease, the etiologic agent is the microorganism causing that disease.

The terms signs and symptoms are often used when diagnosing disease. A sign is an objective indication of some medical fact or characteristic that may be detected by a health care professional during a physical examination. They include such objective indications as blood pressure, respiration, rate, pulse, and temperature. A symptom is a condition experienced and reported by the patient.

To cause disease, a microorganism must maintain a reservoir before and after infection

The reservoir of an infectious agent is the habitat in which that microbe normally lives, grows, and multiplies. Reservoirs can include humans, animals, and the environment. Many common human infectious diseases have human reservoirs and are transferred person-to-person without intermediaries. Examples include sexually transmitted diseases, measles, most respiratory pathogens, and strep throat. Some infections are transmitted from an animal to a human in which case the infection is called a zoonosis. Examples include rabies, plague, and much salmonellosis. Plants, soil, and water in the environment are also reservoirs for some infectious agents such as histoplasmosis, coccidioidomycosis, and Legionnaires disease.

To cause disease, a microorganism must leave the reservoir and gain access to the new host

The microorganism must leave its reservoir or host through what is called a portal of exit and be transmitted to a new host. For example, the portal of exit for respiratory infections is typically the mouth or nose; for gastrointestinal infections, the feces. Modes of transmission include:

1. Direct contact, as through skin-to-skin contact, kissing, and sexual intercourse. Examples include some *Staphylococcus aureus* infections, infectious mononucleosis, and gonorrhea.
2. Direct droplet contact, as in the case of aerosols produced by sneezing and coughing. Examples include meningococcal infections and pertussis (whooping cough).
3. Indirect transmission of an infectious agent from a reservoir to a host by suspended air particles, inanimate objects, or vectors.
4. Airborne transmission occurs when infectious agents are carried by dust or droplets suspended in air. Some respiratory infections can be transmitted this way although most are transmitted by contact with infectious mucus.
5. Inanimate objects include water, food, blood, and fomites (inanimate objects such as toys, handkerchiefs, bedding, or

clothing). Examples include cholera, salmonellosis, listeriosis, viral hepatitis).
6. Vectors such as ticks, mosquitoes, and fleas. Examples include Lyme's disease, malaria, and typhus fever.

The manner in which a pathogen enters a susceptible host is referred to as its portal of entry. For example, the portal of entry for most respiratory infections is the mouth or nose; for gastrointestinal infections, the mouth. The portal of entry must provide access to tissues with the correct physical and chemical environment (an environment with the proper oxygen content, pH, nutrients, temperature, etc.) in which the pathogen can multiply.

To cause disease, a microorganism must Adhere to cells of the skin or mucosa of its new host and colonize the body

Almost every part of the body has a mechanism for flushing microbes out of or off of the body, including the shedding of epithelial cells from the skin and mucous membranes, urination, defecation, coughing, and sneezing. Unless the microorganisms can replicate fast enough to replace those being flushed out, as in the case of much of the normal microbiota that colonize the lumen of the intestines, they need to adhere to the epithelial cells of the skin and mucous membranes. Also, this body environment must have the correct nutrients, the proper amount of oxygen or lack of oxygen, the right pH, and the right temperature to support the growth of that microorganism. Furthermore, since the body has excellent immune defense mechanisms, anything the microorganism can do to resist body defenses to some degree will also promote colonization.

To cause disease, a microorganism must Harm or damage the body

As stated above, an infection is simply when a microorganism has established itself in a host. To cause disease, that microorganism (or toxin) must inflict damage to the host.

Summary

1. Only a relatively few bacteria cause human disease.
2. The complex mutually beneficial symbiotic relationship between humans and their natural microbes is critical to good health.
3. An infection is when a microorganism has established itself in a host - has colonized that host - whether not it causing harm or imparting damage.
4. A disease is where there is impairment to host function as a result of damage or injury.
5. Etiology refers to the causes of diseases or pathologies; in terms of infectious disease, the etiologic agent is the microorganism causing that disease.
6. A sign is an objective indication of some medical fact or characteristic that may be detected by a health care professional during a physical examination; a symptom is a condition experienced and reported by the patient.
7. The reservoir of an infectious agent is the habitat in which that microbe normally lives, grows, and multiplies.
8. Transmission of microorganisms by direct contact refers to transfer by such means as skin-to-skin contact, kissing, and sexual intercourse.
9. Transmission of microorganisms by direct droplet contact refers to transfer by aerosols produced by sneezing and coughing.
10. Transmission of microorganisms by indirect contact refers to transfer by suspended air particles, inanimate objects, or vectors (ticks, mosquitoes, fleas).
11. The manner in which a pathogen enters a susceptible host is referred to as its portal of entry; the manner in which it leaves its host is its portal of exit.
12. If relatively few bacteria enter the body then the body's natural defenses against infection have a much better chance of removing them before they can colonize, multiply, and cause harm; if a large number of bacteria enter then the body's defenses may not be as successful.
13. A person with good innate and adaptive immune defenses will be much more successful in removing potentially harmful bacteria than a person that is immunocompromised.
14. Bacterial virulence factors influence a bacterium’s ability to cause infectious disease. These include virulence factors that enable bacteria to colonize the host as well as those that harm or damage the host.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write

them out. This will not test your understanding of this tutorial.

1. Define pathogenicity. *(ans)*
2. Define virulence. *(ans)*
3. Define infection. *(ans)*
4. Define disease. *(ans)*
5. Define vector. *(ans)*
6. Define medical sign. *(ans)*
7. Even though a microorganism may be considered pathogenic, it still may not be able to cause disease upon entering the body. Discuss why. *(ans)*
8. Multiple Choice *(ans)*

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5.0: Prelude to Virulence Factors that Promote Bacterial Colonization

List six virulence factors that promote bacterial colonization of the host.

In this section on Bacterial Pathogenesis, we are looking at bacterial virulence factors that can influence its ability to cause infectious disease. Virulence factors are molecules expressed and secreted by that enable them to colonize the host, evade or inhibit the immune responses of the host, enter into or out of a host cell, and/or obtain nutrition from the host. These virulence factors will be divided into two categories:

- Virulence factors that promote bacterial colonization of the host.
- Virulence factors that damage the host.

In this section we will look at virulence factors that promote bacterial colonization of the host.

Virulence Factors that Promote Bacterial Colonization of the Host

The following are virulence factors that promote bacterial colonization of the host .

1. The ability to use motility and other means to contact host cells and disseminate within a host.
2. The ability to adhere to host cells and resist physical removal.
3. The ability to invade host cells.
4. The ability to compete for iron and other nutrients.
5. The ability to resist innate immune defenses such as phagocytosis and complement.
6. The ability to evade adaptive immune defenses.

As mentioned in the previous section, most of the virulence factors that better enable bacteria to colonize the body are the products of quorum sensing genes. It will also be seen that bacteria often carry out these abilities by co-opting the host cell's machinery and communication ability. Many bacteria are able to produce specialized secretion machinery that enables the bacterium to inject proteins into the host cell that reprogram various aspects of the host cell's machinery to benefit the bacterium.

Summary

Virulence factors are molecules expressed on or secreted by microorganisms that enable them to colonize the host, evade or inhibit the immune responses of the host, enter into or out of a host cell, and/or obtain nutrition from the host. To cause infectious disease, a bacterium must produce virulence factors that promote bacterial colonization of the host, as well as virulence factors that impair or damage the host.

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5.1: The Ability to Use Motility and Other Means to Contact Host Cells

Learning Objectives

1. State why it might be of an advantage for a bacterium trying to colonize the bladder or the intestines to be motile.
2. **Describe** specifically how certain bacteria are able to use motility to contact host cells and state how this can promote colonization.
3. Briefly describe why being extremely thin and being motile by means of axial filaments may be an advantage to pathogenic spirochetes.
4. Give one example of how a nonmotile bacterium may be able to better disseminate within a host.
5. Give a brief description of how a bacterium may use toxins to better disseminate from one host to another.

Highlighted Bacterium

1. Read the description of *Helicobacter pylori* and match the bacterium with the description of the organism and the infection it causes.

The mucosal surfaces of the respiratory tract, the intestinal tract, and the genitourinary tract constantly flush bacteria away in order to prevent colonization of host mucous membranes. Motile bacteria can use their motility and chemotaxis to swim through mucus towards mucosal epithelial cells. Many bacteria that can colonize the mucous membranes of the bladder and the intestines, in fact, are motile. Motility probably helps these bacteria move through the mucus between the mucin strands or in places where the mucus is less viscous. Examples of motile opportunists and pathogens include *Helicobacter pylori, Salmonella* species, *Escherichia coli, Pseudomonas aeruginosa*, and *Vibrio cholerae*. Once bacteria contact host cells they can subsequently attach, and colonize. (Attachment will be discussed in the next section.)

- Movie of motile *Escherichia coli* with fluorescent labelled-flagella #1 Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
- Movie of motile *Pseudomonas* from YouTube.

For example, *Helicobacter pylori* , the bacterium that causes most gastric and duodenal ulcers, produces urease, an enzyme that breaks down urea into ammonia and carbon dioxide. The ammonia neutralizes the hydrochloric acid in the stomach. In addition, the urease is thought to alter the proteins in the mucus changing it from a solid gel to a thinner fluid that the bacteria are able to swim through by way of their flagella, and subsequently use adhesins to adhere to the epithelial cells of the mucous membranes. To further help protect the bacterium from the acid, *H. pylori* produces an acid-inhibitory protein that blocks acid secretion by surrounding parietal cells in the stomach. Bacterial toxins then lead to excessive production of cytokines and chemokines , as well as mucinase and phospholipase that damage the gastric mucosa. The cytokines and chemokines, in turn, result in a massive inflammatory response. Neutrophils leave the capillaries, accumulate at the area of infection, and discharge their lysosomes for extracellular killing. This not only kills the bacteria, it also destroys the mucus-secreting mucous membranes of the stomach. Without this protective layer, gastric acid causes ulceration of the stomach. This, in turn, leads to either gastritis or gastric and duodenal ulcers.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

YouTube movie of a video endoscopy exam showing duodenal ulcers caused by Helicobacter pylori.

Click on this link, read the description of *Helicobacter pylori*, and be able to match the bacterium with its description on an exam.

Planktonic *Pseudomonas aeruginosa* uses its polar flagellum to move through water or mucus and make contact with a solid surface such as the body's mucous membranes (Figure 5.1.5.1.1). It then can use pili and cell wall adhesins to attach to the epithelial cells of the mucous membrane. Attachment activates signaling and quorum sensing genes to eventually enable the population of *P. aeruginosa* to start synthesizing a polysaccharide biofilm composed of alginate. As the biofilm grows, the bacteria lose their flagella to become nonmotile and secrete a variety of enzymes that enable the population to obtain nutrients from the host cells. Eventually the biofilm mushrooms up and develops water channels to deliver water and nutrients to all the bacteria within the biofilm. As the biofilm begins to get too crowded with bacteria, quorum sensing enables some of the *Pseudomonas* to again produce flagella, escape the biofilm, and colonize a new location.

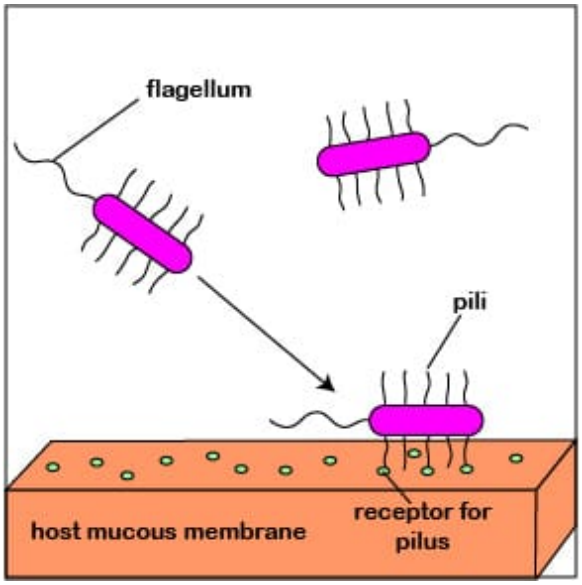


Figure 5.1.5.1.1: Development of a Biofilm by Pseudomonas aeruginosa. Planktonic Pseudomonas aeruginosa use their polar flagella and chemotaxis to swim towards host mucous membranes. Pili then bind to host cell receptors for initial but reversible bacterial attachment.

Because of their thinness, their internal flagella (axial filaments), their corkscrew shape, and their motility (Figure 5.1.5.1.2), spirochetes are more readily able to penetrate host mucous membranes, skin abrasions, etc., and enter the body. Motility and penetration may also enable the spirochetes to penetrate deeper in tissue and enter the lymphatics and bloodstream and disseminate to other body sites. Spirochetes that infect humans include *Treponema pallidum* , *Leptospira* , and *Borrelia burgdorferi*).

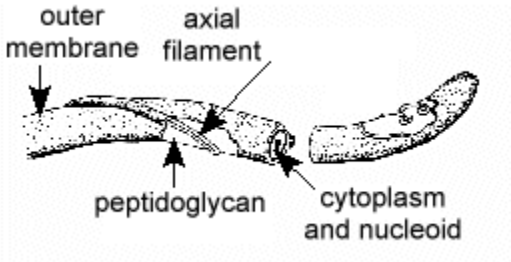


Figure 5.1.2: Spirochete Axial Filaments

- Movie of motile *Borrelia bergdorferi*, the spirochete that causes Lyme disease. From You Tube, courtesy of CytoViva.
- Movie of motile *Borrelia bergdorferi*, the spirochete that causes Lyme disease.

Along a different line, many bacteria produce enzymes such as elastases and proteases that degrade the extracellular matrix proteins that surround cells and tissues and make it easier for those bacteria to disseminate within the body. For example, *Streptococcus pyogenes* produces streptokinase that lyses the fibrin clots produced by the body in order to localize the infection. It also produces DNase that degrades cell-free DNA found in pus and reduces the viscosity of the pus. Both of these enzymes

facilitate spread of the bacterium from the localized site to new tissue.

Staphylococcus aureus, on the other hand, produces surface adhesins that bind to extracellular matrix proteins and polysaccharides surrounding host cell tissue, including fibronectin, collagen, laminin, hyaluronic acid, and elastin. *S. aureus* proteases and hyaluronidase then dissolve these components of the extracellular matrix providing food for the bacteria and enabling the bacteria to spread.

Finally, as will be seen later in this unit under toxins, some bacteria produce toxins that induce diarrhea in the host. Diarrhea is also a part of our innate immunity to flush harmful microbes and toxins out of the intestines. On one hand, diarrhea is an advantage to the body because it flushes out harmful microbes and toxins. On the other hand, it is beneficial for the bacterium inducing the diarrhea because it also flushes out a good deal of the normal flora of the intestines and this reduces the competition for nutrients between normal flora and pathogens. In addition, diarrhea enables the pathogen to more readily leave one host and enter new hosts through the fecal-oral route.

Summary

Bacteria have to make physical contact with host cells before they can adhere to those cells and resist being flushed out of the body. Motile bacteria can use their flagella and chemotaxis to swim through mucus towards mucosal epithelial cells. Because of their thinness, their internal flagella (axial filaments), their corkscrew shape, and their motility, certain spirochetes are more readily able enter lymph vessels and blood vessels and spread to other body sites. Many bacteria produce enzymes that degrade the extracellular matrix proteins that surround cells and tissues and help to localize infection, making it easier for those bacteria to spread within the body. Some bacteria produce toxins that induce diarrhea in the host enabling the pathogen to more readily leave one host and enter new hosts through the fecal-oral route.

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5.2: The Ability to Adhere to Host Cells and Resist Physical Removal

Learning Objectives

1. Briefly describe 3 different mechanisms by which bacteria can adhere to host cells and colonize and state how this can promote colonization.
2. State an advantage for bacteria in being able to switch the adhesive tips of their pili.
3. Define biofilm and state at least 3 benefits associated with bacteria living as a community within a biofilm.

Highlighted Bacterium

1. Read the description of *Neisseria memingitidis* andmatch the bacterium with the description of the organism and the infection it causes.

One of the body's innate immune defenses is the ability to physically remove bacteria from the body through such means as the constant shedding of surface epithelial cells from the skin and mucous membranes, the removal of bacteria by such means as coughing, sneezing, vomiting, and diarrhea, and bacterial removal by bodily fluids such as saliva, blood, mucous, and urine. Bacteria may resist this physical removal by producing pili, cell wall adhesin proteins, and/or biofilm-producing capsules. In addition, the physical attachment of bacteria to host cells can also serve as a signal for the activation of genes involved in bacterial virulence. This process is known as signal transduction.

Using Pili (fimbriae) to Adhere to Host Cells

As seen in Unit 1, pili enable some organisms to adhere to receptors on target host cells (Figure 5.2.5.2.1) and thus colonize and resist flushing by the body. Pili are thin, protein tubes originating from the cytoplasmic membrane and are found in virtually all Gram-negative bacteria, but not in many Gram-positive bacteria.

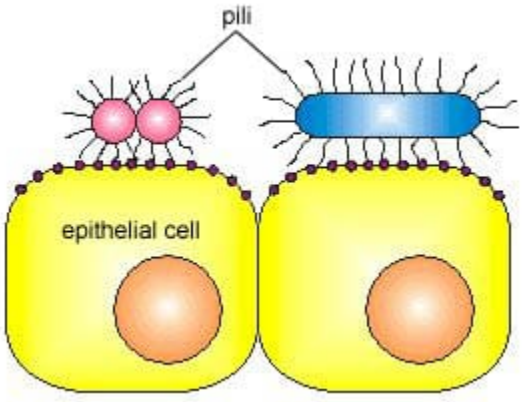


Figure 5.2.5.2.1: Bacterial Adherence with Pili

The pilus has a shaft composed of a protein called pilin. At the end of the shaft is the adhesive tip structure having a shape corresponding to that of specific glycoprotein or glycolipid receptors on a host cell (Figure 5.2.5.2.3). Because both the bacteria and the host cells have a negative charge, pili may enable the bacteria to bind to host cells without initially having to get close enough to be pushed away by electrostatic repulsion. Once attached to the host cell, the pili can depolymerize and enable adhesions in the bacterial cell wall to make more intimate contact. There is also evidence that the binding of pili to host cell receptors can serve as a trigger for activating the synthesis of some cell wall adhesins.

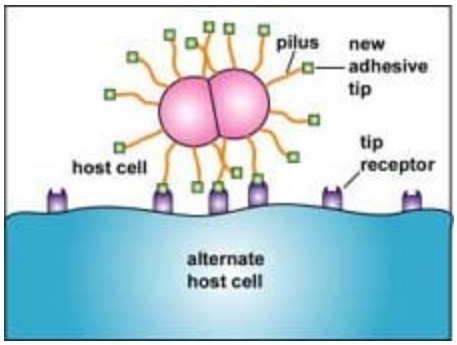


Figure 5.2.5.2.3: By genetically altering the adhesive tips of their pili, certain bacteria are able to: 1) adhere to and colonize different cell types with different receptors, and 2) evade antibodies made against the previous pili.

Bacteria are constantly losing and reforming pili as they grow in the body and the same bacterium may switch the adhesive tips of the pili in order to adhere to different types of cells and evade immune defenses (Figure 5.2.2.2.3). *E. coli*, for example, is able to make over 30 different types of pili.

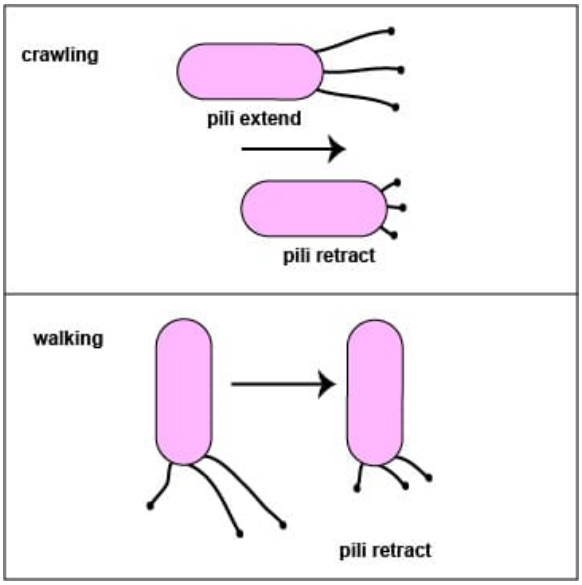


Figure5). The top illustration shows a bacterium dragging itself or "crawling" along a surface. Bacteria with polar pili are also able to pull themselves upright and "walk" along the surface as shown in the bottom illustration.

One class of pili, known as type IV pili, not only allows for attachment but also enable a twitching motility. They are located at the poles of bacilli and allow for a gliding motility along a solid surface such as a host cell. Extension and retraction of these pili allows the bacterium to drag itself along the solid surface (Figure 5.2.4). In addition, bacteria can use their type IV pili to "slingshot" the bacterium over a cellular surface. In this case, as the pili contract they are thought to become taut like a stretched rubber band. When an anchoring pilus detaches, the taut pili "slingshot" the bacterium in the opposite direction (Figure 5.2.5). This motion typically alternates with the twitching motility and enables a more rapid motion and direction change than with the twitching motility because the rapid slingshotting motion reduces the viscosity of the surrounding biofilm.

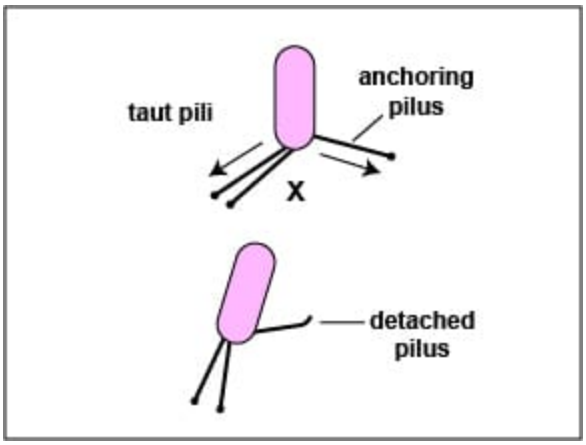


Figure 5.2.4) also caused by type IV pili and enables a more rapid motion and direction change than with the twitching motility because the rapid "slingshotting" motion reduces the viscosity of the surrounding biofilm.

This enables bacteria with these types of pili within a biofilm to move around a cellular surface and find an optimum area on that cell for attachment and growth once they have initially bound. Bacteria with type IV pili include *Pseudomonas aeruginosa, Neisseria gonorrhoeae, Neisseria meningitidis*, and *Vibrio cholerae*.

Examples of bacteria using pili to colonize:

1. To cause infection, *Neisseria gonorrhoeae* must first colonize a mucosal surface composed of columnar epithelial cells. Pili allow for this initial binding and, in fact, *N. gonorrhoeae* is able to rapidly lose pili and synthesize new ones with a different adhesive tip, enabling the bacterium to adhere to a variety of tissues and cells including sperm, the epithelial cells of the mucous membranes lining the throat, genitourinary tract, rectum, and the conjunctiva of the eye. Subsequently, the bacterium is able to make more intimate contact with the host cell surface by way of a cell wall adhesin called Opa (see below).

2. The pili of *Neisseria meningitidis* allow it to adhere to mucosal epithelial cells in the nasopharynx where it is often asymptomatic. From there, however, it sometimes enters the blood and meninges and causes septicemia and meningitis. Type IV pili are thought to help the bacterium cross the blood brain barrier.

> Click on this link, read the description of *Neisseria meningitidis*, and be able to match the bacterium with its description on an exam.

3. Uropathogenic strains of *Escherichia coli* can produce pili that enable the bacterium to adhere to the urinary epithelium and cause urinary tract infections. They also produce afimbrial adhesins (see below) for attachment to epithelial cells. Enteropathogenic *E. coli* (EPEC) use pili to adhere to intestinal mucosal cells.

- To view an electron micrograph *E. coli* with pili, see Dennis Kunkel's Microscopy at the University of Hawaii-Manoa.
- To view electron micrographs of enteropathogenic *E. coli* (EPEC) adhering to intestinal cells, see Donnenberg Lab Images at the University of Maryland Medical School.

4. Pili of *Vibrio cholerae* allow it to adhere to cells of the intestinal mucosa and resist the flushing action of diarrhea.
5. Pili of *Pseudomonas aeruginosa* allow it to initially colonize wounds or the lung.

Using Adhesins to Adhere to Host Cells

Adhesins are surface proteins found in the cell wall of various bacteria that bind to specific receptor molecules on the surface of host cells and enable the bacterium to adhere intimately to that cell in order to colonize and resist physical removal (Figure 5.2.6). Many, if not most bacteria probably use one or more adhesins to colonize host cells.

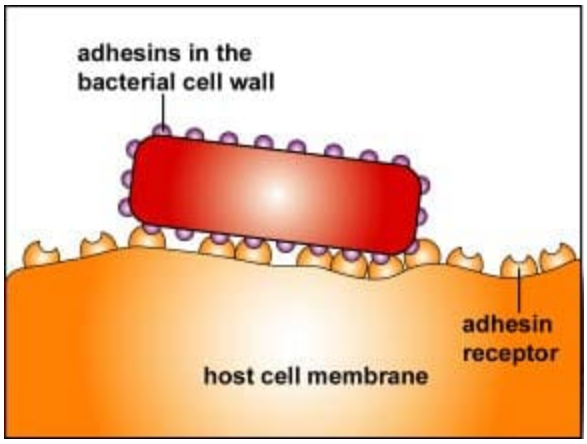


Figure 5.2.6: Bacterial Adhesins. Surface proteins called adhesins in the bacterial cell wall bind to receptor molecules on the surface of a susceptible host cell enabling the bacterium to make intimate contact with the host cell, adhere, colonize, and resist flushing.

For example:

1. *Streptococcus pyogenes* (see electron micrograph) (group A beta streptococci) produce a number of adhesins

    a. Protein F that binds to fibronectin , a common protein on epithelial cells. In this way it is able to adhere to the lymphatics and mucous membranes of the upper respiratory tract and cause streptococcal pharyngitis (strep throat).

    b. Lipoteichoic acid binds to fibronectin on epithelial cells.

    c. M-protein also functions as an adhesin.

2. The tip of the spirochete *Treponema pallidum* contains adhesins that are able to bind to fibronectin on epithelial cells.

    Scanning electron Micrograph of *T. pallidum* adhering to a host cell by its tip.

3. The tip of the spirochete *Borrelia burgdorferi* contains adhesins that can bind to various host cells.

4. *Escherichia coli* O157 utilizes a type 3 secretion system to inject effector proteins into intestinal epithelial cells. Some of these cause polymerization of actin at the cell surface and this pushes the host cell cytoplasmic membrane up to form a pedestal. Another effector protein inserts into the membrane of the pedestal to serve as a receptor molecule for *E. coli* adhesins (Figure 5.2.7).

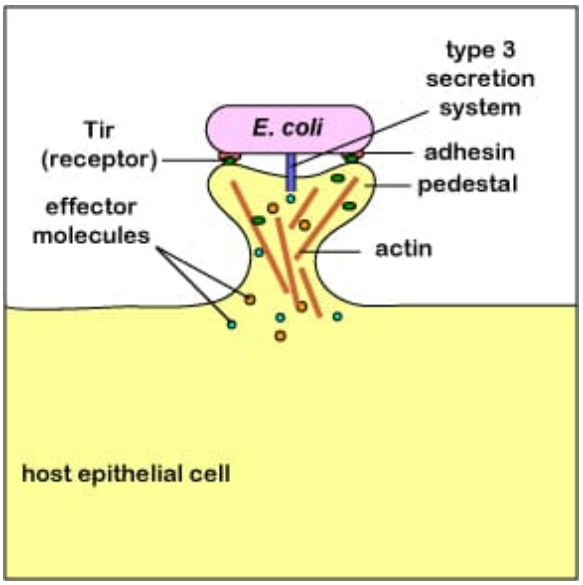


Figure 5.2.7: E. coli Using a Type 3 Secretion System to Induce Pedestal Formation in a Host Cell. Escherichia coli O157 utilizes a type 3 secretion system to inject effector proteins into intestinal epithelial cells. Some of these cause polymerization of actin at the cell surface and this pushes the host cell cytoplasmic membrane up to form a pedestal. Another effector protein inserts into the membrane of the pedestal to serve as a receptor molecule for E. coli adhesins

5. *Helicobacter pylori* use a type 4 secretion system to inject effector proteins into stomach epithelial cells to induce these host cells to display more receptors on their surface for *H. pylori* adhesins.

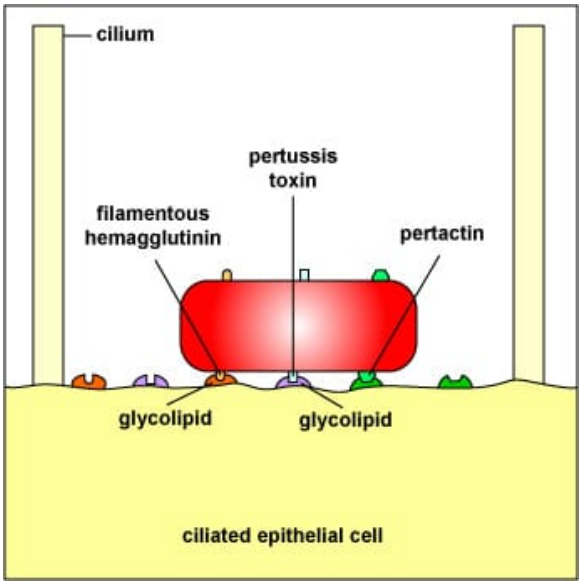


Figure 5.2.8: Bordetella pertussis using Adhesins to Adhere to a Ciliated Epithelial Cell. Bordetella pertussis produces several adhesins: (1) Filamentous hemagglutinin is an adhesin that allows the bacterium to adhere to galactose residues of the glycolipids on the membrane of ciliated epithelial cells of the respiratory tract. (2) Pertussis toxin also functions as an adhesin. One subunit of the pertussis toxin remains bound to the bacterial cell wall while another subunit binds to the glycolipids on the membrane of ciliated epithelial cells of the respiratory tract. (3) B. Pertussis also produces an adhesin called pertactin that further enables the bacterium to adhere to cells.

6. *Bordetella pertussis* produces several adhesins (Figure 5.2.8):

a. Filamentous hemagglutinin is an adhesin that allows the bacterium to adhere to galactose residues of the glycolipids on the membrane of ciliated epithelial cells of the respiratory tract.
b. Pertussis toxin also functions as an adhesin. One subunit of the pertussis toxin remains bound to the bacterial cell wall while another subunit binds to the glycolipids on the membrane of ciliated epithelial cells of the respiratory tract.
c. *B. Pertussis* also produces an adhesin called pertactin that further enables the bacterium to adhere to cells.

7. *Neisseria gonorrhoeae* produces an adhesin called Opa (protein II) that enables the bacterium to make a more intimate contact with the host cell after it first adheres with its pili. Like with adhesive tips of pili, *N. gonorrhoeae* has multiple alleles for Opa protein adhesins enabling the bacterium to adhere to a variety of host cell types.

8. *Staphylococcus aureus* uses protein A as an adhesin to adhere to various host cells. It also helps the bacterium to resist phagocytosis.

Using Biofilms to Adhere to Host Cells

Many normal flora bacteria produce a capsular polysaccharide matrix or glycocalyx to form a biofilm on host tissue. Biofilms are groups of bacteria attached to a surface and enclosed in a common secreted adhesive matrix, typically polysaccharide in nature. Many pathogenic bacteria, as well as normal flora and many environmental bacteria, form complex bacterial communities as biofilms.

Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. By living as a community of bacteria as a biofilm, these bacteria are better able to:

- resist attack by antibiotics;
- trap nutrients for bacterial growth and remain in a favorable niche;
- adhere to environmental surfaces and resist flushing;
- live in close association and communicate with other bacteria in the biofilm; and
- resist phagocytosis and attack by the body's complement pathways.

Biofilms are, therefore, functional, interacting, and growing bacterial communities. Biofilms even contain their own water channels for delivering water and nutrients throughout the biofilm community.

- Electron micrograph of a biofilm of *Haemophilus influenzae* from Biomedcentral.com
- Photomicrograph of a biofilm with water channels from Centers for Disease Control and Prevention Rodney M. Donlan: "Biofilms: Microbial Life on Surfaces"
- Biofilm of *Pseudomonas aeruginosa* from the Ausubel Lab, Department of Molecular Biology, Massachusetts General Hospital
- Scanning electron micrograph of *Staphylococcus aureus* forming a biofilm in an indwelling catheter courtesy of CDC.
- Biofilm of *Staphylococcus aureus* from Montana State University

For example:

1. *Streptococcus mutans*, and *Streptococcus sobrinus* , two bacteria implicated in initiating dental caries, break down sucrose into glucose and fructose. *Streptococcus mutans* can uses an enzyme called dextransucrase to convert sucrose into a sticky polysaccharide called dextran that forms a biofilm enabling the bacteria to adhere to the enamel of the tooth and initiate plaque formation.

This dextran mesh traps the *S. mutans* and *S. sobrinus*, along with other bacteria and debris, and forms plaque. *S. mutans* and *S. sobrinus* also ferment glucose in order to produce energy. The fermentation of glucose results in the production of lactic acid that is released onto the surface of the tooth and initiates decay.

- Scanning electron micrograph of *Streptococcus* growing in the enamel of a tooth.© Lloyd Simonson, author. Licensed for use, ASM MicrobeLibrary.
- Scanning electron micrograph of dental plaque.© H. Busscher, H. van der Mei, W. Jongebloed, R Bos, authors. Licensed for use, ASM MicrobeLibrary.

2. Most children suffering from chronic ear infection (otitis media) have a biofilm of bacteria in their middle ear. This biofilm contains bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* and enables the bacteria to chronically colonize the middle ear as well as resist body defenses and antibiotics.

3. Planktonic *Pseudomonas aeruginosa* uses its polar flagellum to move through water or mucus and make contact with a solid surface such as the body's mucous membranes. It then can use pili and cell wall adhesins to attach to the epithelial cells of the mucous membrane. Attachment activates signaling and quorum sensing genes to eventually enable the population of

P. aeruginosa to start synthesizing a polysaccharide biofilm composed of alginate. As the biofilm grows, the bacteria lose their flagella to become nonmotile and secrete a variety of enzymes that enable the population to obtain nutrients from the host cells. Eventually the biofilm mushrooms up and develops water channels to deliver water and nutrients to all the bacteria within the biofilm. As the biofilm begins to get too crowded with bacteria, quorum sensing enables some of the *Pseudomonas* to again produce flagella, escape the biofilm, and colonize a new location (See Figs. 9A-9H).

Many chronic and difficult-to-treat infections are caused by bacteria in biofilms. Within biofilms, bacteria grow more slowly, exhibit different gene expression than free planktonic bacteria, and are more resistant to antimicrobial agents such as antibiotics because of the reduced ability of these chemicals to penetrate the dense biofilms matrix. Biofilms have been implicated in tuberculosis, kidney stones, *Staphylococcus* infections, Legionnaires' disease, and periodontal disease. It is further estimated that as many as 10 million people a year in the US may develop biofilm-associated infections as a result of invasive medical procedures and surgical implants.

- Scanning electron micrograph of *Listeria* growing on a stainless steel surface. © Amy Lee Wong, author. Licensed for use, ASM MicrobeLibrary.
- Scanning electron micrograph of *Pseudomonas* growing on bronchial mucosa. © Hiroyuki Kobayashi, author. Licensed for use, ASM MicrobeLibrary.
- Scanning electron micrograph of *Staphylococcus aureus* forming a biofilm in an indwelling catheter courtesy of CDC.
- Article and computer-generated model of biofilm formation courtesy of NIH.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

YouTube movie and animation: What are Biofilms?

Exercise: Think-Pair-Share Questions

Pseudomonas aeruginosa, a common cause of serious respiratory infections on people with cystic fibrosis, produces a single polar flagellum, can secrete a polysaccharide slime composed of alginate, and is able to produce both pili and cell wall adhesins. How could each of these factors contribute to the bacterium's pathogenosis and in what order might they be used?

Summary

1. One of the body's innate immune defenses is the ability to physically remove bacteria from the body.
2. Bacteria may resist physical removal by producing pili, cell wall adhesin proteins, and/or biofilm-producing capsules that enable bacteria to adhere to host cells.
3. At the end of the shaft of a bacterial pilus is an adhesive tip structure having a shape corresponding to that of specific receptor on a host cell for initial attachment. Bacteria can typically make a variety of different adhesive tips enabling them to attach to different host cell receptors.
4. Cell wall adhesins are surface proteins found in the cell wall of various bacteria that bind tightly to specific receptor molecules on the surface of host cells. Bacteria can typically make a variety of different cell wall adhesins enabling them to attach to different host cell receptors.
5. Biofilms are groups of bacteria attached to a surface and enclosed in a common secreted adhesive matrix, typically polysaccharide in nature. Many pathogenic bacteria, as well as normal flora and many environmental bacteria, form complex bacterial communities as biofilms.
6. Many chronic and difficult-to-treat infections are caused by bacteria in biofilms.

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5.3: The Ability to Invade Host Cells

Briefly describe the mechanism by which invasins enable certain bacteria to enter host cells and state how this can promote colonization

- Briefly describe how a type 3 secretion system might be used to invade and survive inside host cells.
- State how certain pathogenic spirochetes such as *Treponema pallidum* and *Borrelia bergdorferi* use adhesins, invasins and motility to penetrate host cells.

Highlighted Bacterium

1. Read the description of *Shigella* and match the bacterium with the description of the organism and the infection it causes.
2. Read the description of *Salmonella* and match the bacterium with the description of the organism and the infection it causes.
3. Read the description of *Borrelia bergdorferi* and match the bacterium with the description of the organism and the infection it causes.

Some bacteria produce molecules called invasins that activate the host cell's cytoskeletal machinery enabling bacterial entry into the cell by phagocytosis. Advantages of entering a human cell include (1) providing the bacterium with a ready supply of nutrients and (2) protecting the bacteria from complement, antibodies, and other body defense molecules.

Flash animation of bacteria secreting invasions in order to penetrate non-immune host cells.

html5 version of animation for iPad of bacteria secreting invasions in order to penetrate non-immune host cells.

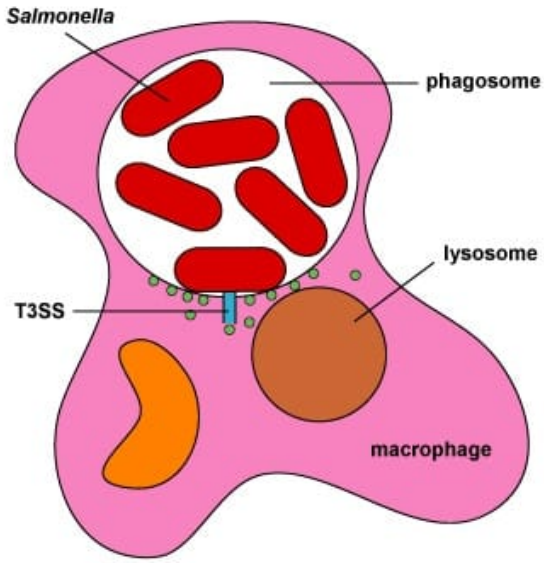


Figure 5.3.2: The Bacterial Type 3 Secretion System. Many bacteria involved in infection have the ability to co-opt the functions of the host cell to the benefit of the bacterium. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication. The most common type is the type 3 secretion system. A secretion apparatus in the cytoplasmic membrane and cell wall of the bacterium polymerizes a hollow needle that is lowered to the cytoplasmic membrane of the host cell and a translocon protein is then delivered to anchor the needle to the host cell. Effector proteins in the bacterium can now be injected into the cytoplasm of the host cell. The delivery system is sometimes called an injectisome.

When these bacteria contact the epithelial cells of the colon, the type III secretion system delivers proteins into the epithelial cells enabling them to polymerize and depolymerize actin filaments. This cytoskeletal rearrangement is a key part of the pseudopod formation in phagocytic cells and is what enables phagocytes to engulf bacteria and place them in a vacuole. Thus the bacterium with its invasins is able to trick the epithelial cell into behaving like a phagocyte and engulfing the bacterium. The bacteria then replicate within the host cell.

html5 version of animation for iPad of bacteria secreting invasions in order to penetrate non-immune host cells.

We will now look at several examples of bacteria that use invasions to invade host cells.

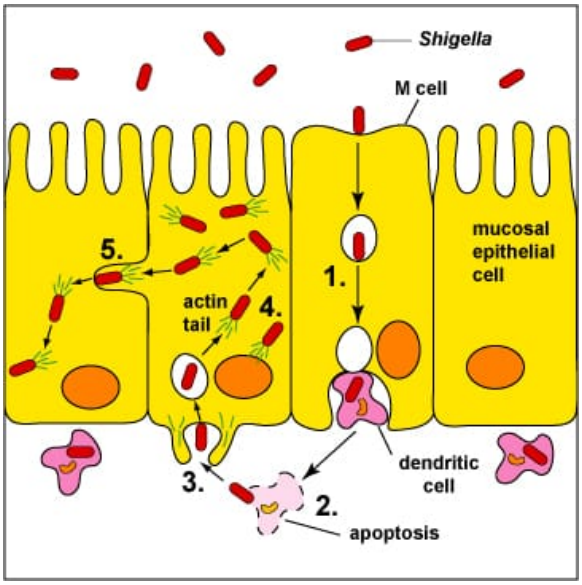


Figure 5.3.5.3.3: Shigella Passing Through the Mucous Membrane and Invading Mucosal Epithelial Cells Via M-Cells. A proposed model for invasion of epithelial cells of the colon. *1) The Shigella first cross the mucosa by passing through specialized cells called M cells. The M cell passes the Shigella on to a dendritic cell. 2) The Shigella subsequently escapes from the dendritic cell by inducing apoptosis, a programmed cell suicide. 3) The Shigella then uses its invasins to enter the mucosal epithelial cells from underneath. The invasins cause actin polymer rearrangements in the cytoskeleton of the host cell resulting in the bacterium being engulfed and placed in an endocytic vesicle in a manner similar to phagocytic cells. Once inside, the Shigella escape from the vacuole into the cytoplasm and multiply. 4) The Shigella are able to move through the host cell and spread to adjacent host cells by a unique process called actin-based motility. In this process, actin filaments polymerize at one end of the bacterium, producing comet-like tails that propel the Shigella through the cytoplasm of the host cell. 5) When they reach the boundary of that cell, the actin filaments push the Shigella across that membrane and into the adjacent cell.*

In addition, *Shigella* can induce the host cells to produce signaling molecules that attract phagocytic, antigen-presenting dendritic cells to the area. It enters the dendritic cells and uses them to carry the *Shigella* through the intestinal wall to the underside. It then uses its type 3 secretion system to inject effector proteins from the phagosome into the cytoplasm. These proteins trigger apoptosis or cell suicide of the dendritic cell. Killing the dendritic cells prevents them from presenting *Shigella* to T4-lymphocytes, a step required for the production of antibodies against the *Shigella* (see Figure 5.3.4).

- For a movie showing *Shigella* being propelled by actin-based motility within a cell, see the Theriot Lab Website at Stanford University Medical School. Click on "Greatest Hits" and then on "*Shigella flexneri* associated with actin tails in PtK2 cells."

2. *Salmonella* use a type 3 secretion system to inject intestinal epithelial cells with effector proteins that stimulate actin re-arrangement and cause the epithelial cell's cytoplasmic to "ruffle" up and engulf the bacteria Figs. 5A - Figure 5.3.5B. The *Salmonella* pass through the epithelial cell where they are engulfed by phagocytic macrophages.

Once in the phagosome of the macrophage the bacterium uses its type 3 secretion system to inject proteins that prevent the lysosomes from fusing with the phagosomes, thus providing a safe haven for *Salmonella* replication within the phagosome and protecting the bacteria from antibodies and other defense elements (see Figs. 5C-5D).

By injecting flagellin into the cytoplasm of the macrophage the *Salmonella* can also eventually kill the macrophage by inducing apoptosis, a programmed cell suicide.

Flash animation showing a bacterium resisting phagocytosis by blocking the fusion of the phagosome with the lysosome.

html5 version of animation for iPad showing a bacterium resisting phagocytosis by blocking the fusion of the phagosome with the lysosome.

Molecules injected into the intestinal epithelial cells also stimulate diarrhea. Advantages of inducing diarrhea include (1) flushing out normal flora bacteria so there is less competition for nutrients; and (2) better enabling *Salmonella* that are not attached to host cells to be transmitted to a new host via the fecal-oral route.

For a movie showing Salmonella invading a human cell, see the Theriot Lab Website at Stanford University Medical School. Click on"Greatest Hits" and then on "*Salmonella typhimurium* invading a fibroblast cell."

3. *Listeria monocytogenes* is another bacterium that enters intestinal cells via invasins and spreads to adjacent cells by actin-based motility. Its actin-based motility enables it to moves approximately 1.5 µm per second within the host cell.

For movies showing *Listeria* entering host cells and being propelled by actin-based motility within a cell, see the Theriot Lab Website at Stanford University Medical School. Click on "Greatest Hits" and then on "Life history of a single infecting *Listeria monocytogenes*" and "*Listeria monocytogenes* moving in PtK2 cells."

4. Although enteroinvasive *Escherichia coli* (EIEC) don't have actin-based motility, they invade and kill epithelial cells of the colon in a manner similar to *Shigella*.

5. *Legionella pneumophila*, after being ingested by macrophages and placed in a phagosome, uses a type 4 secretion system to inject effector proteins that prevent the lysosomes from fusing with the phagosomes and turning the macrophage into a safe haven for bacterial replication. The same mechanism allows the *Legionella* to survive inside amoebas in nature. These amoebas serve as a reservoir for the bacterium in the environment.

6. F protein and M-protein of *Streptococcus pyogenes* (Group A beta streptococci) enables the bacterium to invade epithelial cells. This is thought to help maintain persistent streptococcal infections and enable the bacterium to spread to deeper tissues.

7. The spirochete *Borrelia bergdorferi* probably uses a combination of invasins and motility to penetrate host cells. In this case the host cell doesn't phagocytose the bacterium. Instead, one tip of the spirochete attaches to the host cell and some form of invasin apparently causes the host cell to release digestive enzymes that enable the spirochete with its corkscrewing motility to penetrate the host cell membrane. Once in the host cell the bacteria may remain dormant for years and hide from the immune system and antibiotics.

8. Another spirochete, *Treponema pallidum*, is thought to enter cells in a similar fashion. Motility also helps *B. bergdorferi* and *T. pallidum* to invade and leave blood vessels by passing between and through endothelial cells, thus enabling the spirochetes to disseminate to other locations in the body.

Electron micrograph of *Treponema pallidum* invading a host cell.

Flash animation showing spirochetes using motility and invasins to enter a blood vessel.

html5 version of animation for iPad showing spirochetes using motility and invasins to enter a blood vessel.

Briefly describe how they enter the epithelial cell and state 2 advantages this might provide the bacterium in terms of its pathogenicity.

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5.4: The Ability to Compete for Nutrients

State why the ability to compete for iron and other nutrients is important for bacteria to cause disease and describe briefly three ways bacteria may accomplish this as part of their pathogenicity.

Often the ability to be pathogenic is directly related to the bacterium's ability to compete successfully with host tissue and normal flora for limited nutrients. One reason the generation time of bacteria growing in the body is substantially slower than in lab culture is because essential nutrients are limited. In fact this is a major reason why the overwhelming majority of bacteria found in nature are not harmful to humans.

To be pathogenic, a bacterium must be able to multiply in host tissue. The more rapid the rate of replication, the more likely infection may be established. Pathogens, therefore, are able to compete successfully for limited nutrients in the body. Generally bacteria compete for nutrients by synthesizing specific transport systems or cell wall components capable of binding limiting substrates and transporting them into the cell. A good example of this is the ability of bacteria to compete for iron.

As we will see later in Unit 5 under innate immunity, the body makes considerable metabolic adjustment during infection to deprive microorganisms of iron. Iron is essential for both bacterial growth and human cell growth. Bacteria synthesize iron chelators - compounds capable of binding iron - called siderophores. Many siderophores are excreted by the bacterium into the environment, bind free iron, and then re-enter the cell and release the iron. Other siderophores are found on the cell wall where they bind iron and transport it into the bacterium.

Meanwhile, the body produces iron chelators of its own (transferrin, lactoferrin, ferritin, and hemin) so the concentration of free iron is very low. The ability of bacterial iron chelators to compete successfully with the body's iron chelators as well as those of normal flora may be essential to pathogenic bacteria. In addition to their own siderophores, some bacteria:

1. Produce receptors for siderophores of other bacteria in this way take iron from other bacteria.
2. Are able to bind human transferrin, lactoferrin, ferritin, and hemin and use that as their iron source. For example, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Haemophilus influenzae* are able to use iron bound to human transferrin and lactoferrin for their iron needs, while pathogenic *Yersinia* species are able to use transferrin and hemin as iron sources.
3. Produce proteases that degrade human lactoferrin, transferrin, or heme to release the bound iron for capture by bacterial siderophores.
4. Do not use iron as a cofactor. *Borrelia burgdorferi* instead uses manganese as a cofactor.
5. Are able to produce exotoxins that kill host cells only when iron concentrations are low. In this way the bacteria can gain access to the iron that was in those cells.

Staphylococcus aureus, on the other hand, produces surface adhesins that bind to extracellular matrix proteins and polysaccharides surrounding host cell tissue, including fibronectin, collagen, laminin, hyaluronic acid, and elastin. *S. aureus* proteases and hyaluronidase then dissolve these components of the extracellular matrix providing food for the bacteria and enabling the bacteria to spread.

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5: VIRULENCE FACTORS THAT PROMOTE COLONIZATION

Virulence factors are molecules expressed and secreted by that enable them to colonize the host, evade or inhibit the immune responses of the host, enter into or out of a host cell, and/or obtain nutrition from the host. The following are virulence factors that promote bacterial colonization of the host .

1. The ability to use motility and other means to contact host cells and disseminate within a host.
2. The ability to adhere to host cells and resist physical removal.
3. The ability to invade host cells.
4. The ability to compete for iron and other nutrients.
5. The ability to resist innate immune defenses such as phagocytosis and complement.
6. The ability to evade adaptive immune defenses.

5.0: Prelude to Virulence Factors that Promote Bacterial Colonization

5.1: The Ability to Use Motility and Other Means to Contact Host Cells

5.2: The Ability to Adhere to Host Cells and Resist Physical Removal

5.3: The Ability to Invade Host Cells

5.4: The Ability to Compete for Nutrients

5.5: The Ability to Resist Innate Immune Defenses

5.5A: An Overview to Resisting Innate Immune Defenses

5.5B: The Ability to Resist Phagocytic Engulfment (Attachment and Ingestion) and Antibacterial Peptides

5.5C: The Ability to Resist Phagocytic Destruction

5.6: The Ability to Evade Adaptive Immune Defenses

5.E: Virulence Factors that Promote Colonization (Exercises)

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5.5: THE ABILITY TO RESIST INNATE IMMUNE DEFENSES

Some bacteria are able to resist innate immune defenses such as phagocytosis and the body's complement pathways. We will break this down into two categories:

- The ability to resist phagocytic engulfment (attachment and ingestion)
- The ability to resist phagocytic destruction and complement serum lysis



-  Topic hierarchy

5.5A: An Overview to Resisting Innate Immune Defenses

5.5B: The Ability to Resist Phagocytic Engulfment (Attachment and Ingestion) and Antibacterial Peptides

5.5C: The Ability to Resist Phagocytic Destruction

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5.5A: An Overview to Resisting Innate Immune Defenses

Learning Objectives

1. Describe the following as they relate to phagocytosis:
   a. unenhanced attachment
   b. enhanced attachment
   c. ingestion
   d. destruction
2. State 4 different body defense functions of the body's complement pathways.
3. State what is meant by antibacterial peptides and give an example.

An Overview of Phagocytosis

As will be seen in Unit 5, there are several steps involved in phagocytosis.

a. Attachment

First the surface of the microbe must be attached to the cytoplasmic membrane of the phagocyte. Attachment of microorganisms is necessary for ingestion and may be unenhanced or enhanced.

1. **Unenhanced attachment** is a general recognition of what are called pathogen-associated molecular patterns or PAMPs - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, and glucans common in microbial cell walls but not found on human cells - by means of glycoprotein known as endocytic pattern-recognition receptors on the surface of the phagocytes (Figure $5.5A.1$).

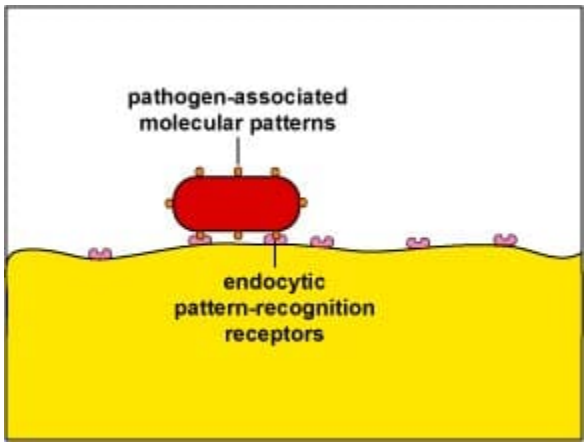


Figure $5.5A.1$: Unenhanced Attachment of Bacteria to Phagocytes. Glycoprotein molecules known as pattern-recognition receptors are found on the surface of phagocytes. They are so named because they recognize and bind to pathogen-associated molecular patterns - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, and glucans - found in many microorganisms.

2. **Enhanced attachment** is the attachment of microbes to phagocytes by way of molecules such as an antibody molecule called IgG and two proteins produced during the complement pathways called C3b and C4b (Figure $5.5A.2$). Molecules such as IgG, C3b, and C4b that promote enhanced attachment are called opsonins and the process is called opsonization. Enhanced attachment is much more specific and efficient than unenhanced.

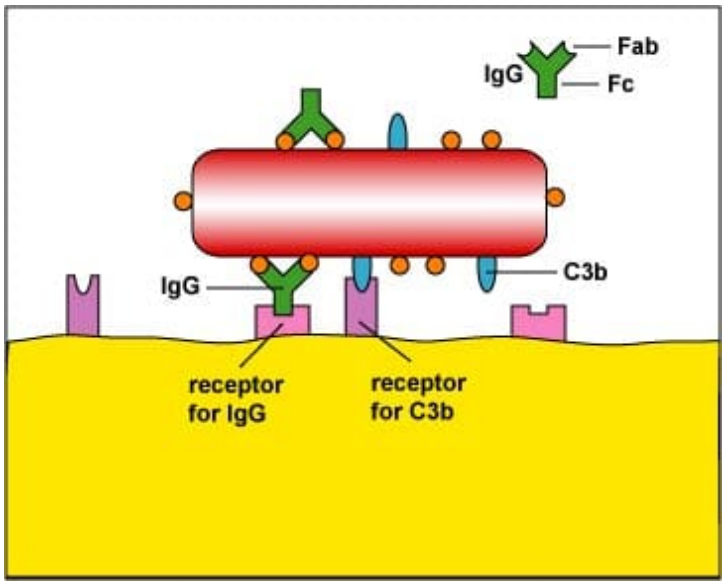


Figure 5.5A.2: One of the functions of certain antibody molecules known as IgG is to stick antigens such as bacterial proteins and polysaccharides to phagocytes. The tips of the antibody, the Fab portion, have a shape that fits epitopes, portions of an antigen with a complementary shape. The stalk of the antibody is called the Fc portion and is able to bind to Fc receptors on phagocytes. Also, when body defense pathways known as the complement pathways are activated, one of the beneficial defense proteins made is called C3b. C3b binds by one end to bacterial surface proteins and by the other end to C3b receptors on phagocytes. The IgG and C3b are also known as opsonins and the process of enhanced attachment is also called opsonization.

b. Ingestion

Following attachment, polymerization and then depolymerization of actin filaments send pseudopods out to engulf the microbe (Figure 5.5A.3) and place it in a vesicle called a phagosome (Figure 5.5A.4).

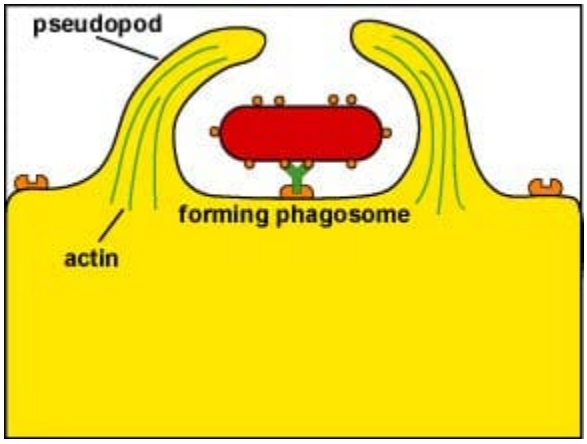


Figure 5.5A.3: Formation of Pseodopods by Rearrangement of Actin Molecules. Following attachment, polymerization and depolymerization of actin molecules send pseudopods out to engulf the bacterium and place it in a vesicle called a phagosome.

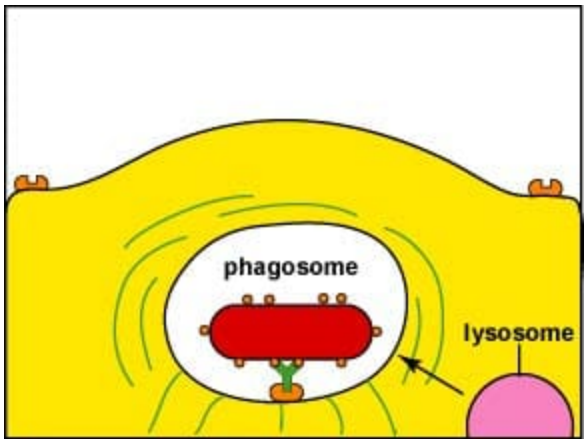


Figure 5.5A.4: Placing the Bacterium in a Phagosome. Following engulfment, the bacterium is placed in a vesicle called a phagosome.

During this process, an electron pump brings hydrogen ions (H^+) into the phagosome. This lowers the pH within the phagosome so that when a lysosome fuses with the phagosome, the pH is correct for the acid hydrolases to effectively break down cellular proteins.

c. Destruction

1. **Intracellular destruction**: Finally, lysosomes, containing digestive enzymes and microbicidal chemicals, fuse with the phagosome containing the ingested microbe and the microbe is destroyed (Figure 5.5A.5).

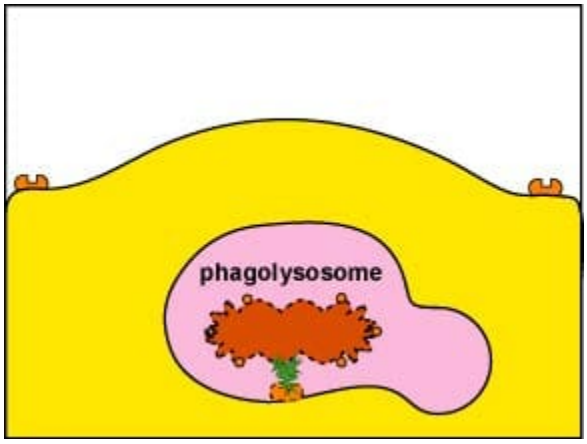


Figure 5.5A.5: Fusion of Phagosome and Lysosome. The lysosome its digestive enzymes and microbicidal chemicals fuses with the phagosome containing the ingested bacteria to form a phagolysosome and the bacterium is killed.

2. **Extracellular destruction**: If the the infection site contains very large numbers of microorganisms and high levels of inflammatory cytokines and chemokines are being produced in response to PAMPs, the phagocyte will empty the contents of its lysosomes by a process called *degranulation* to kill the microorganisms or cell extracellularly.

To view a scanning electron micrograph of a macrophage with pseudopods and phagocytosis of *E. coli* by a macrophage on a blood vessel, see Dennis Kunkel's Microscopy, University of Hawaii-Manoa.

An Overview of the Body's Complement Pathways

Some bacteria are able to interfere with the body's complement pathways. The complement pathways will be discussed in detail later in Unit 4, but a brief summary is relevant here. There are three complement pathways: the classical complement pathway, the alternative complement pathway, and the lectin pathway. While the three pathways differ in the way they are activated, once activated they all produce the same beneficial complement proteins. Basically the complement proteins are a series of serum proteins that when activated participate in four important body defense functions. These include:

a. Inflammation

Inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around an injured or infected site. Complement proteins known as C5a, C3a, and C4a lead to vasodilation, increased capillary permeability, and the expression of the adhesion molecules on leukocytes and the vascular endothelium. This enables leukocytes to adhere to the inner wall of the capillaries, pass between the endothelial cells, and enter the surrounding tissue. Vasodilation also enables a variety of defense chemicals in the plasma of the blood to enter the tissue. These defense chemicals include antibodies and complement proteins. C5a also causes neutrophils to release proteases and toxic oxygen radicals for extracellular killing of microbes.

b. Phagocyte Chemotaxis

Complement proteins C3a and C4a are chemoattractants for leukocytes. Chemotaxis enables the phagocytes to move toward the infected area in order to remove microorganisms.

c. Opsonization (Enhanced Attachment)

The complement proteins C3b and C4b are known as opsonins because they bind microbes to phagocytes (Figure $5.5A.2$). One portion of the molecule binds to microbial proteins while the other portion binds to receptors on phagocytes. In this way, microbes can be engulfed by phagocytes more effectively.

d. MAC Lysis of Biological Membranes

A series of complement proteins known as the *membrane attack complex* or MAC put pores in cellular membranes resulting in lysis. This is used to kill such things as Gram-negative bacteria, virus-infected cells, and tumor cells.

These processes will be discussed in greater detail in Unit 5.

Exercise: Think-Pair-Share Questions

1. Capsules often enable bacteria to resist phagocytosis by unenhanced attachment. Based on what we just learned, explain how.
2. Some bacteria are able to inhibits the C3 convertase enzyme, the enzyme that splits complement protein C3 into C3a and C3b. Explain how this might make it harder for that bacterium to be phagocytosed.

Antibacterial Peptides

The body produces a number of antibacterial peptides such as human *defensins* and *cathelicidins* that are directly toxic by forming pores in the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs. They also activate cells for an inflammatory response. Defensins are produced by leukocytes, epithelial cells, and other cells. They are also found in blood plasma and mucus.

Some bacteria are able to resist phagocytosis and interfere with the body's complement pathways. In the next two sections we will look at the following virulence factors:

1. The ability to resist phagocytic engulfment (attachment and ingestion)
2. The ability to resist phagocytic destruction and serum lysis

Summary

1. For phagocytosis to occur, the surface of the microbe must be attached to the cytoplasmic membrane of the phagocyte through unenhanced or enhanced attachment.
2. Following attachment, the microbe must be engulfed and placed on a membrane-bound vesicle called a phagosome. The phagosome then becomes acidified to provide the correct pH for killing by lysosomal enzymes.

3. Lysosomes, containing digestive enzymes and microbicidal chemicals, fuse with the phagosome containing the ingested microbe and the microbe is destroyed. This is referred to as intracellular killing by phagocytes and happens when microbial numbers are relatively low.
4. If the the infection site contains very large numbers of microorganisms and high levels of inflammatory cytokines and chemokines are being produced, the phagocyte will empty the contents of its lysosomes by a process called degranulation in order to kill the microorganisms extracellularly. This is referred to as extracellular killing.
5. The body's complement pathways consist of a variety of complement proteins that when activated participate in four important body defense functions: promoting inflammation, phagocyte chemotaxis, opsonization (enhanced attachment), and lysis of membrane-bound cells.
6. The body produces a number of antibacterial peptides that are directly toxic by forming pores in the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs.

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5.5B: The Ability to Resist Phagocytic Engulfment (Attachment and Ingestion) and Antibacterial Peptides

Learning Objectives

1. Briefly describe at least 3 ways capsules may enable bacteria to resist phagocytic engulfment and state how this can promote colonization.
2. State at least 2 mechanisms other than capsules that certain bacteria might use to resist phagocytic engulfment.
3. State 3 ways bacteria might resist antibacterial peptides like defensins.

Highlighted Bacterium

1. Read the description of *Haemophilus influenzae* and match the bacterium with the description of the organism and the infection it causes.

We will now look virulence factors that enable bacteria to resist phagocytic engulfment (attachment and ingestion) and antibacterial peptides. As we learned in Unit 1, capsule enable many organisms to resist phagocytic engulfment. For example, *Streptococcus pneumoniae* is able to initially evade phagocytosis and cause infections such as pneumococcal pneumonia, sinusitis, otitis media, and meningitis because of its capsule. Encapsulated strains of *Haemophilus influenzae* type b can causes severe respiratory infections, septicemia, epiglottitis, and meningitis in children (other non-encapsulated strains of *H. influenzae* usually cause mild respiratory infections such as sinusitis and otitis media). Other encapsulated bacteria include *Neisseria meningitidis*, *Bacillus anthracis*, and *Bordetella pertussis*.

Click on this link, read the description of *Haemophilus influenzae*, and be able to match the bacterium with its description on an exam.

Capsules that resist Unenhanced Attachment

Capsules can resist unenhanced attachment by preventing pathogen-associated molecular patterns or PAMPs - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, and glucans common in microbial cell walls but not found on human cells - from binding to endocytic pattern-recognition receptors on the surface of the phagocytes (Figure $5.5B.1$).

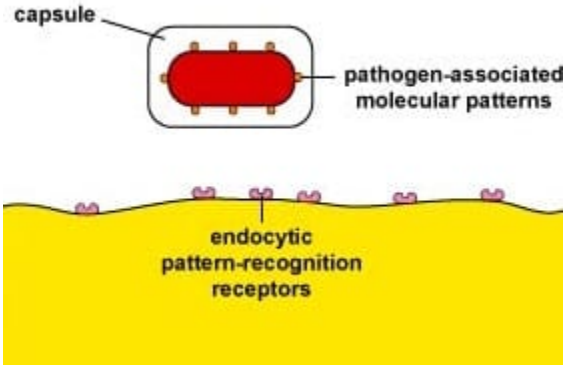


Figure $5.5B.1$: Capsules Blocking the Unenhanced Attachment of Bacteria to Phagocytes. Glycoprotein molecules known as endocytic pattern-recognition receptors are found on the surface of phagocytes. They are so named because they recognize and bind to pathogen-associated molecular patterns - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, and glucans - found in many microorganisms. Capsules can cover up these surface molecules preventing their attachment to the endocytic pattern-recognition sites on the phagocyte.

Capsules that Interfere with Complement Pathways

The capsules of some bacteria interfere with the host's complement pathways and do so in a number of ways:

The capsules of some bacteria prevent the formation of C3 convertase, an early enzyme in the complement pathways. Without this enzyme, the opsonins C3b and C4b involved in enhanced attachment, as well as the other beneficial complement proteins like C5a, are not produced.

Some capsules are rich in sialic acid, a common component of host cell glycoprotein. Sialic acid has an affinity for serum protein H, a complement regulatory protein that leads to the degradation of the opsonin C3b and the formation of C3 convertase. (Our body uses serum protein H to degrade any C3b that binds to host cell glycoproteins so that we don't stick our own phagocytes to our own cells with C3b.) Some *Neisseria meningitidis* strains synthesize their own sialic acid capsule. While *Neisseria gonorrhoeae* and *Hemophilus influenzae* type b do not have a sialic acid capsule, they are able to scavenge sialic acid from host cells and enzymatically transfer it to their surface where it subsequently binds protein H.

Some capsules simply cover the C3b that does bind to the bacterial surface and prevent the C3b receptor on phagocytes from making contact with the C3b (Figure $5.5B.2$). This is seen with the capsule of *Streptococcus pneumoniae*.

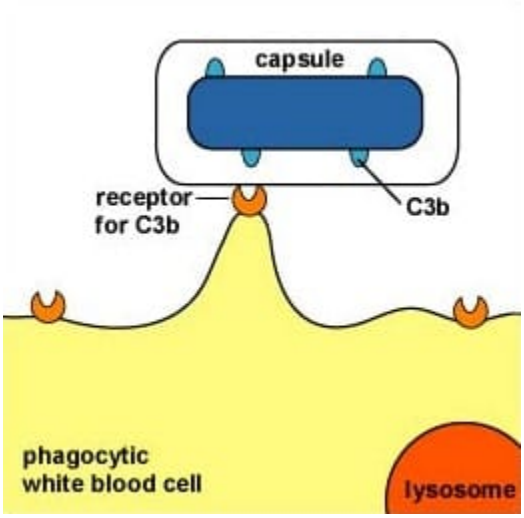


Figure $5.5B.2$: Bacterial Capsule Preventing C3b Receptors on Phagocytes from Binding to C3b Attached to a Bacterial Cell Wall. In some bacteria, the capsule covers the opsonin C3b bound to the bacterial cell wall so that it can't bind to C3b receptors (called CR1) on the surface of phagocytes.

Staphylococcus aureus produces a protein called Staphylococcal complement inhibitor that binds and inhibits the C3 convertase enzyme needed for all three complement pathways.

The body's immune defenses, however, can eventually get around these capsule by producing opsonizing antibodies (IgG) that stick capsules to the phagocyte. In vaccines against pneumococccal pneumonia and *Haemophilus influenzae* type b, it is capsular polysaccharide that is given as the antigen to stimulate the body to make opsonizing antibodies against the encapsulated bacterium.

Biofilms

Many pathogenic bacteria, as well as normal flora, form complex bacterial communities as biofilms. Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. By living as a community of bacteria as a biofilm, these bacteria are better able to:

- resist attack by antibiotics;
- trap nutrients for bacterial growth and remain in a favorable niche;
- adhere to environmental surfaces and resist flushing;
- live in close association and communicate with other bacteria in the biofilm; and

- resist phagocytosis and attack by the body's complement pathways.

Biofilms are, therefore, functional, interacting, and growing bacterial communities. Biofilms even contain their own water channels for delivering water and nutrients throughout the biofilm community. For example, *Pseudomonas aeruginosa* produces a glycocalyx composed of alginate. This enables strains producing the glycocalyx to block neutrophil chemotaxis, scavenge the hypochlorite molecules produced by neutrophils to kill bacteria, decrease phagocytosis, and inhibit activation of the complement pathways.

Other Mechanisms

The M-protein of *Streptococcus pyogenes* allows these bacteria to be more resistant to phagocytic engulfment. The M-protein of *S. pyogenes* binds factor H, a complement regulatory protein that leads to the degradation of the opsonin C3b and the formation of C3 convertase. (Our body uses serum protein H to degrade any C3b that binds to host cell glycoproteins so that we don't stick our own phagocytes to our own cells with C3b.) *S. pyogenes* also produces a protease that cleaves the complement protein C5a.

Coagulase, produced by *Staphylococcus aureus*. Coagulase causes fibrin clots to form around the organism that help enable it to resist phagocytosis. Our adaptive immune system has difficulty in recognizing the *S. aureus* as foreign when it is coated with a human protein.

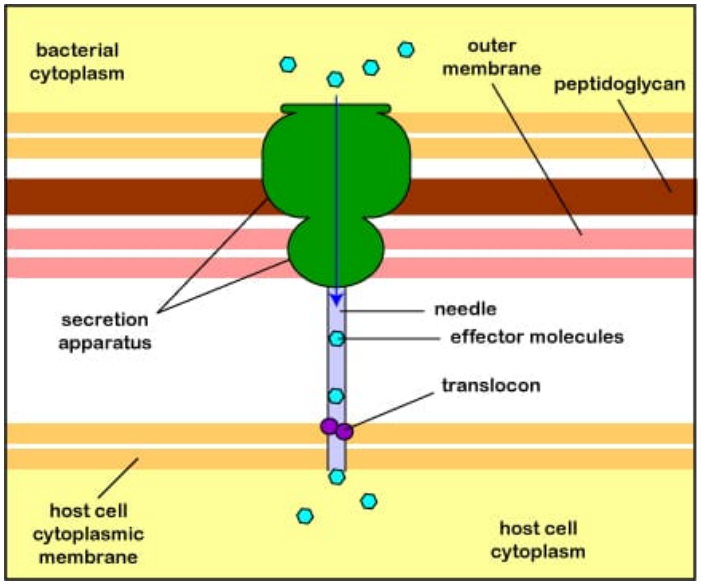


Figure 5.5B.3: The Bacterial Type 3 Secretion System. *Many bacteria involved in infection have the ability to co-opt the functions of the host cell to the benefit of the bacterium. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication. The most common type is the type 3 secretion system. A secretion apparatus in the cytoplasmic membrane and cell wall of the bacterium polymerizes a hollow needle that is lowered to the cytoplasmic membrane of the host cell and a translocon protein is then delivered to anchor the needle to the host cell. Effector proteins in the bacterium can now be injected into the cytoplasm of the host cell. The delivery system is sometimes called an injectisome.*

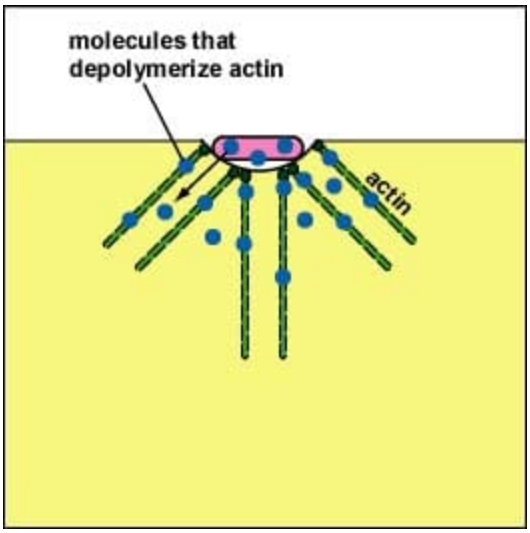
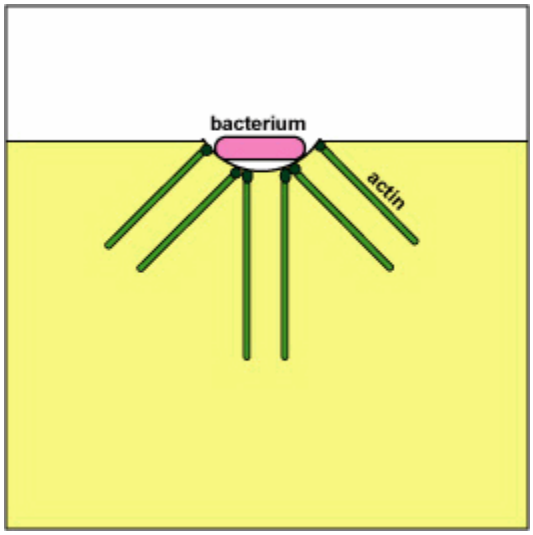


Figure $5.5B.4$: Blocking Phagosome Formation by Depolymerizing Actin. Molecules of some bacteria, through a type III secretion system, deliver effector proteins that depolymerize the actin microfilaments of the phagocyte used for phagocytic engulfment.

Pathogenic *Yersinia*, such as the species that causes plague, *Y. pestis*, contact phagocytes and, by means of a type III secretion system (Figure $5.5B.3$), deliver proteins that depolymerize the actin microfilaments needed for phagocytic engulfment into the phagocytes (Figure $5.5B.4$).



Blocking Phagosome Formation by Depolymerizing Actin. Molecules of some bacteria, through a type III secretion system, deliver proteins that depolymerize the phagocyte's actin microfilaments used for phagocytic engulfment.

The pili (fimbriae) of *Streptococcus pyogenes* both blocks the activation of the complement pathways on the bacterial cell wall and helps to resist phagocytic engulfment.

Exercise: Think-Pair-Share Questions

The vaccine for *Haemophilus influenzae* type b contains capsular material from this bacterium. The body recognizes this capsular material as foreign and produces antibodies against it. Describe how this might this protect the person from infection with this bacterium compared to a person who is not immunized.

Certain bacteria can resist antibacterial peptides

Human defensins are short cationic peptides 29-34 amino acids long that are directly toxic by forming pores in the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs. They also activate cells for an inflammatory response. Defensins are produced by leukocytes, epithelial cells, and other cells. They are also found in blood plasma and mucus. Cathelicidinsare proteins produced by skin and mucosal epithelial cells. The two peptides produced upon cleavage of the cathelicidin are directly toxic to a variety of microorganisms. One pepitide also can bind to and neutralize LPS from Gram-negative cell walls to reduce inflammation.

a. Capsules help prevent antibacterial peptides from reaching the cytoplasmic membrane of some bacteria.
b. The *lipopolysaccharide* (LPS) of the gram-negative cell wall binds cationic antibacterial peptides and prevents them from reaching the cytoplasmic membrane.
c. Some bacteria secrete peptidases that break down antibacterial peptides.

Summary

1. Capsules can resist unenhanced attachment by by preventing pathogen-associated molecular patterns or from binding to endocytic pattern-recognition receptors on the surface of the phagocytes.
2. The capsules of some bacteria interfere with the body's complement pathway defenses.
3. The body's immune defenses can eventually get around the capsule by producing opsonizing antibodies (IgG) against the capsule that stick the capsule to the phagocyte. This is the principle behind some vaccines.
4. Biofilms enable bacteria to: resist attack by antibiotics; trap nutrients for bacterial growth and remain in a favorable niche; adhere to environmental surfaces and resist flushing; live in close association and communicate with other bacteria in the biofilm; and resist phagocytosis and attack by the body's complement pathways.
5. Certain bacteria can resist antibacterial peptides.

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5.5C: The Ability to Resist Phagocytic Destruction

State at least 4 different ways bacteria might be able to resist phagocytic destruction once engulfed.

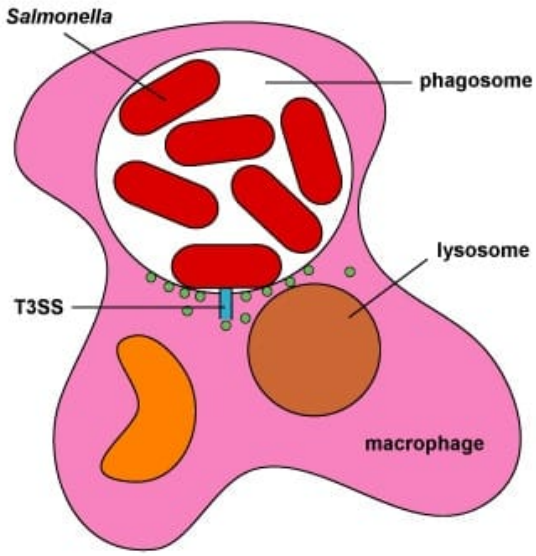


Figure $5.5C.1$: Salmonella Surviving Inside Macrophages. Once in the phagosome of the macrophage the bacterium uses its type 3 secretion system to inject proteins that prevent the lysosomes from fusing with the phagosomes, thus providing a safe haven for Salmonella replication within the phagosome and protecting the bacteria from antibodies and other defense elements.

Legionella pneumophila, after being ingested by macrophages and placed in a phagosome, uses a type 4 secretion system to inject effector proteins that prevent the lysosomes from fusing with the phagosomes and turning the macrophage into a safe haven for bacterial replication. *Neisseria gonorrhoeae* produces Por protein (protein I) that prevents phagosomes from fusing with lysosomes enabling the bacteria to survive inside phagocytes.

Cell wall lipids of *Mycobacterium tuberculosis*, such as lipoarabinomannan, arrest the maturation of phagosomes preventing delivery of the bacteria to lysosomes. Some bacteria, such as species of *Salmonella*, *Mycobacterium tuberculosis*, *Legionella pneumophila*, and *Chlamydia trachomatis*, block the vesicular transport machinery that enables the lysosome to move to the phagosome for fusion.

Escaping from the Phagosome

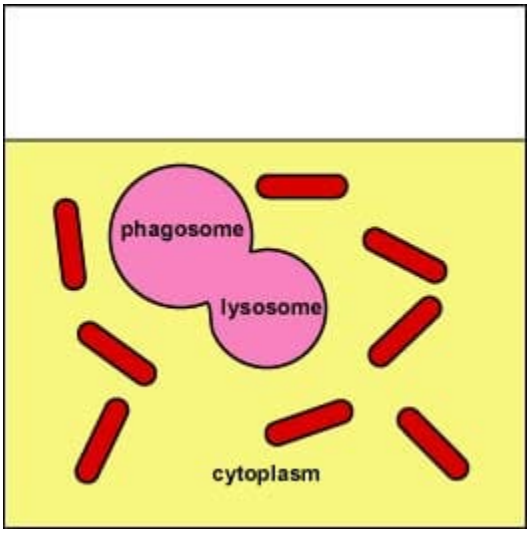


Figure 5.5C.2: Bacteria Escaping from a Phagosome. Some bacteria resist phagocytosis by escaping from the phagosome prior to its fusing with a lysosome.

Preventing Acidification of the Phagosome

Some bacteria, such as pathogenic *Mycobacterium* and *Legionella pneumophilia*, prevent the acidification of the phagosome that is needed for effective killing of microbes by lysosomal enzymes. (Normally after the phagosome forms, the contents become acidified because the lysosomal enzymes used for killing (acid hydrolases) function much more effectively at an acidic pH.)

Resisting killing by Lysosomal Chemicals

Some bacteria, such as *Salmonella*, are more resistant to toxic forms of oxygen and to defensins, the toxic peptides that kill bacteria by damaging their cytoplasmic membranes. The carotenoid pigments that give *Staphylococcus aureus* species its golden color and group B streptococci (GBS) its orange tint shield the bacteria from the toxic oxidants that neutrophils use to kill bacteria.

Resisting phagocytic destruction: killing the phagocyte

Some bacteria are able to kill phagocytes. Bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes* produce the exotoxin leukocidin that damages either the cytoplasmic membrane of the phagocyte or the membranes of the lysosomes, resulting in the phagocyte being killed by its own enzymes. *Shigella* and *Salmonella*, induce macrophage apoptosis, a programmed cell death.

Some bacteria, such as pathogenic *Mycobacterium* and *Legionella pneumophilia* prevent the acidification of the phagosome within phagocytes. Why might this protect these bacteria from being killed within the phagocyte?

- *Staphylococcus aureus* and *Streptococcus pyogenes* both produce a toxin called leukocydin. How might this enable these bacteria to resist phagocytosis?

Summary

1. Some bacteria resist phagocytic destruction by preventing fusion of the lysosome with the phagosome.
2. Some bacteria resist phagocytic destruction by escaping from the phagosome before the lysosome fuses.
3. Some bacteria resist phagocytic destruction by preventing acidification of the phagosome.
4. Some bacteria resist phagocytic destruction by resisting killing by lysosomal chemicals.

5. Some bacteria resist phagocytic destruction by killing phagocytes.

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5.6: The Ability to Evade Adaptive Immune Defenses

Learning Objectives

1. State four ways the antibody molecules made during adaptive immunity protect us against bacteria.
2. Briefly describe at least three ways a bacterium might evade our adaptive immune defenses and name a bacterium that does each.

Overview of Adaptive Immune Defenses

One of the major defenses against bacteria is the immune defenses' production of antibody molecules against the organism. The "tips" of the antibody, called the Fab portion (Figure 5.6.1) have shapes that are complementary to portions of bacterial proteins and polysaccharides called *epitopes*. The "bottom" of the antibody, called the Fc portion (Figure 5.6.1) binds to receptors on phagocytes and NK cells) and can activate the classical complement pathway.

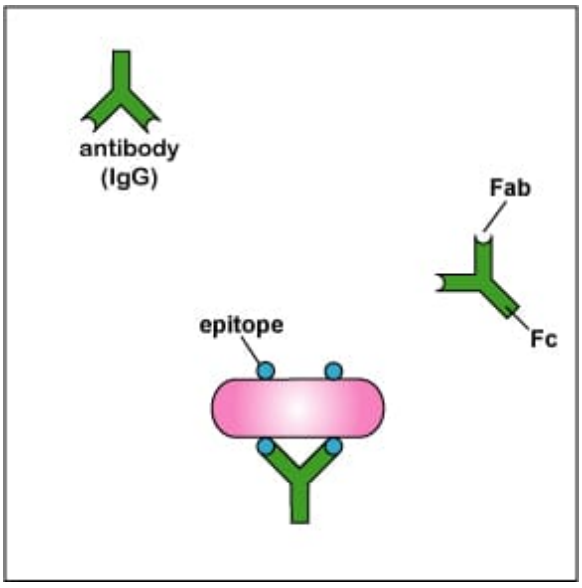


Figure 5.6.1: Normal Antibody-Antigen Reaction. The Fab portion of the antibody has specificity for binding an epitope of an antigen. An epitope is the portion of an antigen - such as a few amino acids sticking out of a protein - to which the Fab portion of an antibody molecule fits. The Fc portion directs the biological activity of the antibody. In the case of IgG, the Fc portion can bind to phagocytes for enhanced attachment (opsonization) as well as activate the classical complement pathway. Antibodies are composed of 4 protein chains: 2 identical heavy chains and 2 identical light chains. Disulfide (S-S) bonds join the protein chains together.

There are various ways that the antibodies the body makes during adaptive immunity protect the body against bacteria:

a. As mentioned above under phagocytosis, some antibodies such as IgG and IgE function as opsonins and stick bacteria to phagocytes (Figure 5.6.2).

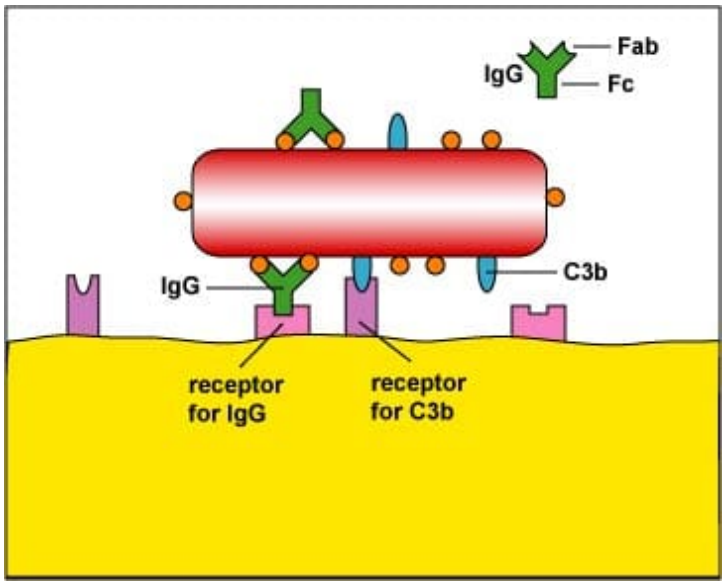


Figure 5.6.2: An epitope is the portion of an antigen - such as a few amino acids sticking out of a protein - to which the Fab portion of an antibody molecule fits. One of the functions of certain antibody molecules known as IgG is to stick antigens such as bacterial proteins and polysaccharides to phagocytes. The tips of the antibody, the Fab portion, have a shape that fits epitopes, portions of an antigen with a complementary shape. The stalk of the antibody is called the Fc portion and is able to bind to Fc receptors on phagocytes. Also, when body defense pathways known as the complement pathways are activated, one of the beneficial defense proteins made is called C3b. C3b binds by one end to bacterial surface proteins and by the other end to C3b receptors on phagocytes. The IgG and C3b are also known as opsonins and the process of enhanced attachment is also called opsonization.

b. Antibodies, such as IgG, IgA, and IgM, can bind to bacterial adhesins, pili, and capsules and in this way block their attachment to host cells.

c. IgG and IgM can also activate the classical complement pathway providing all of its associated benefits.

d. IgA and IgM can clump bacteria together enabling them to be more readily removed by phagocytes (Figure 5.6.3).

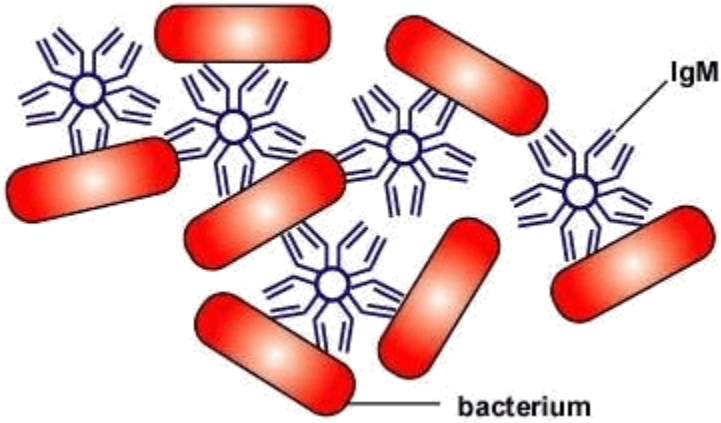


Figure 5.6.3: Agglutination of Microorganisms. The multiple Fab portions of IgM link microorganism together so out of the lymph and blood and phagocytosed more effectively.

These mechanisms will be discussed in greater detail in Unit 6.

Exercise: Think-Pair-Share Questions

1. *Staphylococcus aureus* produces protein A, a protein that binds to the Fc portion of antibodies.

How might this enable S. *aureus* to resist adaptive immunity?

2. Many bacteria that colonize the mucous membranes produce immunoglobulin protease, an enzyme that hydrolizes antibodies of the IgA class.

   How might this enable these bacteria to resist adaptive immunity?

Resisting Adaptive Immune Defenses

Bacteria utilize a variety of mechanisms to resist antibodies made during adaptive immunity. These include the following:

a. Certain bacteria can evade antibodies is by changing the adhesive tips of their pili as mentioned above with *Escherichia coli* and *Neisseria gonorrhoeae* (Figure 5.6.4).

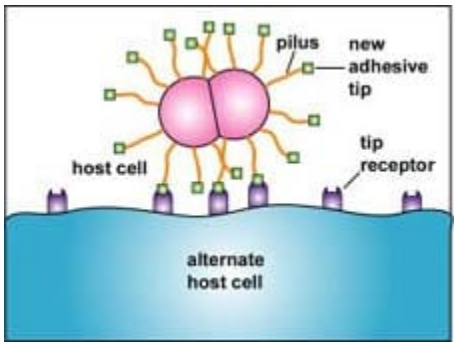


Figure 5.6.4: Bacteria Altering the Adhesive Tips of Their Pili. By genetically altering the adhesive tips of their pili, certain bacteria are able to: 1) adhere to and colonize different cell types with different receptors, and 2) evade antibodies made against the previous pili.

Bacteria can also vary other surface proteins so that antibodies previously made against those proteins will no longer "fit." (Figure 5.6.5). For example, *N. gonorrhoeae* produces Rmp protein (protein III) that protects against antibody attack by antibodies made against other surface proteins (such as adhesins) and the lipooligosaccharide (LOS) of the bacterium.

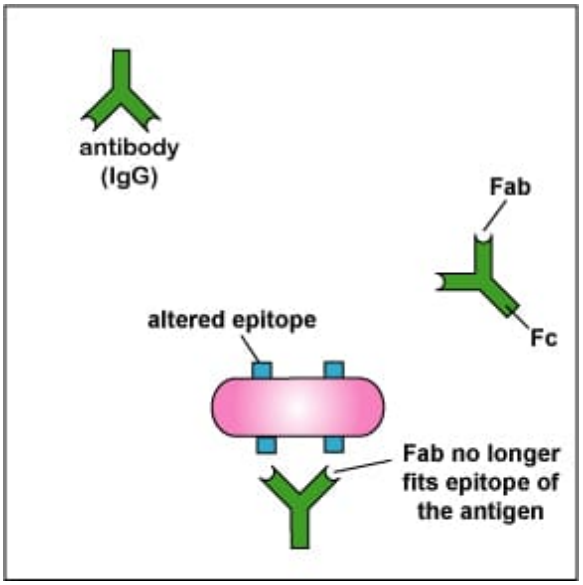


Figure 5.6.5: (A) Normal Antibody-Antigen Reaction. The Fab portion of the antibody has specificity for binding an epitope of an antigen. An epitope is the portion of an antigen - such as a few amino acids sticking out of a protein - to which the Fab portion of an antibody molecule fits. The Fc portion of an antibody directs the biological activity of the antibody. In the case of IgG, the Fc portion can bind to phagocytes for enhanced attachment (opsonization) as well as activate the classical complement pathway. (B) Altering Epitopes of an Antigen in order to Resist Antibody Molecules. The Fab portion of the antibody has specificity for binding an epitope of an antigen. By altering the molecular shape of an epitope of an antigen through mutation or genetic recombination, previous antibody molecules agains the original shaped epitope no longer fit or bind to the antigen.

b. Strains of *Neisseria meningitidis* have a capsule composed of sialic acid while strains of *Streptococcus pyogenes* (group A beta streptococci) have a capsule made of hyaluronic acid. Both of these polysaccharides closely resemble carbohydrates found in human tissue and because they are not recognized as foreign by the lymphocytes that carry out the adaptive immune responses, antibodies are not made against those capsules. Likewise, some bacteria are able to coat themselves with host proteins such as fibronectin, lactoferrin, or transferrin and in this way avoid having antibodies being made against them because they are unable to be recognized as foreign by lymphocytes.

c. *Staphylococcus aureus* produces protein A while *Streptococcus pyogenes* produces protein G. Both of these proteins bind to the Fc portion of the antibody IgG, the portion that is supposed to bind the bacterium to phagocytes during enhanced attachment (Figure 5.6.1). The bacteria become coated with antibodies in a way that does not result in opsonization (Figure 5.6.6).

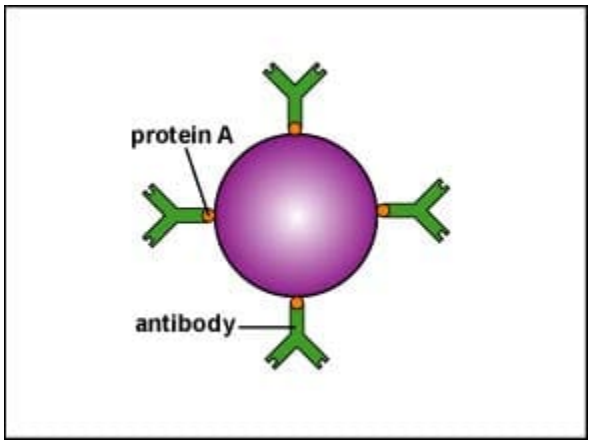


Figure 5.6.6: Staphylococcus aureus Resisting Opsonization via Protein A. The Fc portion of the antibody IgG, the portion that would normally binds to Fc receptors on phagocytes, instead binds to protein A on Staphylococcus aureus. In this way the bacterium becomes coated with a protective coat of antibodies that do not allow for opsonization.

d. *Salmonella* species can undergo phase variation of their capsular (K) and flagellar (H) antigens, that is, they can change the molecular shape of their capsular and flagellar antigens so that antibodies made against the previous form no longer fit the new form (Figure 5.6.5).

e. Bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Helicobacter pylori*, *Shigella flexneri*, *Neisseria meningitidis*, *Neisseria gonorrhoeae* and enteropathogenic *E. coli* produce immunoglobulin proteases. Immunoglobulin proteases degrade the body's protective antibodies (immunoglobulins) that are found in body secretions, a class of antibodies known as IgA.

f. Many pathogenic bacteria, as well as normal flora, form complex bacterial communities as biofilms. Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing (discussed later in this unit) and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. By living as a community of bacteria as a biofilm, these bacteria are better able to resist attack by antibiotics and are better able to resist the host immune system.

Summary

1. There are various ways that the antibodies the body makes during adaptive immunity protect the body against bacteria.
2. Some antibodies such as IgG and IgE function as opsonins and stick bacteria to phagocytes (opsonization or enhanced attachment).
3. Antibodies, such as IgG, IgA, and IgM, can bind to bacterial adhesins, pili, and capsules and in this way block their attachment to host cells.
4. IgG and IgM can activate the classical complement pathway providing all of its associated benefits.
5. IgA and IgM can clump bacteria together enabling them to be more readily removed by phagocytes.
6. Antitoxin antibodies, mainly IgG, are made against bacterial exotoxins. They combine with the exotoxin molecules before they can interact with host target cells and thus neutralize the toxin.
7. Bacteria utilize a variety of mechanisms to resist antibodies made during adaptive immunity.
8. Some bacteria can vary their surface proteins or polysaccharides so that antibodies previously made against those proteins

will no longer "fit."

9. Some bacteria are able to coat themselves with host proteins and in this way avoid having antibodies being made against them because they are unable to be recognized as foreign
10. Some bacteria produce immunoglobulin proteases that degrade the body's protective antibodies (immunoglobulins) that are found in body secretions.

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5.E: Virulence Factors that Promote Colonization (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

5.0: virulence factors that promote bacterial colonization of the host

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. List 6 virulence factors that promote bacterial colonization of the host.
   a.
   b.
   c.
   d.
   e.
   f.

5.1: The Ability to Use Motility and Other Means to Contact Host Cells

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State why it might be of an advantage for a bacterium trying to colonize the bladder or the intestines to be motile.
2. Briefly describe how the spirochete *Treponema pallidum* that causes syphilis uses its motility to disseminate from the initial infection site to other parts of the body.
3. Give a brief description of how a bacterium may use toxins to better disseminate from one host to another.

5.2: The Ability to Adhere to Host Cells and Resist Physical Removal

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe 3 different mechanisms by which bacteria can adhere to host cells and colonize. Name 2 bacteria that utilize each mechanism and name an infection that each bacterium causes.
   A.
   B.
   C.
2. Define biofilm and state 5 benefits associated with bacteria living as a community within a biofilm.
3. By activating different genes, *Neisseria gonorrhoeae* is able to rapidly alter the amino acid sequence of the adhesive tip of its pili. Why might this be an advantage?

5.3: The Ability to Invade Host Cells

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write

them out. This will not test your understanding of this tutorial.

1. Briefly describe a mechanism by which invasins enable certain bacteria to enter host cells.
2. Briefly describe how a type 3 secretion system might be used to invade and survive inside host cells.

5.4: The Ability to Compete for Nutrients

Questions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State why the ability to compete for iron is important for bacteria to cause disease.

5.5: The Ability to Resist Innate Immune Defenses

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe unenhanced attachment as it relates to phagocytosis.
2. Describe enhanced attachment as it relates to phagocytosis.
3. Describe ingestion as it relates to phagocytosis.
4. Describe destruction as it relates to phagocytosis.
5. State 4 different body defense functions of the body's complement pathways.

5.5B

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe 3 ways capsules may enable bacteria to resist phagocytic engulfment.
2. State 2 mechanisms other than capsules that certain bacteria might use to resist phagocytic engulfment.
3. The vaccine for *Haemophilus influenzae* type b contains capsular material from this bacterium. The body recognizes this capsular material as foreign and produces antibodies against it. One part of the antibody is able to bind to the capsular material while another part has a shape that fits a receptor on phagocytic cells. Why might this protect the person from infection with this bacterium?

5.C: The Ability to Resist Phagocytic Destruction

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State 4 different ways bacteria might be able to resist phagocytic destruction once engulfed.

5.6: The Ability to Evade Adaptive Immune Defenses

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write

them out. This will not test your understanding of this tutorial.

1. State 4 four ways the antibody molecules made during adaptive immunity protect us against bacteria.
2. Briefly describe 3 ways a bacterium might evade our immune defenses and name a bacterium that does each.
   A.
   B.
   C.

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6: VIRULENCE FACTORS THAT DAMAGE THE HOST

Virulence factors that damage the host include: (1) the ability of PAMPs to trigger the production of inflammatory cytokines that result in an excessive inflammatory response; (2) the ability to produce harmful exotoxins; (3) and the ability to induce autoimmune responses. Most of the virulence factors we will discuss in this section that enable bacteria to harm the body are the products of quorum sensing genes. We will now look at each of these factors in greater detail.

6.1: The Ability of PAMPs to Trigger the Production of Inflammatory Cytokines that Result in an Excessive Inflammatory Response

6.1A: Overall Mechanism

6.1B: Gram-Negative Bacterial PAMPs

6.1C: Gram-Positive Bacterial PAMPs

6.1D: Acid-Fast Bacterial PAMPs

6.2: The Ability to Produce Harmful Exotoxins: An Overview

6.2A: Type I Toxins: Superantigens

6.2B: Type II Toxins: Toxins that Damage Host Cell Membranes

6.2C: Type III Toxins: A-B Toxins and other Toxins that Interfere with Host Cell Function

6.3: The Ability to Induce Autoimmune Responses

6.E: Virulence Factors that Damage the Host (Exercises)

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6.1: THE ABILITY OF PAMPS TO TRIGGER THE PRODUCTION OF INFLAMMATORY CYTOKINES THAT RESULT IN AN EXCESSIVE INFLAMMATORY RESPONSE



- Topic hierarchy

6.1A: Overall Mechanism

6.1B: Gram-Negative Bacterial PAMPs

6.1C: Gram-Positive Bacterial PAMPs

6.1D: Acid-Fast Bacterial PAMPs

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6.1A: Overall Mechanism

Define cytokine and chemokine and name 3 inflammatory cytokines.

- State the mechanism forinflammation and state why it is primarily beneficial to the body.
- Briefly describe why inflammation during a minor or moderate infection is essentially beneficial while inflammation during a massive infection can cause considerable damage to the body.
- Looking at the overall mechanism behind septic shock, answer the following:

1. Describe how bacterial PAMPS initiate SIRS.
2. Define hypotension and describe the biological mechanism behind 3 factors that contribute to hypotension.
3. Define hypovolemia and describe the biological mechanism behind 3 factors that contribute to hypovolemia.
4. Define hypoperfusion and describe the biological mechanism behind at least 3 factors that contribute to hypoperfusion.
5. Describe the biological mechanism behind ARDS and how ARDS contributes to hypoperfusion.
6. Describe the sequence of events that enables hypoperfusion to lead to irreversible cell damage.

- Define pyroptosis and inflammasome and state their role in inducing inflammation.
- Define the following:

A. vasodilation
B. septicemia
C. hypotension
D. hypovolemia
E. septic shock
F. DIC
G. ARDS
H. MOSF
I. hypoperfusion

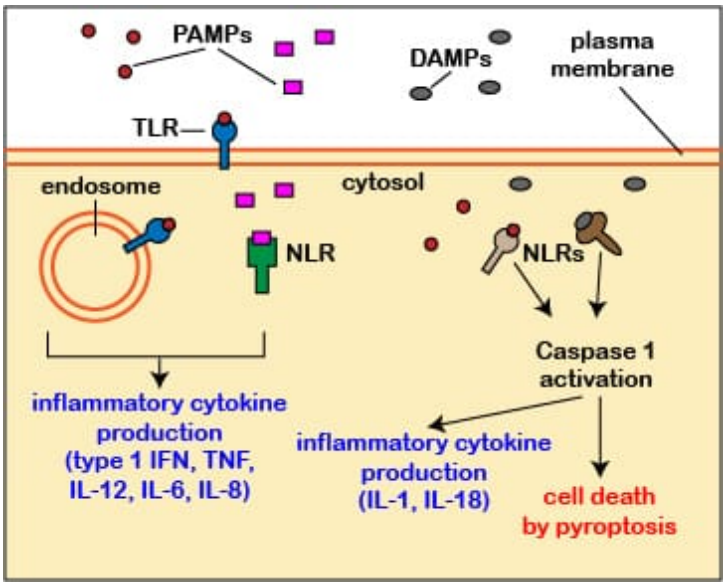


Figure 6.1A.6.1A.1: Activation of Pyroptosis Pyroptosis is initiated by PAMPs binding to pattern-recognition receptors (PRRs) on various defense cells, such as the Toll-like receptors (TLR) shown here. This, in turn, triggers the production of type-1 interferons and inflammatory cytokines such as TNF, IL-12, IL-6, and IL-8. Other PRRs, called nod-like receptors (NLRs) located in the cytosol of these defense cells recognize PAMPs and DAMPs that have entered the host cell's cytosol. Some NLRs trigger the production of inflammatory cytokines such as IL-1 and IL-18 while others activate caspase 1-dependent pyroptosis of the cell causing the release of its intracellular inflammatory cytokines. (While not shown here, the binding of PAMPs or DAMPs to their respective NLRs triggers the assembly of multiprotein complexes called inflammasomes in the cytosol of the host cell. It is these inflammasomes that activate caspase 1 and induce inflammation and pyroptosis.)

The binding of PAMPs to PRRs also leads to activation of the complement pathways and activation of the coagulation pathway.

Cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-8 (IL-8) are known as inflammatory cytokines because they promote inflammation. Some cytokines, such as IL-8, are also known as chemokines. Chemokines promote an inflammatory response by enabling white blood cells to leave the blood vessels and enter the surrounding tissue, by chemotactically attracting these white blood cells to the infection site, and by triggering neutrophils to release killing agents for extracellular killing.

Inflammation is the first response to infection and injury and is critical to body defense. Basically, the inflammatory response is an attempt by the body to restore and maintain homeostasis after injury. Most of the body defense elements are located in the blood, and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around an injured or infected site. The release of inflammatory cytokines eventually leads to vasodilation of blood vessels. Vasodilation is a reversible opening of the junctional zones between endothelial cells of the blood vessels and results in increased blood vessel permeability. This enables plasma, the liquid portion of the blood, to enter the surrounding tissue. The plasma contains defense chemicals such as antibody molecules, complement proteins, lysozyme, and human defensins. Increased capillary permeability also enables white blood cells to squeeze out of the blood vessels and enter the tissue. As can be seen, inflammation is necessary part of body defense. Excessive or prolonged inflammation can, however, cause harm as will be discussed below.

(Scanning electron micrographs of a cross section of a capillary showing an endothelial cell and a capillary with a red blood cell; courtesy of Dennis Kunkel's Microscopy.)

Flash animation of a capillary prior to vasodilation.

Flash animation showing vasodilation.

html5 version of animation for iPad of a capillary prior to vasodilation.

html5 version of animation for iPad of vasodilation.

For more information: Preview of inflammation from Unit 5

As mentioned in a previous section, products of the complement pathways lead to: 1)more inflammation; 2) opsonization of bacteria; 3) chemotaxis of phagocytes to the infected site; and 4) MAC lysis of gram-negative bacteria.

For more information : Preview of the complement pathways from Unit 5

The products of the coagulation pathway lead to the clotting of blood to stop bleeding, more inflammation, and localization of infection.

At moderate levels, inflammation, products of the complement pathways, and products of the coagulation pathway are essential to body defense. However, these same processes and products when excessive can cause considerable harm to the body.

Flash animation illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

During minor local infections with few bacteria present, low levels of PAMPs are released leading to moderate cytokine production by defense cells such as monocytes, macrophages, and dendritic cells and, in general, promoting body defense by stimulating inflammation and moderate fever, breaking down energy reserves to supply energy for defense, activating the complement pathway and the coagulation pathway, and generally stimulating immune responses (see Figure 6.1A.2). Also as a result of these cytokines, circulating phagocytic white blood cells such as neutrophils and monocytes stick to the walls of capillaries, squeeze out and enter the tissue, a process termed diapedesis. The phagocytic white blood cells such as neutrophils then kill the invading microbes with their proteases and toxic oxygen radicals. These defenses will be covered in greater detail in Units 5 and 6.

However, during severe systemic infections with large numbers of bacteria present, high levels of PAMPs are released resulting in excessive cytokine production by the defense cells and this can harm the body (see Figure 6.1A.3). In addition, neutrophils start releasing their proteases and toxic oxygen radicals that kill not only the bacteria, but the surrounding tissue as well. Harmful effects include high fever, hypotension, tissue destruction, wasting, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and damage to the vascular endothelium. This can result in shock, multiple system organ failure (MSOF), and death.

YouTube animation illustrating macrophages releasing cytokines.
Nucleus Medical Art, www. nucleusinc.com

Concept Map for Synthesizing and Secreting Inflammatory Cytokines and Chemokines in Response to PAMPs

Sepsis and Systemic Inflammatory Response Syndrome (SIRS)

Keep in mind that a primary function of the circulatory system is perfusion, the delivery of nutrients and oxygen via arterial blood to a capillary bed in tissue. This, in turn, delivers nutrients for cellular metabolism and oxygen for energy production via aerobic respiration to all of the cells of the body. Sepsis is an infection that leads to a systemic inflammatory response resulting in physiologic changes occurring at the capillary endothelial level. This systemic inflammatory response is referred to as Systemic Inflammatory Response Syndrome or SIRS.

Based on severity, there are three sepsis syndromes based on severity:

1. Sepsis. SIRS in the setting of an infection.

2. Severe sepsis. An infection with end-organ dysfunction as a result of hypoperfusion, the reduced delivery of nutrients and oxygen to tissues and organs via the blood.

3. Septic shock. Severe sepsis with persistent hypotension and tissue hypoperfusion despite fluid resuscitation.

We will now take a look at the underlying mechanism of SIRS that can result in septic shock.

Systemic Inflammatory Response Syndrome (SIRS) Resulting in Septic Shock

During a severe systemic infection, an excessive inflammatory response triggered by overproduction of inflammatory cytokines such as TNF-alpha, IL-1, IL-6, IL-8, and PAF in response to PAMPs often occurs.

The release of inflammatory cytokines eventually leads to vasodilation of blood vessels. Vasodilation is a reversible opening of the junctional zones between endothelial cells of the blood vessels and results in increased blood vessel permeability. Normally, this fights the infection by enabling plasma, the liquid portion of the blood, to enter the surrounding tissue. The plasma contains defense chemicals such as antibody molecules, complement proteins, lysozyme, and human defensins. Increased capillary permeability also enables white blood cells to adhere to the inner capillary wall, squeeze out of the blood vessels, and enter the tissue to fight infection, a process called diapedesis.

Excessive productions of cytokines during a systemic infection results in the following events:

1. During diapedesis, phagocytic WBCs called neutrophils adhere to capillary walls in massive amounts. Chemokines such as IL-8 activate extracellular killing by neutrophils, causing them to release proteases and toxic oxygen radicals while still in the capillaries. These are the same toxic chemicals neutrophils use to kill microbes, but now they are dumped onto the vascular endothelial cells to which the neutrophils have adhered.

    a. This results in damage to the capillary walls and leakage of blood into surrounding tissue (see Figure 6.1A.4).

    b. Blood leakage, in turn, can result in hypovolemia, a decreased volume of circulating blood. (Bleeding from physical trauma, internal bleeding, insufficient rehydration, and loss of fluids from vomiting and diarrhea can also lead to hypovolemia.)

    c. Hypovolemia then contributes to hypotension, or low blood pressure.

    d. Hypotension then contributes to hypoperfusion.

Flash animation summarizing early inflammation and diapedesis.

html5 version of animation for iPad summarizing early inflammation and diapedesis.

Flash animation summarizing late inflammation and diapedesis.

html5 version of animation for iPad summarizing late inflammation and diapedesis.

Flash animation of extracellular killing by neutrophils.

html5 version of animation for iPad of extracellular killing by neutrophils.

2. Prolonged vasodilation and the resulting increased capillary permeability causes plasma to leave the bloodstream and enter the tissue.

    a. This too contributes to a decreased volume of circulating blood or hypovolemia.

    b. Hypovolemia then contributes to hypotension.

    c. Hypotension then contributes to hypoperfusion *def)*.

Prolonged vasodilation also leads to decreased vascular resistance within blood vessels.

    a. The lower the vascular resistance, the lower the blood pressure. This too contributes to a drop in blood pressure or hypotension.

    b. Hypotension then contributes to hypoperfusion.

Flash animation showing vasodilation.

html5 version of animation for iPad showing vasodilation.

3. At high levels of TNF, vascular smooth muscle tone and myocardial contractility are inhibited.

a. Decreased myocardial contractility results in a marked hypotension.

b. Hypotension then contributes to hypoperfusion.

c. Cytokine-induced overproduction of nitric oxide (NO) by cardiac muscle cells and vascular smooth muscle cells can also lead to heart failure.

4. Activation of the blood coagulation pathway can cause clots called microthrombi to form within the blood vessels throughout the body. This is called disseminated intravascular coagulation (DIC).

a. These microthrombi physically block the capillaries and contributes to hypoperfusion.

b. Activation of neutrophils also leads to their accumulation and plugging of the vasculature.

c. Depletion of clotting factors as a result of DIC leads to hemorrhaging in many parts of the body following the neutrophil-induced capillary damage. This, as mentioned above, contributes to a decreased volume of circulating blood or hypovolemia.

d. Hypovolemia then contributes to hypotension.

e. Hypotension then contributes to hypoperfusion.

5. In the lungs, the increased capillary permeability as a result of inflammation and vasodilation, as well as neutrophil-induced injury to capillaries in the alveoli leads to pulmonary edema. As the alveoli fill with fluid gas exchange does not occur in the lungs. This condition is called acute respiratory distress syndrome (ARDS).

a. As a result, the blood does not become oxygenated.

b. Lack of oxygenation of the blood via the lungs then causes hypoperfusion.

6. Hypoperfusion and capillary damage In the liver results in impaired liver function and a failure to maintain normal blood glucose levels.

Overuse of glucose by muscles and a failure of the liver to replace glucose can lead to a drop in blood glucose level below what is needed to sustain life. (Glucose is needed to make ATP via aerobic respiration.)

7. Hypoperfusion in the kidneys, bowels, or brain can lead to injury of these organs.

8. The combination of hypotension, hypovolemia, DIC, ARDS, and the resulting hypoperfusion then leads to acidosis.

a. Without oxygen, cells switch to fermentation and produce lactic acid that lowers the pH of the blood. A blood pH range between 6.8 and 7.8 is needed for normal cellular enzyme activity in humans.

b. Changes in the pH of arterial blood extracellular fluid outside this range lead to irreversible cell damage.

In summary, the release of excessive levels of inflammatory cytokines in response to PAMPs binding to PRRs during a systemic infection results in:

1. A drop in blood volume or hypovolemia. This is caused by the following events:

a. Extracellular killing by neutrophils damages the capillary walls results in blood and plasma leaving the bloodstream and entering the surrounding tissue.

b. Depletion of clotting factors during disseminated intravascular coagulation (DIC) can lead to hemorrhaging as the capillaries are damaged.

c. Prolonged vasodilation results in plasma leaving the bloodstream and entering the surrounding tissue.

2. A drop in blood pressure or hypotension. This is a result of the following events:

a. Prolonged vasodilation causes decreased vascular resistance within blood vessels decreases blood pressure.

b. High levels of TNF, inhibit vascular smooth muscle tone and myocardial contractility decreasing the ability of the heart to pump blood throughout the body.

c. Hypovolemia from capillary damage, plasma leakage, and hemorrhaging.

3. The inability to deliver nutrients and oxygen to body cells or hypoperfusion. This is a result of the following events:

a. Activation of the blood coagulation pathway can cause clots called microthrombi to form within the blood vessels throughout the body causing disseminated intravascular coagulation (DIC) which blocks the flow of blood through the capillaries and, as mentioned above, depletion of clotting factors can lead to hemorrhaging in many parts of the body.

b. Increased capillary permeability as a result of vasodilation in the lungs, as well as neutrophil-induced injury to capillaries in the alveoli leads to acute inflammation, pulmonary edema, and loss of gas exchange in the lungs (acute respiratory distress syndrome or ARDS). As a result, the blood does not become oxygenated.

c. Hypovolemia decreases the volume of circulating blood and leads to hypotension.

d. Hypotension decreases the pressure needed to deliver blood throughout the body.

6. Hypoperfusion in the liver can result in a drop in blood glucose level from liver dysfunction. Glucose is needed for ATP production during glycolysis and aerobic respiration. A drop in glucose levels can result in decreased ATP production and insufficient energy for cellular metabolism.

7. The lack of oxygen delivery as a result of hypoperfusion causes cells to switch to fermentation for energy production. The acid end products of fermentation lead to acidosis and the wrong pH for the functioning of the enzymes involved in cellular metabolism. This can result in irreversible cell death.

Collectively, this can result in :

- End-organ ischemia Ischemia is a restriction in blood supply that results in damage or dysfunction of tissues or organs.
- Multiple system organ failure (MSOF). Multiple organs begin to fail as a result of hypoperfusion.
- Death.

For more on SIRS and Septic Shock, see Septic Shock.

Concept map for SIRS and Septic Shock.

Define hypotension and describe the biological mechanism behind 2 factors that contribute to hypotension.

- Define hypovolemia and describe the biological mechanism behind 3 factors that contribute to hypovolemia.
- Define hypoperfusion and describe the biological mechanism behind 3 factors that contribute to hypoperfusion.
- Describe the biological mechanism behind ARDS and how ARDS contributes to hypoperfusion.
- Describe the sequence of events that enables hypoperfusion to lead to irreversible cell damage.
- What is end-organ ischemia?

Septicemia is a condition where bacteria enter the blood and cause harm. According to the NIH *Sepsis Fact Sheet*, “Every year, severe sepsis strikes about 750,000 Americans. It’s been estimated that between 28 and 50 percent of these people die - far more than the number of U.S. deaths from prostate cancer, breast cancer and AIDS combined.” Factors contributing to this high rate of sepsis include:

1. An aging US population.
2. Increased longevity of people with chronic diseases.
3. An increase in number of invasive medical procedures performed.
4. Increased use of immunosuppressive and chemotherapeutic agents.
5. The spread of antibiotic-resistant microorganisms.

People that survive severe sepsis may have permanent damage to the lungs or other organs. Approximately 45% of the cases of

septicemia are due to Gram-positive bacteria, 45% are a result of Gram-negative bacteria, and 10% are due to fungi (mainly the yeast *Candida*). Many of these cases of septicemia are health care-associated infections (HA Is).

The Centers for Disease Control and Prevention (CDC) Health care-associated infection's website reports that "In American hospitals alone, health care-associated infections account for an estimated 1.7 million infections and 99,000 associated deaths each year. Of these infections:

- 32 percent of all health care-associated infection are urinary tract infections
- 22 percent are surgical site infections
- 15 percent are pneumonia (lung infections)
- 14 percent are bloodstream infections"

Estimates of Health care-Associated Infections (HCIs) 2011; from CDC

We will now look at various bacterial PAMPs that lead to cytokine production, inflammation, and activation of the complement and coagulation pathways.

Summary

1. In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms.
2. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs.
3. PAMPS bind to pattern-recognition receptors (PRRs) on defense cells which lead to the production of cytokines that trigger inflammation, activate the complement pathways, and activate the coagulation pathway. This inflammatory response is accomplished primarily by an inflammatory programmed cell death called pyroptosis involving protein cellular complexes called inflammasomes.
4. Cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8) are known as inflammatory cytokines because they promote inflammation.
5. Inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around an injured or infected site.
6. Vasodilation is a reversible opening of the junctional zones between endothelial cells of the blood vessels and results in increased blood vessel permeability. This enables plasma, the liquid portion of the blood, to enter the surrounding tissue. Increased capillary permeability also enables white blood cells to squeeze out of the blood vessels and enter the tissue.
7. When there is a minor infection with few bacteria present, low levels of PAMPs are present. This leads to moderate cytokine production by defense cells and, in general, promotes body defense.
8. During severe systemic infections with large numbers of bacteria present, high levels of PAMPs are released resulting in excessive cytokine production by the defense cells and this can harm the body.
9. Perfusion refers to the delivery of nutrients and oxygen via arterial blood to a capillary bed in tissue.
10. Sepsis is an infection that leads to a systemic inflammatory response resulting in physiologic changes occurring at the capillary endothelial level. This systemic inflammatory response is referred to as Systemic Inflammatory Response Syndrome or SIRS.
11. Cytokine-induced extracellular killing by neutrophils adhere to capillary walls results in damage to the capillary walls and leakage of blood into surrounding tissue. This contributes to a decreased volume of circulating blood (hypovolemia).
12. Prolonged vasodilation and the resulting increased capillary permeability causes plasma to leave the bloodstream and enter the tissue. This contributes to a decreased volume of circulating blood (hypovolemia).
13. Prolonged vasodilation also leads to decreased vascular resistance within blood vessels resulting in a drop in blood pressure (hypotension).
14. At high levels of TNF, vascular smooth muscle tone and myocardial contractility are inhibited. This results in a marked hypotension.
15. Hypovolemia as a result of hemorrhaging, systemic edema, insufficient hydration, or loss of fluids through vomiting and diarrhea also leads to hypotension.
16. Activation of the blood coagulation pathway can cause clots called microthrombi to form within the blood vessels throughout the body (disseminated intravascular coagulation or DIC). These microthrombi block the capillaries. Depletion of clotting factors leads to hemorrhaging in many parts of the body following neutrophil-induced capillary damage.
17. Increased capillary permeability as a result of vasodilation in the lungs, as well as neutrophil-induced injury to capillaries in the alveoli leads to acute inflammation, pulmonary edema, and loss of gas exchange in the lungs (acute respiratory distress

syndrome or ARDS). As a result, the blood does not become oxygenated.
18. The combination of hypotension, hypovolemia, DIC, ARDS, results in hypoperfusion.
19. Without oxygen, cells switch to fermentation and produce lactic acid that lowers the pH of the blood (acidosis). A blood pH range between 6.8 and 7.8 is needed for normal cellular enzyme activity in humans. Changes in the pH of arterial blood extracellular fluid outside this range lead to irreversible cell damage.
20. Collectively, this can result in end-organ ischemia (a restriction in blood supply that results in damage or dysfunction of tissues or organs), multiple system organ failure (MSOF), and death.
21. According to the NIH Sepsis Fact Sheet, “Every year, severe sepsis strikes about 750,000 Americans. It’s been estimated that between 28 and 50 percent of these people die - far more than the number of U.S. deaths from prostate cancer, breast cancer and AIDS combined.”
22. Approximately 45% of the cases of septicemia are due to Gram-positive bacteria, 45% are a result of Gram-negative bacteria, and 10% are due to fungi (mainly the yeast Candida).

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ Defense regulatory chemicals that promote an inflammatory response by enabling white blood cells to leave the blood vessels and enter the surrounding tissue, by chemotactically attracting these white blood cells to the infection site, and by triggering neutrophils to release killing agents for extracellular killing. *(ans)*

   _____ A decreased volume of circulating blood. *(ans)*

   _____ Reduced delivery of nutrients and oxygen via the blood. This can lead to ischemia, a restriction in blood supply that results in damage or dysfunction of tissue. *(ans)*

   _____ Respiratory failure from acute inflammation in the lungs, injury to capillaries in the alveoli of the lungs, and pulmonary edema. *(ans)*

   _____ The formation of clots within the blood vessels throughout the body. *(ans)*

   A. inflammation
   B. septicemia
   C. chemokines
   D. cytokines
   E. DIC
   F. ARDS
   G. septic shock
   H. hypovolemia
   I. hypotension
   J. hypoperfusion
2. Define hypotension and describe the biological mechanism behind 3 factors that contribute to hypotension. *(ans)*
3. Define hypovolemia and describe the biological mechanism behind 3 factors that contribute to hypovolemia. *(ans)*
4. Define hypoperfusion and describe the biological mechanism behind 3 factors that contribute to hypoperfusion. *(ans)*
5. Describe the biological mechanism behind ARDS and how ARDS contributes to hypoperfusion. *(ans)*
6. Define pyroptosis and state its role in inducing inflammation. *(ans)*
7. Multiple Choice *(ans)*

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6.1B: Gram-Negative Bacterial PAMPs

State what is meant by endotoxin and indicate where it is normally found.

- List 3 Gram-negative PAMPS and briefly describe how they initiate SIRS.
- Define healthcare-associated infection and name 3 common Gram-negative bacteria that cause HAIs.

Highlighted Bacterium

1. Read the description of *Pseudomonas aeruginosa* andmatch the bacterium with the description of the organism and the infection it causes.

In this section on Bacterial Pathogenesis we are looking at **virulence factors that damage the host**. Virulence factors that damage the host include:

1. The ability to produce Pathogen-Associated Molecular Patterns or PAMPs that bind to host cells causing them to synthesize and secrete inflammatory cytokines and chemokines;

2. The ability to produce harmful exotoxins.

3. The ability to induce autoimmune responses.

We will now look at the ability of Gram-negative bacteria to produce PAMPs that bind to host cells and cause them to synthesize and secrete inflammatory cytokines.

The Ability of PAMPs to Trigger the Production of Inflammatory Cytokines that Result in an Excessive Inflammatory Response

b. Gram-Negative PAMPs: LPS (Endotoxin), Porins in the Outer Membrane, Peptidoglycan Monomers, Mannose-Rich Glycans, and Flagellin

In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by **recognizing molecules unique to microorganisms that are not associated with human cells**. These unique molecules are called **pathogen-associated molecular patterns (PAMPs)**. (Because all microbes, not just pathogenic microbes, possess PAMPs, **pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs**.)

Molecules unique to bacteria, such as peptidoglycan monomers, teichoic acids, LPS, porins, mycolic acid, mannose-rich glycans, and flagellin, are **PAMPs that bind to pattern-recognition receptors (PRRs)** on a variety of defense cells of the body causing them to **synthesize and secrete a variety of proteins called cytokines** *(def)*. These cytokines can, in turn **promote innate immune defenses** such as inflammation, fever, and phagocytosis. This is accomplished primarily by an inflammatory programmed cell death called **pyroptosis** involving protein cellular complexes called **inflammasomes**.

Pyroptosis *(def)*, is a programmed **inflammatory death of host cells** that is mediated by an enzyme called caspase 1 and can be triggered by a variety of stimuli, including pathogen-associated molecular patterns (PAMPs) from microbial infections, as well as danger-associated molecular patterns (DAMPs) produced as a result of tissue injury during cancer, heart attack, and stroke. **Pyroptosis results in production of proinflammatory cytokines, rupture of the cell's plasma membrane, and subsequent release of proinflammatory intracellular contents**. It plays an **essential role in innate immunity** by promoting inflammation to control microbial infections. **At highly elevated levels, however, it can cause considerable harm** to the body and even death. The **binding of PAMPs to PRRs also leads to activation of the complement pathways** *(def)* **and activation of the coagulation pathway** *(def)*.

Cytokines such as **tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-8 (IL-8)** are known as **inflammatory cytokines** *(def)* because they **promote inflammation**. Some cytokines, such as IL-8, are also known as **chemokines** *(def)*. Chemokines promote an inflammatory response by enabling white blood cells to leave the blood vessels and enter the surrounding tissue, by chemotactically attracting these white blood cells to the infection site, and by **triggering**

neutrophils *(def)* **to release killing agents for extracellular killing**.

As mentioned in Unit 1, the **lipopolysaccharide (LPS) in the outer membrane** of the Gram-negative cell wall (see Figure 6.1B.1) is also known as **endotoxin** *(def)*. While **porins, mannose-rich glycans, peptidoglycan fragments, and flagellin also function as PAMPs**, the most significant Gram-negative-associated PAMP is LPS. Gram-negative bacteria release some endotoxin during their normal replication but endotoxin is released in quantity upon death and degradation of the bacterium. The degree of damage from endotoxin is related to the degree of release of the LPS from the bacterium's cell wall.

For More Information: The Gram-Negative Cell Wall from Unit 1

1. The **LPS** released from the outer membrane of the Gram-negative cell wall typically **binds first to a LPS-binding protein** circulating in the blood and this complex, in turn, **binds to a receptor molecule called CD_{14} that is found on the surface of defense cells such as macrophages** *(def)* **and dendritic cells** *(def)* (see Figure 6.1B.2) located in most tissues and organs of the body.

2. The interaction of the LPS-binding protein with CD_{14} is thought to **promote the ability of the toll-like receptor** *(def)* **TLR-4** *(def)* **to respond to the LPS**.

3. The interaction between LPS and its TLRs **triggers the macrophage to release various defense regulatory chemicals called cytokines**, including **tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8), and platelet-activating factor (PAF)** (see Figure 6.1B.2). The cytokines then bind to cytokine receptors on target cells and initiate an inflammatory response *(def)*. They also activate both the complement pathways *(def)* and the coagulation pathway *(def)* (see Figure 6.1B.2).

YouTube animation illustrating macrophages releasing cytokines.
Nucleus Medical Art, www. nucleusinc.com

Flash animation illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

For More Information: Cytokines from Unit 5

4. **The binding of of LPS molecules to their TLRs** on the surfaces of phagocytic white blood cells called **neutrophils** *(def)* **causes them to release proteases** *(def)* **and toxic oxygen radicals** *(def)* for extracellular killing. Chemokines *(def)* such as interleukin-8 (IL-8) also stimulate extracellular killing. In addition, LPS and cytokines stimulate the synthesis of a vasodilator called **nitric oxide**.

Flash animation of extracellular killing by neutrophils triggered by the binding of LPS and chemokines to receptors on neutrophils.

html version of animation for iPAD illustrating extracellular killing by neutrophils triggered by the binding of LPS and chemokines to receptors on neutrophils.

During **minor local infections** with few bacteria present, **low levels of Gram-negative PAMPs are released** leading to **moderate cytokine production** by defense cells such as monocytes *(def)*, macrophages *(def)*, and dendritic cells *(def)* and, in general, **promoting body defense** by stimulating inflammation and moderate fever, breaking down energy reserves to supply energy for defense, activating the complement pathway *(def)* and the coagulation pathway *(def)*, and generally stimulating immune responses (see Figure 6.1B.2). Also as a result of these cytokines, **circulating phagocytic white blood cells such as neutrophils** *(def)* **and monocytes** *(def)* **stick to the walls of capillaries, squeeze out and enter the tissue, a process termed diapedesis** *(def)*. The phagocytic white blood cells such as neutrophils then kill the invading microbes with their proteases and toxic oxygen radicals. These defenses will be covered in greater detail in Units 5 and 6.

For More Information: Inflammation from Unit 5

For More Information: the Complement Pathways from Unit 5

However, during **severe systemic infections** with large numbers of bacteria present, **high levels of Gram-negative PAMPs are released** resulting in **excessive cytokine production** by the defense cells and this can **harm the body** (see Figure 6.1B.3). In addition, neutrophils *(def)* start releasing their proteases and toxic oxygen radicals that kill not only the bacteria, but the surrounding tissue as well.

Harmful effects include high fever, hypotension *(def)*, tissue destruction, wasting, acute respiratory distress syndrome (ARDS) *(def)*, disseminated intravascular coagulation (DIC) *(def)*, and damage to the vascular endothelium. This can result in shock *(def)*, multiple system organ failure (MSOF), and often death.

Describe the mechanism by which gram-negative bacteria initiate the inflammatory response and activate the coagulation pathway and the complement pathway.

State how this can be both beneficial and harmful to the body.

As seen earlier in this unit, the release of excessive levels of inflammatory cytokines in response to a systemic infection results in:

1. **A drop in blood volume or hypovolemia** *(def)*. This is caused by the following events:

    a. **Extracellular killing by neutrophils damages the capillary walls** results in blood and plasma leaving the bloodstream and entering the surrounding tissue.

    b. **Depletion of clotting factors** during disseminated intravascular coagulation (DIC) can lead to hemorrhaging as the capillaries are damaged.

    c. **Prolonged vasodilation** results in plasma leaving the bloodstream and entering the surrounding tissue.

2. **A drop in blood pressure or hypotension** *(def)*. This is a result of the following events:

    a. **Prolonged vasodilation causes decreased vascular resistance within blood vessels** decreases blood pressure.

    b. **High levels of TNF, inhibit vascular smooth muscle tone and myocardial contractility** decreasing the ability of the heart to pump blood throughout the body.

    c. **Hypovolemia** from capillary damage, plasma leakage, and hemorrhaging.

3. **The inability to deliver nutrients and oxygen to body cells or hypoperfusion** *(def)*. This is a result of the following events:

a. **Activation of the blood coagulation pathway** can cause clots called **microthrombi to form within the blood vessels** throughout the body causing **disseminated intravascular coagulation (DIC)** which **blocks the flow of blood through the capillaries** and, as mentioned above, depletion of clotting factors can lead to hemorrhaging in many parts of the body.

b. **Increased capillary permeability** as a result of vasodilation in the lungs, as well as **neutrophil-induced injury to capillaries** in the alveoli leads to acute inflammation, pulmonary edema, and **loss of gas exchange in the lungs (acute respiratory distress syndrome or ARDS)**. As a result, the **blood does not become oxygenated**.

c. **Hypovolemia decreases the volume of circulating blood** and leads to hypotension.

d. **Hypotension** decreases the pressure needed to deliver blood throughout the body.

6. Hypoperfusion in the liver can result in a drop in blood glucose level from liver dysfunction. Glucose is needed for ATP production during glycolysis and aerobic respiration. A **drop in glucose levels can result in decreased ATP production and insufficient energy for cellular metabolism**.

7. The **lack of oxygen** delivery as a result of hypoperfusion causes cells to switch to **fermentation** for energy production. The **acid end products** of fermentation lead to **acidosis** and the **wrong pH for the functioning of the enzymes** involved in cellular metabolism. This can result in irreversible **cell death**.

Collectively, this can result in :

- **End-organ ischemia** *(def)* Ischemia is a restriction in blood supply that results in damage or dysfunction of tissues or organs**.**
- **Multiple system organ failure (MSOF)** *(def)*. Multiple organs begin to fail as a result of hypoperfusion.
- **Death**.

For more information : Review of SIRS and Septic Shock from Unit 3

Concept Map for Synthesizing and Secreting Inflammatory Cytokines and Chemokines in Response to PAMPs

Concept map for SIRS and Septic Shock.

Septicemia *(def)* is a condition where bacteria enter the blood and cause harm. According to the NIH *Sepsis Fact Sheet*, “Every year, severe sepsis strikes about 750,000 Americans. It’s been estimated that between 28 and 50 percent of these people die - far more than the number of U.S. deaths from prostate cancer, breast cancer and AIDS combined.” Factors contributing to this high rate of sepsis include:

1. An aging US population.
2. Increased longevity of people with chronic diseases.
3. An increase in number of invasive medical procedures performed.
4. Increased use of immunosuppressive and chemotherapeutic agents.
5. The spread of antibiotic-resistant microorganisms.

People that survive severe sepsis may have permanent damage to the lungs or other organs. Approximately 45% of the cases of septicemia are due to Gram-positive bacteria, 45% are a result of Gram-negative bacteria, and 10% are due to fungi (mainly the yeast *Candida*). Many of these cases of septicemia are **health care-associated infections (HAIs)** *(def)*.

Other examples of damage from Gram-negative PAMPs are Gram-negative **bacterial meningitis** *(def)* and **pneumonia**. The same inflammatory events lead to identical effects in the brain and the decreased delivery of oxygen and glucose to the cells of the brain results in damage and death of brain tissue. When Gram-negative bacteria enter the alveoli *(def)* of the lungs and are lysed by antibiotics or body defenses, Gram-negative bacterial PAMPs bind to receptors on endothelial cells, the alveolar epithelium, and leukocytes causing the release of TNF-alpha, Il-1, and chemokines. **This leads to increased vascular permeability that enables serous fluids, red blood cells, and leukocytes to enter the air spaces of the lung where gas**

exchange occurs. This prevents normal gas exchange and the person drowns on his or her own serous fluids *(def)*.

Medically important Gram-negative bacteria include such classical pathogens as *Neisseria meningitidis (inf)*, *Salmonella (inf)*, *Neisseria gonorrhoeae* (see photomicrograph) *(inf)*, and *Hemophilus influenzae* type b *(inf)*.

In addition, many normal Gram-negative intestinal microbiota such as *Escherichia coli, Proteus, Klebsiella, Enterobacter, Serratia, and Pseudomonas aeruginosa* are responsible for a variety of **opportunistic infections** *(inf)* including urinary tract infections, wound infections, pneumonia, and septicemia. These bacteria owe much of their damage to LPS.

These normal flora Gram-negative bacilli (along with Gram-positive bacteria such as *Staphylococcus aureus* and *Enterococcus faecalis*) are among the most common causes of **health care-associated infections (HAIs)** *(def)*. The four most common Gram-negative bacteria causing HCIs are *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter* species, and *Klebsiella pneumoniae*. Collectively, these four bacteria accounted for 32% of all HAIs in the U.S. between 1990 and 1996. There are over two million nosocomial infections per year in the U.S.

According to the Centers for Disease Control and Prevention (CDC) Health care-associated infection's website, "In American hospitals alone, health care-associated infections account for an estimated 1.7 million infections and 99,000 associated deaths each year. Of these infections:

- 32 percent of all health care-associated infection are urinary tract infections
- 22 percent are surgical site infections
- 15 percent are pneumonia (lung infections)
- 14 percent are bloodstream infections"

Summary

1. PAMPs associated with Gram-negative bacteria include LPS (endotoxin) and porins in the outer membrane, peptidoglycan fragments, mannose-rich sugars, and flagellin.
2. Approximately 45% of the cases of septicemia are due to Gram-negative bacteria.
3. Medically important Gram-negative bacteria include such classical pathogens as Neisseria meningitidis, Salmonella, Neisseria gonorrhoeae, and Hemophilus influenzae type b.
4. Many normal Gram negative intestinal microbiota such as Escherichia coli, Proteus, Klebsiella, Enterobacter, Serratia, and Pseudomonas aeruginosa are responsible for a variety of opportunistic infections including urinary tract infections, wound infections, pneumonia, and septicemia.
5. The four most common Gram-negative bacteria causing Health care-associated infections (HAIs) are Escherichia coli, Pseudomonas aeruginosa, Enterobacter species, and Klebsiella pneumoniae. Collectively, these four bacteria accounted for 32% of all nosocomial infections in the U.S. between 1990 and 1996. There are over two million HAIs per year in the U.S.

Questions

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what is meant by endotoxin and where it is normally found.(ans)
2. Define healthcare-associated infection and name 3 common Gram-negative bacteria that cause HAIs. *(ans)*
3. We just learned that during a severe Gram-negative infection, LPS from the gram-negative cell wall can bind to macrophages causing their release of chemokines and cytokines and this is what then may lead to the often lethal shock cascade. Why would the human body evolve a mechanism for LPS binding to macrophages if it is potentially harmful? *(ans)*
4. Multiple Choice *(ans)*

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6.1C: Gram-Positive Bacterial PAMPs

Some of these paragraphs are the same as 1.B.

Describe how Gram-positive PAMPS initiate SIRS.

Name 2 Gram-positive bacteria that commonly cause healthcare-associated infections (HAIs).

In this section on Bacterial Pathogenesis we are looking at **virulence factors that damage the host**. Virulence factors that damage the host include:

1. The ability to produce Pathogen-Associated Molecular Patterns or PAMPs that bind to host cells causing them to synthesize and secrete inflammatory cytokines and chemokines;

2. The ability to produce harmful exotoxins.

3. The ability to induce autoimmune responses.

We will now look at the ability of Gram-positive bacteria to produce PAMPs that bind to host cells and cause them to synthesize and secrete inflammatory cytokines.

The Ability of PAMPs to Trigger the Production of Inflammatory Cytokines that Result in an Excessive Inflammatory Response

c. Gram-Positive PAMPs: Lipoteichoic Acids, Peptidoglycan Monomers, Mannose-Rich Glycans, and Flagellin

In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by **recognizing molecules unique to microorganisms that are not associated with human cells**. These unique molecules are called **pathogen-associated molecular patterns (PAMPs)**. (Because all microbes, not just pathogenic microbes, possess PAMPs, **pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs**.)

Molecules unique to bacteria, such as peptidoglycan monomers, teichoic acids, LPS, porins, mycolic acid, mannose-rich glycans, and flagellin are **PAMPs that bind to pattern-recognition receptors (PRRs)** on a variety of defense cells of the body causing them to **synthesize and secrete a variety of proteins called cytokines** *(def)*. These cytokines can, in turn **promote innate immune defenses** such as inflammation, fever, and phagocytosis.This is accomplished primarily by an inflammatory programmed cell death called **pyroptosis** involving protein cellular complexes called **inflammasomes**.

Pyroptosis *(def)*, is a programmed **inflammatory death of host cells** that is mediated by an enzyme called caspase 1 and can be triggered by a variety of stimuli, including pathogen-associated molecular patterns (PAMPs) from microbial infections, as well as danger-associated molecular patterns (DAMPs) produced as a result of tissue injury during cancer, heart attack, and stroke. **Pyroptosis results in production of proinflammatory cytokines, rupture of the cell's plasma membrane, and subsequent release of proinflammatory intracellular contents**. It plays an **essential role in innate immunity** by promoting inflammation to control microbial infections. **At highly elevated levels, however, it can cause considerable harm** to the body and even death. The **binding of PAMPs to PRRs also leads to activation of the complement pathways** *(def)* **and activation of the coagulation pathway** *(def)*.

Cytokines such as **tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-8 (IL-8)** are known as **inflammatory cytokines** *(def)* because they **promote inflammation**. Some cytokines, such as IL-8, are also known as **chemokines** *(def)*. Chemokines promote an inflammatory response by enabling white blood cells to leave the blood vessels and enter the surrounding tissue, by chemotactically attracting these white blood cells to the infection site, and by **triggering neutrophils** *(def)* **to release killing agents for extracellular killing**.

The mechanism is as follows:

1. The lysis of Gram-positive bacteria causes PAMPs such as **peptidoglycan monomers (the building blocks of peptidoglycan**(see Figure 6.1C.1)**, lipotechoic acids, mannose-rich glycans**, and **flagellin** to be released.

For More Information: The Gram-Positive Cell Wall from Unit 1

2. These **PAMPs**, in turn, **bind to pattern-recognition receptors (PRRs)** *(def)* that are specific for these PAMPs that are found on the surface of **body defense cells such as macrophages** *(def)* **and dendritic cells** *(def)*.

3. Binding of the PAMPs to the PRRs of these defense cells triggers them to release various defense regulatory chemicals called cytokines, including **tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), inflammatory chemokines such as IL-8, and platelet-activating factor (PAF)** (see Figure 6.1C.2). The cytokines then bind to cytokine receptors on target cells and initiate an inflammatory response *(def)*. They also activate both the complement pathways *(def)* and the coagulation pathway *(def)* (see Figure 6.1C.2), in a manner similar to endotoxin (LPS) from the Gram-negative cell wall.

YouTube animation illustrating macrophages releasing cytokines.
Nucleus Medical Art, www. nucleusinc.com

Flash animation illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

For More Information: Cytokines from Unit 5

4. The binding of PAMPs to their PRRs on the surfaces of phagocytic white blood cells called **neutrophils** *(def)* causes them to **release proteases** *(def)* and **toxic oxygen radicals** *(def)* for extracellular killing. Chemokines such as interleukin-8 (IL-8) also stimulate extracellular killing. In addition, cytokines stimulate the synthesis of a vasodilator called **nitric oxide**.

Flash animation showing the binding of teichoic acid and chemokines to receptors on neutrophils and their subsequent release of killing agents.

html5 version of animation for iPad showing the binding of teichoic acid and chemokines to receptors on neutrophils and their subsequent release of killing agents.

During **minor local infections** with few bacteria present, **low levels of peptidoglycan monomers, lipoteichoic acids, and other Gram-positive bacterial PAMPs are released** leading to **moderate cytokine production** by defense cells such as monocytes *(def)*, macrophages *(def)* and dendritic cells *(def)* and, in general, **promoting body defense** by stimulating inflammation and moderate fever, breaking down energy reserves to supply energy for defense, activating the complement pathway*(def)* and the coagulation pathway *(def)*, and generally stimulating immune responses (see Figure 6.1C.2). Also as a result of these cytokines, circulating phagocytic white blood cells such as neutrophils *(def)* and monocytes *(def)* stick to the walls of capillaries, squeeze out and enter the tissue, a process termed **diapedesis** *(def)*. The phagocytic white blood cells such as neutrophils then kill the invading microbes with their proteases *(def)* and toxic oxygen radicals *(def)*. These defenses will be covered in greater detail in Units 5 and 6.

For More Information: Inflammation from Unit 5

For More Information: the Complement Pathways from Unit 5

However, during **severe systemic infections** with large numbers of bacteria present, **high levels of these Gram-positive PAMPs are released** resulting in **excessive cytokine production** by the defense cells and this can **harm the body** (see Figure 6.1C.3). In addition, neutrophils *(def)* start releasing their proteases and toxic oxygen radicals that kill not only the bacteria, but the surrounding tissue as well.

Harmful effects include high fever, hypotension *(def)*, tissue destruction, wasting, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and damage to the vascular endothelium. This can result in shock *(def)*, multiple system organ failure (MSOF), and often death.

As seen earlier in this unit,the release of excessive levels of inflammatory cytokines in response to a systemic infection results in:

1. A drop in blood volume or hypovolemia *(def)*. This is caused by the following events:

a. **Extracellular killing by neutrophils damages the capillary walls** results in blood and plasma leaving the bloodstream and entering the surrounding tissue.

b. **Depletion of clotting factors** during disseminated intravascular coagulation (DIC) can lead to hemorrhaging as the capillaries are damaged.

c. **Prolonged vasodilation** results in plasma leaving the bloodstream and entering the surrounding tissue.

2. A drop in blood pressure or hypotension *(def)*. This is a result of the following events:

a. **Prolonged vasodilation causes decreased vascular resistance within blood vessels** decreases blood pressure.

b. **High levels of TNF, inhibit vascular smooth muscle tone and myocardial contractility** decreasing the ability of the heart to pump blood throughout the body.

c. **Hypovolemia** from capillary damage, plasma leakage, and hemorrhaging.

3. The inability to deliver nutrients and oxygen to body cells or hypoperfusion *(def)*. This is a result of the following events:

a. **Activation of the blood coagulation pathway** can cause clots called **microthrombi to form within the blood vessels** throughout the body causing **disseminated intravascular coagulation (DIC)** which **blocks the flow of blood through the capillaries** and, as mentioned above, depletion of clotting factors can lead to hemorrhaging in many parts of the body.

b. **Increased capillary permeability** as a result of vasodilation in the lungs, as well as **neutrophil-induced injury to capillaries** in the alveoli leads to acute inflammation, pulmonary edema, and **loss of gas exchange in the lungs (acute respiratory distress syndrome or ARDS)**. As a result, the **blood does not become oxygenated**.

c. **Hypovolemia decreases the volume of circulating blood** and leads to hypotension.

d. **Hypotension** decreases the pressure needed to deliver blood throughout the body.

6. Hypoperfusion in the liver can result in a drop in blood glucose level from liver dysfunction. Glucose is needed for ATP production during glycolysis and aerobic respiration. A **drop in glucose levels can result in decreased ATP production and insufficient energy for cellular metabolism**.

7. The **lack of oxygen** delivery as a result of hypoperfusion causes cells to switch to **fermentation** for energy production. The **acid end products** of fermentation lead to **acidosis** and the **wrong pH for the functioning of the enzymes** involved in

cellular metabolism. This can result in irreversible **cell death**.

Collectively, this can result in :

- **End-organ ischemia** *(def)* Ischemia is a restriction in blood supply that results in damage or dysfunction of tissues or organs**.**
- **Multiple system organ failure (MSOF)** *(def)*. Multiple organs begin to fail as a result of hypoperfusion.
- **Death**.

For more information : Review of SIRS and Septic Shock from Unit 3

For more information : Review of SIRS and Septic Shock from Unit 3

Concept Map for Synthesizing and Secreting Inflammatory Cytokines and Chemokines in Response to PAMPs

Concept map for SIRS and Septic Shock.

Septicemia *(def)* is a condition where bacteria enter the blood and cause harm. According to the NIH *Sepsis Fact Sheet*, “Every year, severe sepsis strikes about 750,000 Americans. It’s been estimated that between 28 and 50 percent of these people die - far more than the number of U.S. deaths from prostate cancer, breast cancer and AIDS combined.” Factors contributing to this high rate of sepsis include:

1. An aging US population.
2. Increased longevity of people with chronic diseases.
3. An increase in number of invasive medical procedures performed.
4. Increased use of immunosuppressive and chemotherapeutic agents.
5. The spread of antibiotic-resistant microorganisms.

People that survive severe sepsis may have permanent damage to the lungs or other organs. Approximately 45% of the cases of septicemia are due to Gram-positive bacteria, 45% are a result of Gram-negative bacteria, and 10% are due to fungi (mainly the yeast *Candida*). Many of these cases of septicemia are **health care-associated infections (HAIs)** *(def)*.

Pathogenic strains of *Staphylococcus aureus* producingleukocidin *(def)* **and protein A** *(def)***,** including MRSA *(def)***, cause an increased inflammatory response**. **Protein A**, a protein that blocks opsonization *(def)* and functions as an adhesin *(def)*, **binds to cytokine receptors for TNF-alpha** *(def)*. It mimics the cytokine and induces a **strong inflammatory response**. As the inflammatory response attracts neutrophils to the infected area, the leukocidin causes lysis of the neutrophils *(def)*. As a result, tissue is damaged and the bacteria are not phagocytosed. *Staphylococcus aureus*, coagulase-negative staphylococci *(def)*, and *Enterococcus* species are among the leading Gram-positive bacteria to cause septicemia.

Other examples of damage from Gram-positive PAMPs are Gram-positive **bacterial meningitis** *(def)* and **pneumonia**. The same inflammatory events lead to identical effects in the brain and the decreased delivery of oxygen and glucose to the cells of the brain results in damage and death of brain tissue.

One such example is the pneumococcus, *Streptococcus pneumoniae (inf)*. When *S. pneumoniae* enters the alveoli *(def)* of the lungs and is lysed by antibiotics or body defenses, glycopeptide cell wall fragments and teichoic acids bind to receptors on endothelial cells, the alveolar epithelium, and leukocytes causing the release of TNF-alpha, Il-1, and chemokines. **This leads to increased vascular permeability that enables serous fluids, red blood cells, and leukocytes to enter the air spaces of the lung where gas exchange occurs**. This prevents normal gas exchange and the person drowns on his or her own serous fluids *(def)*. From the lungs, *S. pneumoniae* often invades the blood, crosses the blood-brain barrier, and enters the meninges.

The Centers for Disease Control and Prevention (CDC) Health care-associated infection's website reports that "In American hospitals alone, health care-associated infections account for an estimated 1.7 million infections and 99,000 associated deaths each year. Of these infections:

- 32 percent of all health care-associated infection are urinary tract infections
- 22 percent are surgical site infections
- 15 percent are pneumonia (lung infections)
- 14 percent are bloodstream infections"

Estimates of Health care-Associated Infections (HCIs) 2011; from CDC

Gram-positive bacteria such as *Staphylococcus* and *Enterococcus*, along with the normal microbiota Gram-negative bacteria mentioned in the previous section, are among the most common causes of **health care-associated infections (HAIs)** *(def)*. The three most common gram-positive bacteria causing HAIs are *Staphylococcus aureus*, coagulase-negative staphylococci *(def)*, and *Enterococcus* species. Collectively, these three bacteria accounted for 34% of all HAIs in the U.S. between 1990 and 1996. There are over two million HAIs per year in the U.S.

Summary

1. PAMPs associated with Gram-positive bacteria include cell wall teichoic and lipotechoic acids, peptidoglycan fragments, mannose-rich sugars, and flagellin.
2. Approximately 45% of the cases of septicemia are due to Gram-positive bacteria.
3. Medically important Gram-positive bacteria include Staphylococcus aureus, coagulase-negative staphylococci, Enterococcus species, and Streptococcus pneumoniae.
4. The three most common Gram-positive bacteria causing health care-associated infections (HAIs) are Staphylococcus aureus, coagulase-negative staphylococci, and Enterococcus species. Collectively, these three bacteria accounted for 34% of all HAIs in the U.S. between 1990 and 1996. There are over two million HAIs per year in the U.S.

Questions

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ (ans) and _____ *(ans)* are the components of the Gram-positive cell wall that function similarly to the LPS in the gram-negative cell wall in stimulating cytokine production and an inflammatory response.
2. Name 2 Gram-positive bacteria that commonly cause healthcare-associated infections (HAIs).
   A. *(ans)*
   B. *(ans)*
3. Why is the inflammatory response needed for the effective removal of *Streptococcus pneumoniae* in the lungs potentially lethal? *(ans)*
4. Multiple Choice *(ans)*

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6.1D: Acid-Fast Bacterial PAMPs

Name the common PAMPs associated with acid-fast bacteria that stimulate cytokine production and an inflammatory response.

- Name pathogenic 2 acid-fast bacteria and state the infection each causes.

In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Molecules unique to bacterial, such as peptidoglycan monomers, teichoic acids, LPS, porins, mycolic acid, arabinogalactan, mannose-rich glycans, and flagellin are PAMPs that bind to pattern-recognition receptors on a variety of defense cells of the body causing them to synthesize and secrete a variety of proteins called cytokines. These cytokines can, in turn promote innate immune defenses such as inflammation, fever, and phagocytosis. PAMPS binding to PRRs also lead to activation of the complement pathways and activation of the coagulation pathway.

Cytokines are intercellular regulatory proteins produced by one cell that subsequently bind to other cells in the area and influence their activity in some manner. Cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8) are known as inflammatory cytokines *(def)* because they promote inflammation. Some cytokines, such as IL-8, are also known as chemokines. They promote an inflammatory response by enabling white blood cells to leave the blood vessels and enter the surrounding tissue, by chemotactically attracting these white blood cells to the infection site, and by triggering neutrophils to release killing agents for extracellular killing.

For More Information: The Acid-Fast Cell Wall from Unit 1

Concept Map for Synthesizing and Secreting Inflammatory Cytokines and Chemokines in Response to PAMPs

The lysis of pathogenic *Mycobacterium* species, such as *Mycobacterium tuberculosis (inf)*and *Mycobacterium leprae (inf),* releases mycolic acid, arabinogalactan, and peptidoglycan fragments (muramyl dipeptides) from their acid-fast cell wall (see Figure 6.1*D*.1). The mycolic acid molecules, arabinogalactan, and peptidoglycan fragments bind to pattern-recognition receptors on macrophages *(def)* and dendritic cells *(def)* causing them to release cytokines such as tumor necrosis factor-alpha (TNF-alpha). Most of the damage in the lungs during tuberculosis is thought to be due to the effects TNF-alpha along with the release of toxic lysosomal components of the macrophages trying to kill the *Mycobacterium tuberculosis*.

Summary

1. PAMPs associated with acid-fast bacteria include mycolic acid, arabinogalactan, and peptidoglycan fragments.
2. Medically important acid-fast bacterium include Mycobacterium tuberculosis and Mycobacterium leprae.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ (ans) and _____ *(ans)* are the components of the acid-fast cell wall that stimulate cytokine production and an inflammatory response.
2. Name 2 pathogenic acid-fast bacteria and state the infection each causes.

A. *(ans)*
B. *(ans)*

3. Multiple Choice *(ans)*

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6.2: The Ability to Produce Harmful Exotoxins: An Overview

Define exotoxin and list three types of exotoxins.

State the major way the body defends itself against exotoxins.

Exotoxins *(def)* are toxins, often proteins in nature, secreted from a living bacterium but also released upon bacterial lysis. In addition, some bacteria use various secretion systems such as the type 3 secretion system to inject toxins directly into human cells. (As learned earlier, the lipopolysaccharide or LPS portion of the Gram-negative bacterial cell wall is known as endotoxin *(def)*, a PAMP that can initiate an excessive inflammatory response in the host. It was originally called endotoxin because it was located within the Gram-negative cell wall as opposed to being secreted from bacteria as in the case of exotoxins.)

Not all exotoxins are necessarily produced to harm humans. Some may be designed to play a role in bacterial physiology, such as resisting bacteriophages, regulating cellular function, or quorum sensing. Other toxins may be produced primarily to target protozoa, insects, and smaller animals and harming human cells becomes an accidental side effect.

There are three main types of exotoxins:

1. **superantigens (Type I toxins)**;
2. **exotoxins that damage host cell membranes (Type II toxins)**; and
3. **A-B toxins and other toxin that interfere with host cell function (Type III toxins)**.

The body's major **defense against exotoxins** is the production of **antitoxin antibodies**. Once the antibody binds to the exotoxin, the toxin can no longer bind to the receptors on the host cell membrane.

Flash animation showing the neutralization of exotoxins with antibodies.

html5 version of animation for iPad showing the neutralization of exotoxins with antibodies.

We will now look at each of these three types of exotoxins.

Summary

1. Exotoxins are toxins, often protein in nature, secreted from a living bacterium.
2. Some bacteria use various secretion systems to inject toxins directly into human cells.
3. There are three main types of exotoxins: superantigens (type I toxins); exotoxins that damage host cell membranes (type II toxins); and A-B toxins and other toxin that interfere with host cell function (type III toxins).
4. The body's major defense against exotoxins is the production of antitoxin antibodies. Once the antibody binds to the exotoxin, the toxin can no longer bind to the receptors on the host cell membrane.

Questions

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. List three types of exotoxins.
   A. (ans)
   B. *(ans)*
   C. *(ans)*
2. Define exotoxin. *(ans)*
3. The body's major defense against exotoxins is _____. *(ans)*

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6.2A: Type I Toxins: Superantigens

Learning Objectives

1. Define superantigen.
2. Briefly describe the mechanism by which superantigens cause harm to the body.
3. Name 2 superantigens and give an example of a bacterium that produces each.

Highlighted Bacterium

1. Read the description of *Streptococcus pyogenes* and match the bacterium with the description of the organism and the infection it causes.

Superantigens are unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes. They bind to the surface of the target cell but do not enter the cell.

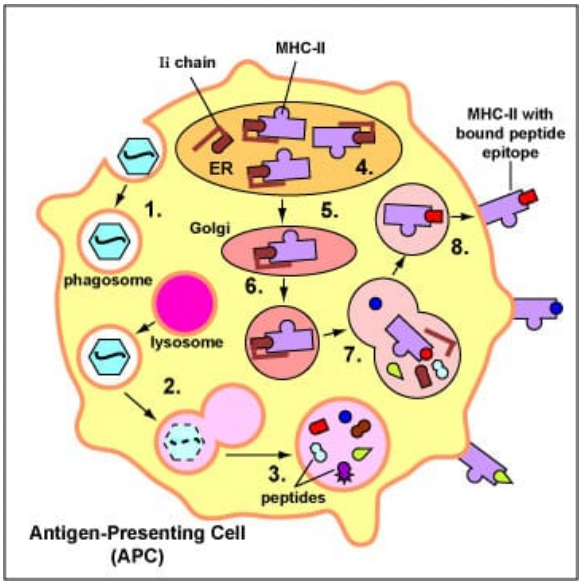


Figure 6.2A.1: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules. 1. Exogenous antigens, such as viruses, are engulfed and placed in a phagosome. 2. Lysosomes fuse with the phagosome forming an phagolysosome. 3. Protein antigens are degraded into a series of peptides. 4. MHC-II molecules are synthesized in the endoplasmic reticulum and transported to the Golgi complex. Once assembled, within the endoplasmic reticulum, a protein called the invarient chain (Ii) attaches to the the peptide-binding groove of the MHC-II molecules and in this way prevents peptides designated for binding to MHC-I molecules within the ER from attaching to the MHC-II. 5&6. The MHC-II molecules with bound Ii chain are now transported to the Golgi complex, and placed in vesicles. 7. The vesicles containing the MHC-II molecules fuse with the peptide-containing phaglysosomes. The Ii chain is removed and the peptides are now free to bind to the grooves of the MHC-II molecules. 8. The MHC-II molecules with bound peptides are transported to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-II complexes can be recognized by T4-lymphocytes by way of TCRs and CD4 molecules having a complementary shape.

Conventional antigens are engulfed by antigen presenting cells (APCs), degraded into epitopes, bind to the peptide groove of MHC-II molecules, and are put on the surface of the APC (Figure 6.2A.1). Here they are recognized by specific T4-lymphocytes having a TCR with a corresponding shape (Figure 6.2A.2).

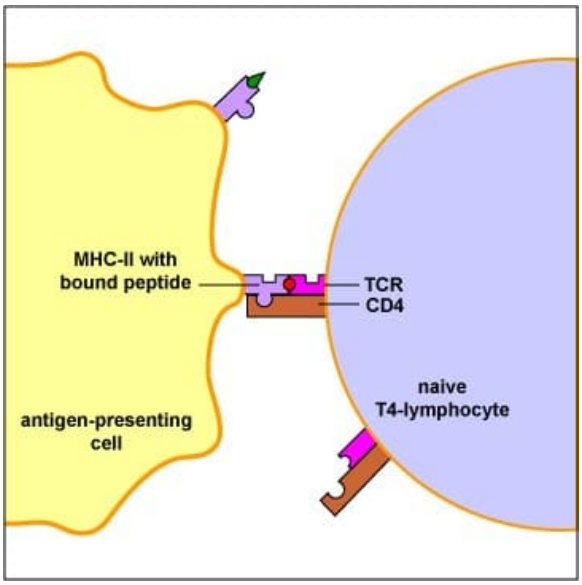


Figure 6.2A.2: Binding of T4-Lymphocytes to Conventional Antigens. Conventional antigens are only recognized by specific T4-lymphocytes having a TCR with a shape that corresponds to a peptide of that antigen bound to MHC-II molecules.

Superantigens, however, bind directly to the outside of MHC-II molecules and activate large numbers of T4-lymphocytes (Figure 6.2A.3). This activation of very large numbers of T4-lymphocytes results in the secretion of excessive amounts of a cytokine called interleukin-2 (IL-2) as well as the activation of self-reactive T-lymphocytes. The normal response to a conventional antigen results in the activation of maybe 1 in 10,000 T-lymphocytes; superantigens can activate as many as 1 in 5 T-lymphocytes.

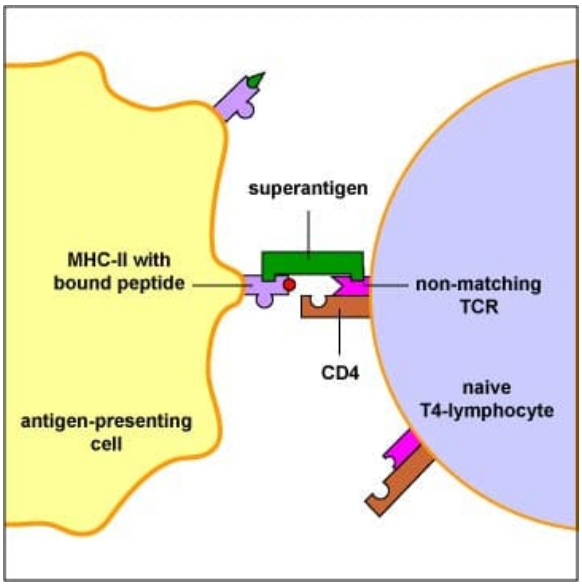


Figure 6.2A.3: Binding of Superantigens. Conventional antigens are only recognized by specific T4-lymphocytes having a TCR with a shape that corresponds to a peptide of that antigen bound to MHC-II molecules. Superantigens, on the other hand, bind directly to the outside of MHC-II molecules and the TCRs and activate many T4-lymphocytes. A specific TCR is not required for activation.

Production of high levels of IL-2 can result in circulation of IL-2 in the blood leading to symptoms such as fever, nausea, vomiting, diarrhea, and malaise. However, excess stimulation of IL-2 secretion can also lead to production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), inflammatory chemokines such as IL-8, and platelet-activating factor (PAF), and can lead to the same endothelial damage, acute respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiple organ system failure seen above with LPS and other bacterial cell wall factors. Activation of self-reactive T-lymphocytes can also lead to autoimmune attack.

The following are examples of superantigens.

1. Toxic shock syndrome toxin-1 (TSST-1), produced by some strains of *Staphylococcus aureus.* This exotoxin causes toxic shock syndrome (TSS). Excessive cytokine production leads to fever, rash, and shock.
2. Streptococcal pyrogenic exotoxin (Spe), produced by rare invasive strains and scarlet fever strains of *Streptococcus pyogenes* (the group A beta streptococci). *S pyogenes* produces a number of SPEs that are cytotoxic, pyrogenic, enhance the lethal effects of endotoxins, and contribute to cytokine-induced inflammatory damage. SPEs are responsible for causing streptococcal toxic shock syndrome (STSS) whereby excessive cytokine production leads to fever, rash, and triggering the shock cascade. The SPEs also appear to be responsible for inducing necrotizing fasciitis, a disease that can destroy the skin, fat, and tissue covering the muscle (the fascia). SPE B is also a precursor for a cysteine protease that can destroy muscles tissue.

> Read the description of *Streptococcus pyogenes*, and be able to match the bacterium with its description on an exam.

3. Staphylococcal enterotoxins (SE), producedby many strains of *Staphylococcus aureus.* These exotoxins cause staphylococcal food poisoning. Excessive Il-2 production results in fever, nausea, vomiting,and diarrhea. The vomiting may also be due to these toxins stimulating the vagus nerve in the stomach lining that controls vomiting.
4. ETEC enterotoxin, produced by enterotoxogenic *E. coli* (ETEC), one of the most common causes of traveler's diarrhea.

Exercise: Think-Pair-Share Questions

What is the mechanism by which superantigens ultimately lead to SIRS?

Summary

1. Conventional antigens are only recognized by specific T4-cells having a TCR with a corresponding shape.
2. Superantigens are unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes.
3. Activation of very large numbers of T4-lymphocytes results in the secretion of excessive amounts of a cytokine called interleukin-2 (IL-2).
4. Excess stimulation of IL-2 secretion can also lead to production of inflammatory and can lead to the same endothelial damage, acute respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiple organ system failure seen with PAMP-induced inflammation.
5. Examples of superantigens include toxic shock syndrome toxin-1 (TSST-1), Streptococcal pyrogenic exotoxins (SPE), Staphylococcal enterotoxins (SE), and enterotoxogenic E. coli (ETEC) enterotoxin.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define superantigen *(ans)*.
2. Briefly describe the mechanism by which superantigens cause harm to the body. *(ans)*
3. Name 2 superantigens and give an example of a bacterium that produces each.
   A. *(ans)*
   B. *(ans)*
4. Multiple Choice *(ans)*

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6.2B: Type II Toxins: Toxins that Damage Host Cell Membranes

Briefly describe the roles of alpha toxin, kappa toxin, and mu toxin, and fermentation by *Clostridium perfringens* in the pathogenesis of gas gangrene.

- State how the following toxins cause harm and name a bacterium producing each:

  a. leukotoxins such as leukocydin
  b. *Bordetella* tracheal cytotoxin

- State how Toxin A and Toxin B of *Clostridium difficile* lead to diarrhea and damage to the colon.

Highlighted Bacterium

1. Read the description of *Clostridium difficile* andmatch the bacterium with the description of the organism and the infection it causes.

In this section on Bacterial Pathogenesis we are looking at **virulence factors that damage the host**. Virulence factors that damage the host include:

1. The ability to produce Pathogen-Associated Molecular Patterns or PAMPs that bind to host cells causing them to synthesize and secrete inflammatory cytokines and chemokines;

2. The ability to produce harmful exotoxins.

3. The ability to induce autoimmune responses.

We are currently looking at the ability of bacteria to produce harmful exotoxins.

Exotoxins *(def)* are **toxins**, often proteins in nature, **secreted from a living bacterium** but also **released upon bacterial lysis**. In addition, some bacteria use a type 3 secretion system or a type 4 secretion system to **inject toxins directly into human cells**. There are three main types of exotoxins:

1. **superantigens (Type I toxins)**,

2. **exotoxins that damage host cell membranes (Type II toxins)**

3. **A-B toxins and other toxin that interfere with host cell function (Type II I toxins)**.

We will now look at exotoxins that damage host cell membranes.

The Ability to Produce Harmful Exotoxins

b. Type II Toxins: Toxins that Damage Host Cell Membranes

Type II toxins are typically phospholipases or pore-forming cytotoxins that disrupt the integrity of eukaryotic cell membranes. Damages host cells release danger-associated molecular patterns (DAMPs) *(def)* that bind to pattern-recognition receptors (PRRs) causing the release of inflammatory cytokines. This inflammatory response can also further contribute to tissue damage.

1. The **exotoxins** of *Clostridium perfringens (inf)*. This bacterium produces at least 20 exotoxins that play a role in the pathogenesis of gas gangrene and **producing expanding zones of dead tissue** (necrosis) surrounding the bacteria. Toxins include:

- **alpha toxin** (lecithinase): **increases the permeability of capillaries and muscle cells by breaking down lecithin in**

cytoplasmic membranes. This results in the gross **edema** *(def)* of gas gangrene. If the alpha toxin enters the blood it can damage organs. Alpha toxin is also necrotizing *(def)*, hemolytic, and cardiotoxic.
- **kappa toxin** (collagenase): **breaks down supportive connective tissue** *(def)* resulting in the mushy lesions of gas gangrene. It is also necrotizing *(def)*.
- **mu toxin** (hyaluronidase): **breaks down the tissue cement** that holds cells together in tissue.

- **epsilon toxin**: Increases vascular permeability and causes edema and congestion in various organs including lungs and kidneys.
- Additional **necrotizing toxins** *(def)* include beta toxin, iota toxin, and nu toxin.

A major characteristic of gas gangrene is the ability of *C. perfringens* to **very rapidly spread** from the initial wound site leaving behind an expanding zone of dead tissue. This organism spreads as a result of the pressure from fluid accumulation (due to increased capillary permeability from **alpha toxin**) and **gas production** (**anaerobic fermentation of glucose** by the organisms produces hydrogen and carbon dioxide), coupled with the breakdown of surrounding connective tissue (**kappa toxin**) and tissue cement (**mu toxin**).

2. **Leukotoxins.** Leukotoxins, such as leukocidin, are pore-forming toxins that **cause lysis of white blood cells** and other cells involved in immunity by binding to chemokine receptors on these cells and damaging the cell membrane. Leukotoxins is produced by various pyogenic *(def)* bacteria including *Staphylococcus aureus (inf)* and *Streptococcus pyogenes (inf)*, (group A beta streptococci).

3. *Pseudomonas aeruginosa* **produces a variety of toxins that lead to cell lysis and tissue damage in the host**. Type II toxins include:

- **Exotoxin U** (Exo U): Degrades the plasma membrane of eukaryotic cells, leading to lysis.
- **Phospholipase C** (PLC): Damages cellular phospholipids causing tissue damage; stimulates inflammation. Delivered by a type 3 secretion system.
- **Alkaline protease**: leads to tissue damage.
- **Cytotoxin**: Damages cell membranes of leukocytes causes microvascular damage.
- **Elastase**: Destroys elastin, a protein that is a component of lung tissue.
- **Pyocyanin**: a green to blue water-soluble pigment that catalyzes the formation of tissue-damaging toxic oxygen radicles *(def)*; impairs ciliary function, stimulates inflammation.

You Tube animation showing Pseudomonas using motility, pili, and exotoxins to cause an infection.
3D Medical Animations Library and Downloads, www.rufusrajadurai. wetpaint.com

4. **Toxin A** and **Toxin B**, produced by *Clostridium difficile (inf)*. **Toxin A damages the membranes of intestinal mucosal cells causing hypersecretion of fluids**. In addition, it **triggers the production of inflammatory cytokines**. Finally, it also **attracts and destroys neutrophils**, causing them to **release their lysosomal enzymes** for further tissue damage leading to **hemorrhagic necrosis** *(def)*. **Toxin B depolymerizes actin damaging mucosal cells cytoskeleton**. ***Clostridium difficile*** causes severe **antibiotic-associated colitis** and is an opportunistic Gram-positive, endospore-producing bacillus transmitted by the fecal-oral route. ***C. difficile* is a common health care-associated infection (HAIs) and is the most frequent cause of health-care-associated diarrhea**.

5. *Streptococcus pyogenes (inf)* **produces a number of enzymes and toxins that damage cells and tissues and causes inflammation**:

- **Streptolysin S** : Causes lysis of red blood cell membranes.
- **Streptolysin O**: Lytic to cells that contain cholesterol in their plasma membrane.
- **Proteases**: Degrade cellular proteins;helps organism spread.
- **DNases**: Degrade cellular DNA; helps organism spread.
- **Streptokinase**: Breaks down fibrin in clots; helps organism spread.
- **Streptococcal pyrogenic exotoxin B** (SPE B): A protease that facilitates bacterial spreading and survival; induces inflammation during *S. pyogenes* infections.

For More Information: Inflammation from Unit 5

6. **Urease and phospholipase**, produced by *Helicobacter pylori (inf)*. Urease contributes to acid resistance and epithelial cell damage while phospholipase damages the membrane of gastric or intestinal mucosal cells.

Flash animation showing induction of stomach and intestinal ulcers by *Helicobacter pylori*.

html5 version of animation for iPad showing induction of stomach and intestinal ulcers by *Helicobacter pylori*.

YouTube movie of a video endoscopy exam showing duodenal ulcers caused by *Helicobacter pylori*.

7. ***Bordetella* tracheal cytotoxin**, produced by *Bordetella pertussis (inf),***causes the respiratory cell damage during whooping cough**. Cell death, inhibition of ciliary movement by ciliated epithelial cells, and release of the inflammatory cytokine IL-1 **triggers the violent coughing episodes**, the only way the body can now remove inflammatory debris, bacteria, and mucus.

As mentioned earlier in this unit, many bacteria are able to **sense their own population density, communicate with each other by way of secreted chemical factors, and behave as a population rather than as individual bacteria** . This is referred to as cell-to-cell signaling or **quorum sensing** and plays an important role in pathogenicity and survival for many bacteria.

Quorum sensing involves the **production, release, and community-wide sensing of molecules called autoinducers that modulate gene expression in response to the density of a bacterial population**. When autoinducers produced by one bacterium cross the membrane of another, they bind to receptors in the cytoplasm. This autoinducer/receptor complex is then able to bind to DNA promoters and activate the transcription of quorum sensing-controlled genes. In this way, individual bacteria within a group are able to benefit from the activity of the entire group.

The outcomes of bacteria-host interaction are often related to bacterial population density. Bacterial virulence, that is its ability to cause disease, is largely based on the bacterium's ability to **produce gene products called virulence factors that enable that bacterium to colonize the host, resist body defenses, and harm the body**. If a relatively small number of a specific bacteria were to enter the body and immediately start producing their virulence factors, chances are the body's immune systems would have sufficient time to recognize and counter those virulence factors and remove the bacteria before there was sufficient quantity to cause harm. Many bacteria are able to delay production of those virulence factors by not expressing the genes for those factors until there is a sufficiently large enough population of that bacterium (a quorum). As the bacteria geometrically increase in number, so does the amount of their secreted autoinducers.

When a critical level of autoinducer is reached, the entire population of bacteria is able to simultaneously activate the transcription of their quorum-sensing genes and the body's immune systems are much less likely to have enough time to counter those virulence factors before harm is done.

, to simultaneously produce toxins and other virulence factors through quorum sensing would be an advantage to that population, as opposed to individual bacteria producing toxins and other virulence factors as soon as they enter the body.

Concept map for Type II Toxins (Toxins that Damage Membranes).

Summary

1. Type II toxins are typically phospholipases or pore-forming cytotoxins that disrupt the integrity of eukaryotic cell membranes.

2. Damages host cells release danger-associated molecular patterns (DAMPs) that bind to pattern-recognition receptors (PRRs) causing the release of inflammatory cytokines. This inflammatory response can also further contribute to tissue damage.
3. Examples include the exotoxins of Clostridium perfringens that cause gas gangrene, exotoxins of Pseudomonas aeruginosa that causes a variety of opportunistic infections, exotoxins of Streptococcus pyogenes that causes strep throat, the exotoxins of Clostridium difficile that causes antibiotic-associated colitis, and leukotoxins, pore-forming toxins that causes lysis of white blood cells.

Questions

_____ Causes the respiratory damage and violent coughing episodes seen during whooping cough. *(ans)*

_____ Damages the membranes of intestinal mucosal cells causing hypersecretion of fluids; triggers the production of inflammatory cytokines; attracts and destroys neutrophils causing them to release their lysosomal enzymes for further tissue damage leading to hemorrhagic necrosis.

a. leukotoxins
b. Toxin A
c. Toxin B
d. Bordetella tracheal cytotoxin

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6.2C: Type III Toxins: A-B Toxins and other Toxins that Interfere with Host Cell Function

Define A-B toxins and state the functions of the A component and the B component.

- State how the following exotoxins cause harm and name a bacterium producing each:

  a. diphtheria exotoxin
  b. cholera exotoxin
  c. enterotoxins
  d. shiga toxin
  e. anthrax lethal toxin and edema toxin
  f. botulism exotoxin
  g. tetanus exotoxin

  Highlighted Bacterium

  1. Read the description of *Corynebacterium diphtheriae* andmatch the bacterium with the description of the organism and the infection it causes.
  2. Read the description of *Bacillus anthracis* andmatch the bacterium with the description of the organism and the infection it causes.

The classic type III toxins are A-B toxins that consist of two parts (see Figure $6.2C.1$):

1. An "A" or active component that enzymatically inactivates some host cell intracellular target or signalling pathway to interfere with a host cell function; and
2. a "B" or binding component (see Figure $6.2C.2$) that binds the exotoxin to a receptor molecule on the surface of the host cell membrane and determines the type of host cell to which the toxin is able to affect.

Once the exotoxin binds, it is translocated across the host cell membrane. Some A-B toxins enter by endocytosis (see Figure $6.2C.3$), after which the A-component of the toxin separates from the B-component and enters the host cell's cytoplasm. Other A-B toxins bind to the host cell and the A component subsequently passes directly through the host cell's membrane and enters the cytoplasm (see Figure $6.2C.4$).

The A components of most A-B toxins then catalyze a reaction by which they remove the ADP-ribosyl group from the coenzyme NAD and covalently attach it to some host cell protein, a process called ADP- ribosylation (see Figure $6.2C.5$). This interferes with the normal function of that particular host cell protein that, in turn, determines the type of damage that is caused. Some A-B toxins work differently.

GIF animation of an A-B toxin binding to and penetrating a susceptible host cell.

The body's major defense against exotoxins is the production of antitoxin antibodies. Once the antibody binds to the exotoxin, the toxin can no longer bind to the receptors on the host cell membrane.

Flash animation showing the neutralization of exotoxins with antibodies.

html5 version of animation for iPad showing the neutralization of exotoxins with antibodies.

Examples of A-B toxins include:

1. Diphtheria exotoxin, produced by *Corynebacterium diphtheriae (inf)*. This toxin interferes with host cell protein synthesis by catalyzing the ADP-ribosylation of host cell elongation factor 2 (EF-2), necessary in order for tRNA to insert new amino acids into the growing protein chain. This results in cell death. Initially cells of the throat are killed by the toxin. The toxin is also released into the blood where it damages internal organs and can lead to organ failure. The "D" portion of the DTP vaccine contains diphtheria toxoid to stimulate the body to make neutralizing antibodies against the binding component of the diphtheria exotoxin. Once the antibody binds to the exotoxin, the toxin can no longer bind to the receptors on the host cell membrane.

, and be able to match the bacterium with its description on an exam.

2. Cholera exotoxin (choleragen), produced by *Vibrio cholerae (inf)*. This exotoxin catalyzes the ADP-ribosylation of a host cell protein called Gs that turns the synthesis of a metabolic regulator molecule called cyclic AMP (cAMP) on and off. In this case, synthesis stays turned on. High levels of cAMP block intestinal epithelial cells from taking in sodium from the lumen of the intestines and stimulates them to secrete large quantities of chloride. Water and other electrolytes osmotically follow. This causes loss of fluids, diarrhea, and severe dehydration. For a movie of showing the effect of cholera exotoxin on human cells, see the Theriot Lab Website at Stanford University Medical School. Click on "*Vibrio cholerae* colonizing human cells."
3. Enterotoxins. A number of bacteria produce exotoxins that bind to the cells of the small intestines. Most of these toxins catalyze the ADP-ribosylation of host cell proteins that turn the synthesis of the metabolic regulator molecules cyclic AMP (cAMP) or cyclic GMP on and off in intestinal mucosal cells. High levels of cAMP and cGMP cause loss of electrolytes and water that results in diarrhea. Organisms producing enterotoxins include *Clostridium perfringens (inf)*,and *Bacillus cereus (inf)*. (As mentioned under Type I toxins, the enterotoxins of *Staphylococcus aureus (inf)* and enterotoxogenic *E. coli (inf)* work differently, functioning as superantigens.)
4. Pertussis exotoxin, produced by *Bordetella pertussis (inf)*. The pertussis exotoxin catalyzes the ADP-ribosylation of a host cell protein called Gi leading to high intracellular levels of cAMP. This disrupts cellular function. In the respiratory epithelium, the high levels of cAMP results in increased respiratory secretions and mucous production and contribute to coughing. In the case of phagocytes, excessive cAMP decreases phagocytic activities such as chemotaxis, engulfment, killing. In the blood, the toxin results in increased sensitivity to histamine. This can result in increased capillary permeability, hypotension and shock. It may also act on neurons resulting in encephalopathy.
5. *Pseudomonas aeruginosa* produces a variety of toxins that lead to tissue damage in the host. Type II toxins include:
    a. Exotoxin A: interferes with host cell protein synthesis by catalyzing the ADP-ribosylation of host cell elongation factor 2 (EF-2), necessary in order for tRNA to insert new amino acids into the growing protein chain; is also immunosuppressive.
    b. Exotoxin S: inhibits host cell protein synthesis causing tissue damage; is immunosuppressive.
6. Shiga toxin, produced by species of *Shigella (inf)* and enterohemorrhagic *Escherichia coli* (EHEC) such as such as *E. coli* O157:H7. This toxin is an A-B toxin that cleaves host cell rRNA and prevents the attachment of charged tRNAs thus stopping host cell protein synthesis. The shiga toxin also enhances the LPS-mediated release of cytokines such as Il-1 and TNF-alpha and appears to be responsible for a complication of shigellosis and *E. coli* O157:H7 infection called hemolytic uremic syndrome (HUS), probably by causing blood vessel damage.
7. Anthrax toxins, produced by *Bacillus anthracis.* In the case of the two anthrax exotoxins, two different A-components known as lethal factor (LF) and edema factor (EF) share a common B-component known as protective antigen (PA). Protective antigen, the B-component, first binds to receptors on host cells and is cleaved by a protease creating a binding site for either lethal factor or edema factor.
    a. Lethal factor is a protease that inhibits mitogen-activated kinase-kinase. At low levels, LF inhibits the release of proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha, (TNF-alpha), and NO. This may initially reduce immune responses against the organism and its toxins. But at high levels, LF is cytolytic for macrophages, causing release of high levels of interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and NO. Excessive release of these cytokines can lead to a massive inflammatory response and the shock cascade, similar to septic shock.
    b. Edema factor is an adenylate cyclase that generates cyclic AMP in host cells. It impairs phagocytosis, and inhibits production of TNF and interleukin-6 (IL-6) by monocytes. This most likely impairs host defenses.

, and be able to match the bacterium with its description on an exam.

For More Information: the Shock Cascade from Unit 2

For More Information: Inflammation from Unit 4

There are a number of other bacterial exotoxins that cause damage by interfering with host cell function. They include the following.

1. Botulinal exotoxin, produced by *Clostridium botulinum (inf)*. This is a neurotoxin that acts peripherally on the autonomic nervous system. For muscle stimulation, acetylcholine must be released from the neural motor end plate of the neuron at the synapse between the neuron and the muscle to be stimulated. The acetylcholine then induces contraction of the muscle fibers. The botulism exotoxin binds to and enters the presynaptic neuron and blocks its release of acetylcholine. This causes a flaccid paralysis , a weakening of the involved muscles. Death is usually from respiratory failure. While two exotoxins of *C. botulinum* catalyze ADP-ribosylation of host cell proteins, the botulinal toxin that affects neurons does not. Since the botulinal toxin is able to cause a weakening of muscles, it is now being used therapeutically to treat certain neurologic disorders such as dystonia and achalasia that result in abnormal sustained muscle contractions, as well as a treatment to remove facial lines.

GIF animation showing acetylcholine-induced contraction of a muscle.

GIF animation showing botulism exotoxin blocking acetylcholine release.

2. Tetanus exotoxin (tetanospasmin), produced by *Clostridium tetani (inf)*. This is a neurotoxin that binds to inhibitory interneurons of the spinal cord and blocks their release of inhibitor molecules. It is these inhibitor molecules from the inhibitory interneurons that eventually allow contracted muscles to relax by stopping excitatory neurons from releasing the acetylcholine that is responsible for muscle contraction. The toxin, by blocking the release of inhibitors, keeps the involved muscles in a state of contraction and leads to spastic paralysis , a condition where opposing flexor and extensor muscles simultaneously contract. Death is usually from respiratory failure. The "T" portion of the DTP vaccine contains tetanus toxoid to stimulate the body to make neutralizing antibodies against the binding component of the diphtheria exotoxin. Once the antibody binds to the exotoxin, the toxin can no longer bind to the receptors on the host cell membrane.

GIF animation showing inhibition of muscle contraction by an inhibitory interneuron.

GIF animation showing tetanus exotoxin blocking inhibitor release from an inhibitory interneuron.

3. Neutrophil activating protein, produced by *Helicobacter pylori (inf)*. Neutrophil activating protein promotes the adhesion of human neutrophils to endothelial cells and the production of reactive oxygen radicals. The toxin induces a moderate inflammation that promote *H. pylori* growth by the release of nutrients factors from the inflamed tissue.

Flash animation showing induction of stomach ulcers by *Helicobacter pylori*.

Explain the adaptive immune mechanism by which this immunization confers protection.

Concept map for Type III Toxins (AB Toxins and Toxins that Interfere with Cell Function).

Summary

The classic type III toxins are A-B toxins that consist of two parts: an “A” or active component that enzymatically inactivates some host cell protein or signalling pathway to interfere with a host cell function; and a “B” or binding component that binds the exotoxin to a receptor molecule on the surface of the host cell membrane and determines the type of host cell to which the toxin is able to affect.

Examples include the diphtheria exotoxin produced by Corynebacterium diphtheria, the cholera exotoxin produced by Vibrio cholerae, certain enterotoxins that cause loss of electrolytes and water resulting in diarrhea, the pertussis exotoxin produced by Bordetella pertussis, shiga toxin, produced by species of Shigella and enterohemorrhagic Escherichia coli (EHEC), the anthrax toxins produced by Bacillus anthracis, the tetanus exotoxin of Clostridium tetani, and the botulism exotoxin of Clostridium botulinum.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ Produced by certain strains of *Escherichia coli* such as *E. coli* O157:H7. These toxins kill intestinal epithelial cells of the colon and cause bloody diarrhea. Less commonly, the toxins enter the blood and are carried to the kidneys where they damage endothelial cells of the blood vessels and cause hemolytic uremic syndrome (HUS). *(ans)*

   _____ Produced by a species of *Clostridium*. This is a neurotoxin that binds to inhibitory interneurons of the spinal cord and blocks their release of inhibitor molecules.The toxin, by blocking the release of inhibitors, keeps the involved muscles in a state of contraction and leads to spastic paralysis, a condition where opposing flexor and extensor muscles simultaneously contract. *(ans)*

   _____ At low levels, this toxin inhibits the release of proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha, (TNF-alpha), and NO. This may initially reduce immune responses against the organism and its toxins. But at high levels, it is cytolytic for macrophages, causing release of high levels of interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and NO. Excessive release of these cytokines can lead to a massive inflammatory response and the shock cascade, similar to septic shock. *(ans)*

   a. diphtheria exotoxin
   b. cholera exotoxin
   c. enterotoxins
   d. pertussis exotoxin
   e. shiga toxin
   f. anthrax lethal toxin
   g. botulism exotoxin
   h. tetanus exotoxin
2. Multiple Choice (ans)

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6.3: The Ability to Induce Autoimmune Responses

State what is meant by autoimmunity.

- Name three bacterial diseases that may result from autoimmunity.

The Ability to Induce Autoimmune Responses

Autoimmunity *(def)* is when the body's immune defenses mistakenly attack the body. In certain cases, bacteria can serve as a trigger for this response.

One way bacteria can do this is by inducing the production of cross-reacting antibodies *(def)* and possibly auto-reactive cytotoxic T-lymphocytes or CTLs *(def)*. These are antibodies and CTLs made in response to bacterial antigens *(def)* that accidently cross react with epitopes *(def)* on host cells. As a result, the antibodies and CTLs wind up destroying the host cells to which they have bound. Furthermore, when the antibodies activate the classical complement pathway *(def)*, this further stimulates the inflammatory response resulting in more tissue damage. Rheumatic fever triggered by rheumatogenic strains of *Streptococcus pyogenes*(inf) is an example. Antibodies and CTLs stimulated by antigens of *S. pyogenes* cross-react with heart and joint tissues damaging the heart and joints.

GIF animation showing opsonization of cells during Type-II hypersensitivity.

GIF animation showing MAC lysis of cells during Type-II hypersensitivity.

Flash animation showing ADCC by NK cells

html5 version of animation for iPad showing ADCC by NK cells

Flash animation showing ADCC apoptosis by NK cells

html5 version of animation for iPad showing ADCC apoptosis by NK cells

For More Information: Type-II Hypersensitivities from Unit 6

Another way autoimmunity can be triggered by certain bacteria is by **stimulating the production of soluble immune complexes**. When high levels of circulating antibodies react with certain bacterial antigens, they form large amounts of immune complexes (antibodies bound to antigens). These immune complexes can lodge in filtering units such as the kidneys where they **activate the complement pathway** *(def)*. The resulting **inflammatory response** then destroys kidney tissues. An example of this is **acute glomerulonephritis** that sometimes following infection by *Streptococcus pyogenes (inf)*.

GIF animation showing inflammation and tissue death during Type-III hypersensitivity.

For More Information: Type-III Hypersensitivities from Unit 6

Two other possible examples of bacterial induced autoimmunity are **chronic Lyme disease** (arthritis, neurological abnormalities, and heart damage) following infection by *Borrelia burgdorferi (inf)*, and **tertiary syphilis** (heart damage, neurological abnormalities, and destructive skin lesion) following infection by *Treponema pallidum (inf)*.

the body by causing an autoimmune response.

Concept map for the Ability to Induce Autoimmune Responses.

Autoimmunity will be discussed in greater detail under Hypersensitivities in Unit 6.

Summary

1. Autoimmunity is when the body's immune defenses mistakenly attack the body and sometimes certain bacteria can serve as a trigger for this response.
2. One way bacteria can trigger autoimmunity by stimulating the production of cross-reacting antibodies. These are antibodies made in response to bacterial antigens then accidently cross-react with and destroy host cells to which they have bound. An example is rheumatic fever following Streptococcus pyogenes infection.
3. Another way autoimmunity can be triggered by certain bacteria is by stimulating the production of soluble antigen-antibody (immune) complexes. These immune complexes can lodge in filtering units such as the kidneys where they activate the complement pathway and trigger an inflammatory response then destroys kidney tissues. An example of this is acute glomerulonephritis that sometimes following infection by Streptococcus pyogenes.

Questions

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what is meant by autoimmunity. (ans)
2. Name 3 bacterial diseases that may result from autoimmunity.
   A. *(ans)*
   B. *(ans)*
   C. *(ans)*

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6.E: Virulence Factors that Damage the Host (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. List 3 general categories of virulence factors that damage the host.
   A.
   B.

2. Matching:

____ Intercellular regulatory proteins produced by one cell that subsequently bind to other cells in the area and influence their activity in some manner. Regulate body defense mechanisms.

____ Defense regulatory chemicals that promote an inflammatory response by enabling white blood cells to leave the blood vessels and enter the surrounding tissue, by chemotactically attracting these white blood cells to the infection site, and by triggering neutrophils to release killing agents for extracellular killing.

____ A condition where bacteria enter the bloodstream causing harm.

____ A decreased volume of circulating blood.

____ Reduced delivery of nutrients and oxygen via the blood. This can lead to ischemia, a restriction in blood supply that results in damage or dysfunction of tissue.

____ Respiratory failure from acute inflammation in the lungs, injury to capillaries in the alveoli of the lungs, and pulmonary edema.

____ The formation of clots within the blood vessels throughout the body.

A. inflammation
B. septicemia
C. chemokines
D. cytokines
E. DIC
F. ARDS
G. septic shock
H. hypovolemia
I. hypotension
J. hypoperfusion

3. Define hypotension and describe the biological mechanism behind 3 factors that contribute to hypotension.

4. Define hypovolemia and describe the biological mechanism behind 3 factors that contribute to hypovolemia.

5. Define hypoperfusion and describe the biological mechanism behind 3 factors that contribute to hypoperfusion.

6. Describe the biological mechanism behind ARDS and how ARDS contributes to hypoperfusion.

7. Define pyroptosis and state its role in inducing inflammation.

8. List three types of exotoxins.

A.

B.

C.

9. Define exotoxin.

10. The body's major defense against exotoxins is _____.

11. Define superantigen .

12. Briefly describe the mechanism by which superantigens cause harm to the body.

13. Name 2 superantigens and give an example of a bacterium that produces each.

A.

B.

14. Match the following descriptions with the exotoxin:

____ Causes lysis of white blood cells and other immune cells by damaging their cell membrane . It is produced by various pyogenic bacteria including Staphylococcus aureus and Streptococcus pyogenes.

_____ Causes the respiratory damage and violent coughing episodes seen during whooping cough.

_____ Damages the membranes of intestinal mucosal cells causing hypersecretion of fluids; triggers the production of inflammatory cytokines; attracts and destroys neutrophils causing them to release their lysosomal enzymes for further tissue damage leading to hemorrhagic necrosis.

a. leukotoxins

b. Toxin A

c. Toxin B

d. Bordetella tracheal cytotoxin

15. Usually deep puncture-type wounds are needed for the development of gas gangrene. The resulting infected tissue shows massive edema, is mushy to the touch, and the infection spreads very rapidly through the tissue. In terms of the causative organism and its products, discuss why.

1. State the functions of the A component and the B component in A-B toxins. .

2. Match the following descriptions with the exotoxin:

____ Produced by certain strains of Escherichia coli such as E. coli O157:H7. These toxins kill intestinal epithelial cells of the colon and cause bloody diarrhea. Less commonly, the toxins enter the blood and are carried to the kidneys where they damage endothelial cells of the blood vessels and cause hemolytic uremic syndrome (HUS).

____ Produced by a species of Clostridium. This is a neurotoxin that acts peripherally on the autonomic nervous system. This toxin binds to and enters the presynaptic neuron and blocks its release of acetylcholine. This causes a flaccid paralysis, a weakening of the involved muscles.

____ Produced by a species of Clostridium. This is a neurotoxin that binds to inhibitory interneurons of the spinal cord and blocks their release of inhibitor molecules.The toxin, by blocking the release of inhibitors, keeps the involved muscles in a state of contraction and leads to spastic paralysis, a condition where opposing flexor and extensor muscles simultaneously contract.

____ At low levels, this toxin inhibits the release of proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha, (TNF-alpha), and NO. This may initially reduce immune responses against the organism and its toxins. But at high levels,

it is cytolytic for macrophages, causing release of high levels of interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and NO. Excessive release of these cytokines can lead to a massive inflammatory response and the shock cascade, similar to septic shock.

a. diphtheria exotoxin	f. anthrax lethal toxin
b. cholera exotoxin	g. botulism exotoxin
c. enterotoxins	h. tetanus exotoxin
d. pertussis exotoxin	
e. shiga toxin	

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UNIT 4: EUKARYOTIC MICROORGANISMS AND VIRUSES

Eukaryote organisms have one or more cells with a nucleus and other organelles enclosed within membranes.

7: The Eukaryotic Cell

7.0: Eukaryotic Cell Anatomy

7.1: The Cytoplasmic Membrane

7.2: The Cell Wall

7.3: The Endomembrane System

7.3A: The Nucleus

7.3B: The Endoplasmic Reticulum

7.3C: The Golgi Complex

7.4: Other Internal Membrane-Bound Organelles

7.4A: Mitochondria

7.4B: Chloroplasts

7.4C: Lysosomes, Peroxisomes, Vacuoles, and Vesicles

7.5: Ribosomes

7.6: The Cytoskeleton

7.7: Flagella and Cilia

7.8: The Endosymbiotic Theory

7.E: The Eukaryotic Cell (Exercises)

8: Fungi

8.1: Overview of Fungi

8.2: Yeasts

8.3: Molds

8.4: Fungal Pathogenicity

8.5: Chemotherapeutic Control of Fungi

8.E: Fungi (Exercises)

9: Protozoa

9.1: Characteristics of Protozoa

9.2: Medically Important Protozoa

9.E: Protozoa (Exercises)

10: Viruses

10.1: General Characteristics of Viruses

10.2: Size and Shapes of Viruses

10.3: Viral Structure

10.4: Classification of Viruses

10.5: Other Acellular Infectious Agents: Viroids and Prions

10.6: Animal Virus Life Cycles

10.6A: The Productive Life Cycle of Animal Viruses
10.6B: Productive Life Cycle with Possible Latency
10.6C: The Life Cycle of HIV
10.6D: Natural History of a Typical HIV Infection
10.6E: The Role of Viruses in Tumor Production
10.7: Bacteriophage Life Cycles: An Overview
10.7A: The Lytic Life Cycle of Bacteriophages
10.7B: The Lysogenic Life Cycle of Bacteriophages
10.8: Pathogenicity of Animal Viruses
10.9: Bacteriophage-Induced Alterations of Bacteria
10.10: Antiviral Agents
10.11: General Categories of Viral Infections
10.E: Viruses (Exercises)

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7: THE EUKARYOTIC CELL

7.0: Eukaryotic Cell Anatomy

7.1: The Cytoplasmic Membrane

7.2: The Cell Wall

7.3: The Endomembrane System

7.3A: The Nucleus

7.3B: The Endoplasmic Reticulum

7.3C: The Golgi Complex

7.4: Other Internal Membrane-Bound Organelles

7.4A: Mitochondria

7.4B: Chloroplasts

7.4C: Lysosomes, Peroxisomes, Vacuoles, and Vesicles

7.5: Ribosomes

7.6: The Cytoskeleton

7.7: Flagella and Cilia

7.8: The Endosymbiotic Theory

7.E: The Eukaryotic Cell (Exercises)

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7.0: Eukaryotic Cell Anatomy

The cell is the basic unit of life. Based on the organization of their cellular structures, all living cells can be divided into two groups: prokaryotic and eukaryotic (also spelled procaryotic and eucaryotic). Animals, plants, fungi, protozoans, and algae all possess eukaryotic cell types. Only bacteria have prokaryotic cell types.

Eukaryotic cells are generally much larger and more complex than prokaryotic. The larger a cell, the smaller is its surface-to-volume ratio (the surface area of a cell compared to its volume). For example, a spherical cell 2 micrometers (µm) in diameter has a surface-to-volume ratio of approximately 3:1, while a spherical cell having a diameter of 20 µm has a surface-to-volume ratio of around 0.3:1. A large surface-to-volume ratio, as seen in smaller prokaryotic cells, means that nutrients can easily and rapidly reach any part of the cells interior. However, in the larger eukaryotic cell, the limited surface area when compared to its volume means nutrients cannot rapidly diffuse to all interior parts of the cell. That is why eukaryotic cells require a variety of specialized internal organelles to carry out metabolism, provide energy, and transport chemicals throughout the cell. Both, however, must carry out the same life processes.

For More Information: A Comparison of Prokaryotic and Eukaryotic Cells from Unit 1

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Video 7.0.1: The Inner Life of a Cell. To view an excellent eight-minute animation on the inner workings of a cell created in NewTek LightWave 3D and Adobe After Effects for Harvard biology students, see . (https://www.youtube.com/watch?v=FzcTgrxMzZk)

We will now look at the various components and organelles found in eukaryotic cells.

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7.1: The Cytoplasmic Membrane

State the chemical composition and major function of the cytoplasmic membrane in eukaryotic cells.

- State the net flow of water when a cell is placed in an isotonic, hypertonic, or hypotonic environment and relate this to the solute concentration.
- Define the following means of transport:

  a. passive diffusion
  b. osmosis
  c. active transport
  d. endocytosis
  e. phagocytosis
  f. pinocytosis
  g. exocytosis

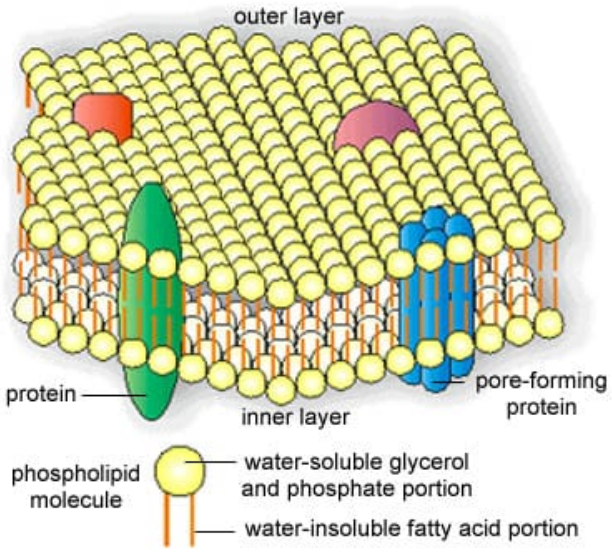


Figure 7.1.7.1.1: Diagram of a Cytoplasmic Membrane

In addition, it contains glycolipids as well as complex lipids called sterols, such as the cholesterol molecules found in animal cell membranes, that are not found in prokaryotic membranes (except for some mycoplasmas). The sterols make the membrane less permeable to most biological molecules, help to stabilize the membrane, and probably add rigidity to the membranes aiding in the ability of eukaryotic cells lacking a cell wall to resist osmotic lysis. The proteins and glycoproteins in the cytoplasmic membrane are quite diverse and function as:

a. channel proteins to form pores for the free transport of small molecules and ions across the membrane
b. carrier proteins for facilitated diffusion and active transport of molecules and ions across the membrane
c. cell recognition proteins that identifies a particular cell
d. receptor proteins that bind specific molecules such as hormones and cytokines
e. enzymatic proteins that catalyze specific chemical reactions.

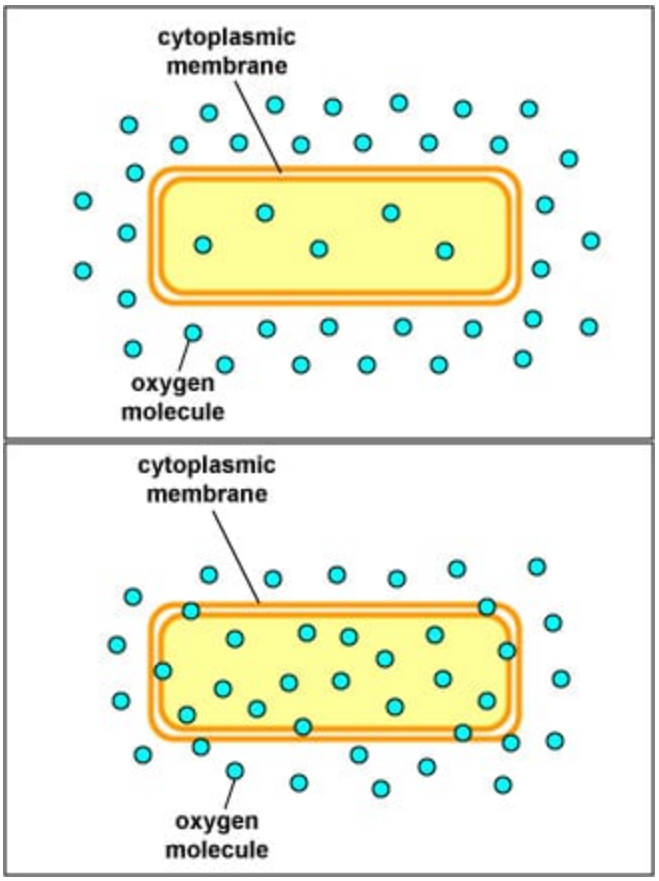


Figure 7.1.7.1.2: Passive Diffusion, Step 1. Passive diffusion is the net movement of gases or small uncharge polar molecules across a phospholipid bilayer membrane from an area of higher concentration to an area of lower concentration . Examples of gases that cross membranes by passive diffusion include N_2, O_2, and CO_2; examples of small polar molecules include ethanol, H_2O, and urea.

All molecules and atoms possess kinetic energy (energy of motion). If the molecules or atoms are not evenly distributed on both sides of a membrane, the difference in their concentration forms a concentration gradient that represents a form of potential energy (stored energy). The net movement of these particles will therefore be down their concentration gradient - from the area of higher concentration to the area of lower concentration. Diffusion is powered by the potential energy of a concentration gradient and does not require the expenditure of metabolic energy.

Flash animation showing passive diffusion of oxygen.

html5 version of animation for iPad showing passive diffusion of oxygen.

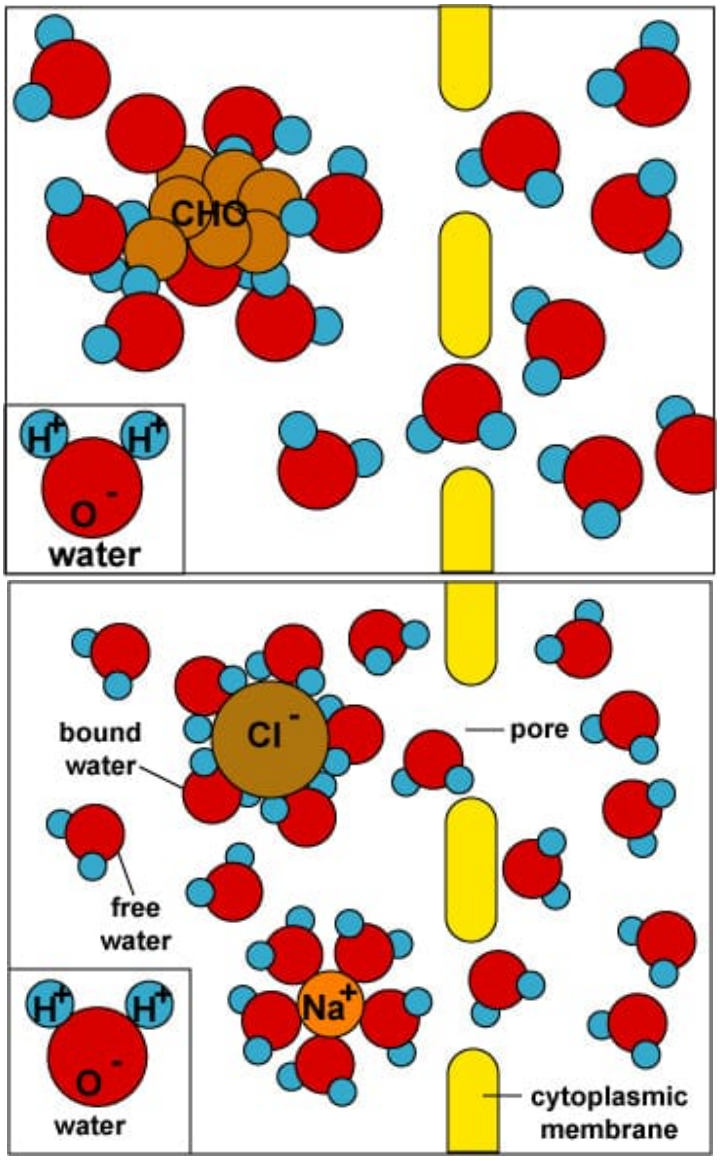


Figure 7.1.7.1.3: Osmosis. Free Water Passing Through Membrane Pores. (left) When a solute such as sugar dissolves in water, it forms weak hydrogen bonds with water molecules. While free, unbound water molecules are small enough to pass through membrane pores, water molecules bound to solute are not. (right) When an ionic solute such as NaCl dissolves in water, the Na^+ ion attracts the partial negative charge of the oxygen atom in the water molecule while the Cl^- ion attracts the partial positive charge of the warter's hydrogen. While free, unbound water molecules are small enough to pass through membrane pores, water molecules bound to solute are not.

A cell can find itself in one of three environments: isotonic, hypertonic, or hypotonic. (The prefixes iso-, hyper-, and hypo- refer to the solute concentration).

- In an isotonic environment (Figure 7.1.5A), both the water and solute concentration are the same inside and outside the cell and water goes into and out of the cell at an equal rate.

Flash animation showing osmosis in an isotonic environment.

html5 version of animation for iPad showing osmosis in a isotonic environment.

- If the environment is hypertonic (Figure 7.1.5B), the water concentration is greater inside the cell while the solute concentration is higher outside (the interior of the cell is hypotonic to the surrounding hypertonic environment). Water goes

out of the cell.

Flash animation showing osmosis in a hypertonic environment.

html5 version of animation for iPad showing osmosis in a hypertonic environment.

- In an environment that is hypotonic (Figure 7.1.5C), the water concentration is greater outside the cell and the solute concentration is higher inside (the interior of the cell is hypertonic to the hypotonic surroundings). Water goes into the cell.

Flash animation showing osmosis in a hypotonic environment.

html5 version of animation for iPad showing osmosis in a hypotonic environment.

Transport of Substances Across the Membrane by Transport (Carrier) Proteins

For the majority of substances a cell needs for metabolism to cross the cytoplasmic membrane, specific transport proteins (carrier proteins) are required. Transport proteins allow cells to accumulate nutrients from even a scarce environment. Examples of transport proteins include channel proteins, uniporters, symporters, antiporters, and the ATP- powered pumps. These proteins transport specific molecules, related groups of molecules, or ions across membranes through either facilitated diffusion or active transport.

Facilitated diffusion is the transport of substances across a membrane by transport proteins, such as uniporters and channel proteins, along a concentration gradient from an area of higher concentration to lower concentration. Facilitated diffusion is powered by the potential energy of a concentration gradient and does not require the expenditure of metabolic energy.

1. Uniporter: Uniporters are transport proteins that transport a substance from one side of the membrane to the other (Figure 7.1.6A1 and Figure 7.1.6A2). Amino acids, sugars, nucleosides, and other small molecules can be transported through eukaryotic membranes by different uniporters.

Flash animation showing transport by way of an uniporter.

html5 version of animation for iPad showing transport by way of an uniporter.

2. Channel proteins transport water or certain ions down either a concentration gradient, in the case of water, or an electric potential gradient in the case of certain ions, from an area of higher concentration to lower concentration (Figure 7.1.6B). While water molecules can directly cross the membrane by passive diffusion, as mentioned above, their transport can be enhanced by channel proteins called aquaporins.

Flash animation showing transport of water across a membrane by channel proteins.

html5 version of animation for iPad showing transport of water across a membrane by channel proteins.

Active transport is a process whereby the cell uses both transport proteins and metabolic energy to transport substances across the membrane against the concentration gradient. In this way, active transport allows cells to accumulate needed substances even when the concentration is lower outside. The energy is provided by either proton motive force, the hydrolysis of ATP, or by

the electric potential (voltage) difference across the membrane.

Proton motive force is an energy gradient resulting from hydrogen ions (protons) moving across the membrane from greater to lesser hydrogen ion concentration. ATP is the form of energy cells most commonly use to do cellular work. Electric potential is the difference in voltage across the cytoplasmic membrane as a result of ion concentration gradients and the selective movement of ions across membranes by ion pumps or through ion channels.

A Review of Proton Motive Force from Unit 6

A Review of ATP from Unit 6

Transport proteins involved in active transport include antiporters, symporters, the proteins of the ATP-powered pumps.

Antiporters are transport proteins that transport one substance across the membrane in one direction, while simultaneously transporting a second substance across the membrane in the opposite direction (Figure 7.1.6C). Antiporters use the potential energy of electrochemical gradients from Na^+ or H^+ to transport ions, glucose, and amino acids against their concentration gradient (Figure 7.1.6E1).

Flash animation showing transport by way of an antiporter.

html5 version of animation for iPad showing transport by way of an antiporter.

Symporters are transport proteins that simultaneously transport two substances across the membrane in the same direction (Figure 7.1.6D). Like antiporters, symporters use the potential energy of electrochemical gradients from Na^+ or H^+ to transport ions, glucose, and amino acids against their concentration gradient (Figure 7.1.6E2).

Flash animation showing transport by way of a symporter.

html5 version of animation for iPad showing transport by way of a symporter.

ATP- powered pumps couple the energy released from the hydrolysis of ATP with the transport of substances across the cytoplasmic membrane. ATP- powered pumps are used to transport ions such as Na^+, Ca^{2+}, K^+, and H^+ across membranes against their concentration gradient.

An example of active transport via an ATP- powered pump is the sodium-potassium pump found in animal cells. Three sodium ions from inside the cell first bind to the transport protein (Figure 7.1.10A). Then a phosphate group is transferred from ATP to the transport protein causing it to change shape (Figure 7.1.10B) and release the sodium ions outside the cell (Figure 7.1.10C). Two potassium ions from outside the cell then bind to the transport protein (Figure 7.1.10D) and as the phosphate is removed, the protein assumes its original shape and releases the potassium ions inside the cell (Figure 7.1.10E).

Flash animation showing the sodium-potassium pump in animal cells.

html5 version of animation for iPad showing the sodium-potassium pump in animal cells.

Flash animation showing the sodium-potassium pump.
Courtesy of Raymond Husthwaite

html5 version of animation showing the sodium-potassium pump.
Courtesy of Raymond Husthwaite

Endocytosis

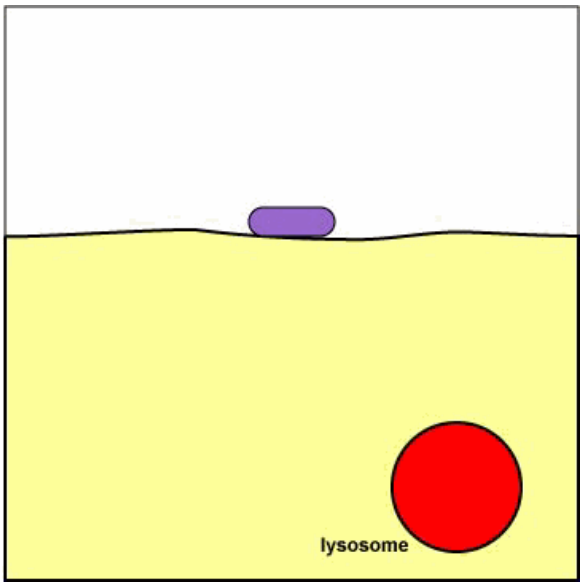


Figure 7.1.7.1.1: Exocytosis. During exocytosis, a cell releases waste products or specific secretion products by the fusion of a vesicle with the cytoplasmic membrane.

Concept map for Eukaryotic Cell Structure

Summary

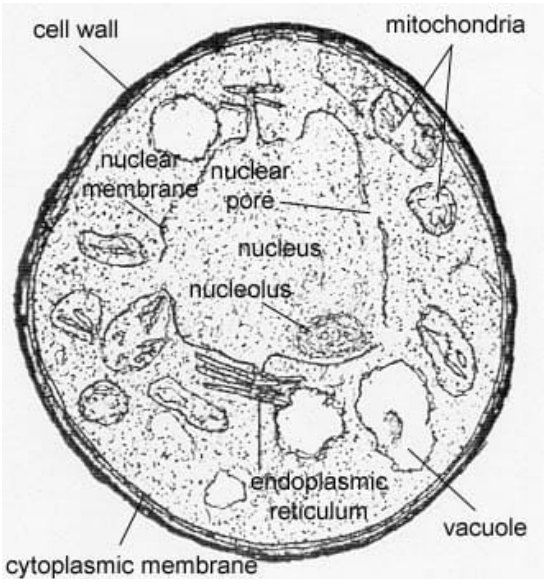
The cytoplasmic membrane (also called the plasma or cell membrane) of eukaryotic cells is a fluid phospholipid bilayer embedded with proteins and glycoproteins. It contains glycolipids as well as complex lipids called sterols. The cytoplasmic membrane is a semipermeable membrane that determines what goes in and out of the cell. Substances may cross the cytoplasmic membrane of eukaryotic cells by simple diffusion, osmosis, passive transport, active transport, endocytosis and exocytosis.

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7.2: The Cell Wall

State which eukaryotic organisms possess a cell wall and which lack a cell wall.

State the function of the cell wall in those eukaryotic cells that have one.



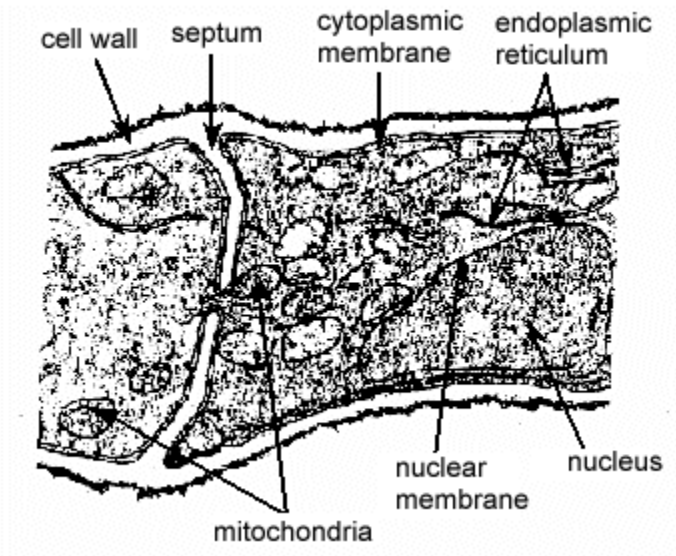


Figure 7.2.32: Candida albicans (Eukaryotic Cell) and 36: Segment of a Mold Hypha

Summary

1. Algae, fungi, and plant cells have a cell wall; animal cells and protozoans lack cell walls.
2. The rigid, tightknit, polysaccharide molecular structure of the cell wall helps the cell resist osmotic lysis.

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7.3: THE ENDOMEMBRANE SYSTEM

The endomembrane system compartmentalizes the cell for various different but interrelated cellular functions. It consists of the nucleus, the endoplasmic reticulum, and the Golgi complex.

We will now look at the various structures that make up the endomembrane system, including the nucleus, the endoplasmic reticulum, and the Golgi complex.



-  Topic hierarchy 

7.3A: The Nucleus

7.3B: The Endoplasmic Reticulum

7.3C: The Golgi Complex

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7.3A: The Nucleus

Describe the structure and the function of the nucleus in eukaryotic cells.

- Define the following:

  a. nuclear envelope
  b. nucleolus
  c. nucleosome

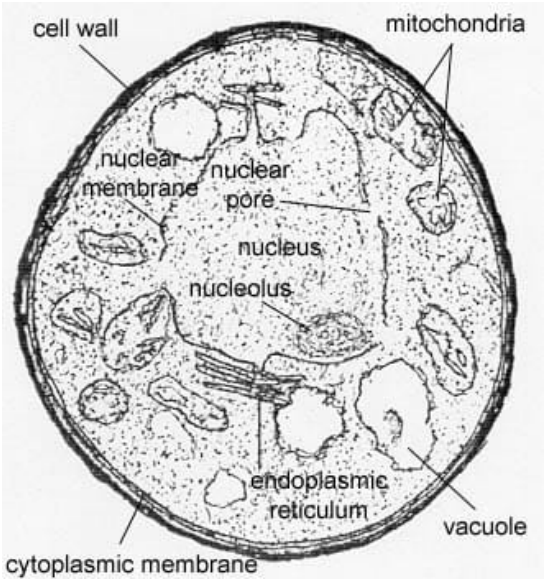


Figure 7.3A.33). The pores in the nuclear membrane allow ribosomal subunits and mRNA transcribed off genes in the DNA to leave the nucleus, enter the cytoplasm, and participate in protein synthesis.

- Electron micrograph of a nucleus courtesy of Dennis Kunkel's Microscopy.

Inside the nucleus is a fluid called nucleoplasm, a nucleolus (see Figure 7.3A.31), and linear chromosomes composed of negatively charged DNA associated with positively charged basic proteins called histones to form structures known as nucleosomes. The nucleosomes are part of what is called chromatin , the DNA and proteins that make up the chromosomes. The nucleolus is an area within the nucleus that is involved in the assembly of ribosomal subunits. An area of DNA called the nucleolar organizer directs the synthesis of ribosomal RNA (rRNA) that subsequently combines with ribosomal proteins to form immature ribosomal subunits that mature after they leave the nucleus by way of the pores in the nuclear envelope and mature in the cytoplasm. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA, and ribosomal RNA (rRNA). Messenger RNA is then translated into protein at the ribosomes. In general then, DNA determines what proteins and enzymes an organism can synthesize and, therefore, what chemical reactions it is able to carry out.

The DNA in eukaryotic cells is packaged in a highly organized way. It consists of a basic unit called a nucleosome , a beadlike structure 11 nm in diameter that consists of 146 base pairs of DNA wrapped around eight histone molecules. The nucleosomes are linked to one another by a segment of DNA approximately 60 base pairs long called linker DNA (see Figure 7.3A.27A). Another histone associated with the linker DNA then packages adjacent nucleotides together to form a nucleosome thread 30nm in diameter. Finally, these packaged nucleosome threads form large coiled loops that are held together by nonhistone scaffolding proteins. These coiled loops on the scaffolding proteins interact to form the condensed chromatin seen in chromosomes during mitosis.

When the cell is not replicating, the DNA and proteins appear as a threadlike mass called chromatin. During mitosis , the chromatin coils into thick rodlike bodies called chromosomes (see Figure 7.3A.31A) and a spindle apparatus guides the separation and movement of the chromosomes for cell division so each cell winds up with a full complement of chromosomes.

During sexual reproduction the nuclei of sex cells divide by meiosis producing cells with half the normal number of chromosomes (one from each homologous pair).

For More Information: DNA from Unit 6

For More Information: DNA Replication from Unit 6

For More Information: Mitosis from Unit 6

Concept map for Eukaryotic Cell Structure

Summary

1. Eukaryotic cells contain much more DNA than do bacteria, and this DNA is organized as multiple chromosomes located within a nucleus.
2. The nucleus in eukaryotic cells is separated from the cytoplasm by a nuclear envelope.
3. The nucleolus is an area within the nucleus that is involved in the assembly of ribosomal subunits.
4. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA, and ribosomal RNA (rRNA). Messenger RNA is then translated into protein at the ribosomes.
5. In general then, DNA determines what proteins and enzymes an organism can synthesize and, therefore, what chemical reactions it is able to carry out.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ Separates the chromosomes from the cytoplasm. *(ans)*

   ____ A basic unit of eukaryotic DNA appearing as beadlike structures consisting of DNA wrapped around histone molecules. (ans)

   a. nuclear envelope
   b. nucleolus
   c. nucleosome
   d. chromosomes

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7.3B: The Endoplasmic Reticulum

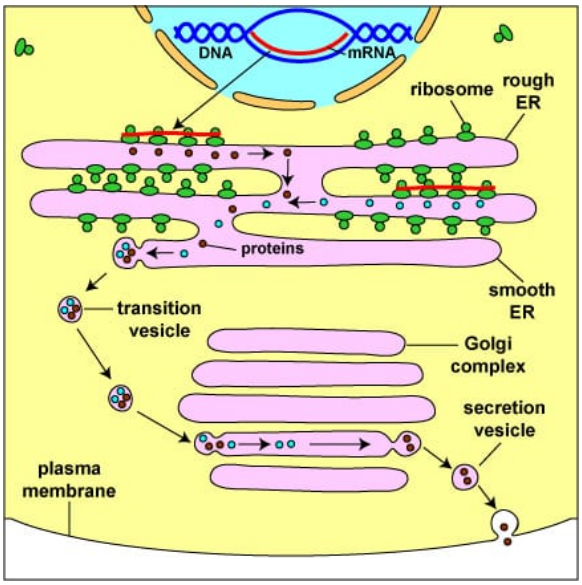
Briefly describe rough endoplasmic reticulum and state its functions.

- Briefly describe smooth endoplasmic reticulum and state its functions.

The endoplasmic reticulum or ER is a maze of parallel membranous tubules and flattened sacs surrounding the nucleus that connects with the nuclear membrane and runs throughout the cytoplasm (Figure $7.3B.33$). The ER functions to:

1. provide a surface area for protein and lipid synthesis;
2. form a pathway for transporting molecules within the cell; and
3. provide a storage area for molecules the cell has synthesized.

The endoplasmic reticulum connects to the pores of the nuclear envelope. The pores in the nuclear membrane allow ribosomal subunits and mRNA transcribed off genes in the DNA to leave the nucleus, enter the cytoplasm, and participate in protein synthesis. There are two distinct regions of the ER: the rough ER and the smooth ER.



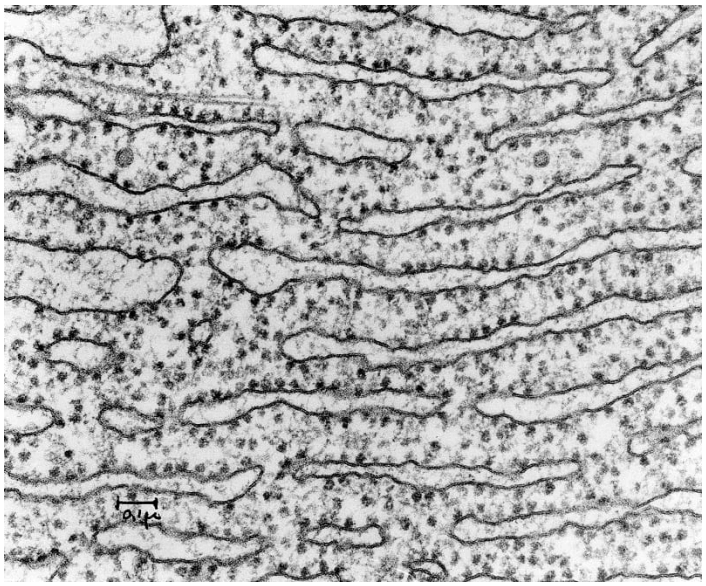


Figure $7.3B.33$).

Flash animation showing the endomembrane system.

html5 version of animation for iPad showing the endomembrane system.

Concept map for Eukaryotic Cell Structure

Summary

1. The endoplasmic reticulum or ER is a maze of parallel membranous tubules and flattened sacs surrounding the nucleus that connects with the nuclear membrane and runs throughout the cytoplasm.
2. ER with ribosomes attached is called rough endoplasmic reticulum and is involved in protein synthesis, production of new membrane, modification of newly formed proteins, and transport of these proteins and membrane to other locations within the cell.
3. ER without ribosomes is called smooth endoplasmic reticulum and contains enzymes for lipid biosynthesis, especially the

synthesis of phospholipids and steroids. The smooth endoplasmic reticulum forms transition vesicles to transfer molecules produced in the rough ER to the Golgi complex.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ Coated with ribosomes.(ans)

   _____ Formstransition vesicles to transfer molecules produced in the rough ER to the Golgi apparatus and other parts of the cell. *(ans)*

   a. smooth endoplasmic reticulum
   b. rough endoplasmic reticulum

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7.3C: The Golgi Complex

Briefly describe the Golgi complex and state its functions.

- Briefly describe how the Golgi complex packages materials for secretion from the cell.

The cell is the basic unit of life. Based on the organization of their cellular structures, all living cells can be divided into two groups: prokaryotic and eukaryotic (also spelled procaryotic and eucaryotic). Animals, plants, fungi, protozoans, and algae all possess **eukaryotic cell types**. Only bacteria have **prokaryotic cell types**.

Eukaryotic cells are generally much **larger** and **more complex** than prokaryotic. Because of their larger size, they **require a variety of specialized internal membrane-bound organelles to carry out metabolism, provide energy, and transport chemicals throughout the cell**.

Eukaryotic cells possess what is referred to as an internal membrane system or **endomembrane system** that compartmentalizes the cell for various different but interrelated cellular functions. Some of these internal membrane-bound organelles, such as the nucleus and the endoplasmic reticulum, have direct connections to one another. Other organelles, such as the endoplasmic reticulum and the Golgi complex transport materials to other organelles in vesicles. A vesicle buds off of one organelle and transports materials when it fuses with another membrane.

We will now look at the Golgi complex of eukaryotic cells.

The Golgi complex or Golgi apparatus consists of 3-20 flattened and stacked saclike structures called cisternae. A complex network of tubules and vesicles is located at the edges of the cisternae. The Golgi complex functions to:

1. sort proteins and lipids received from the ER;
2. modify certain proteins and glycoproteins; and
3. sort and package these molecules into vesicles for transport to other parts of the cell or secretion from the cell.

As mentioned above, proteins that have been produced in the rough ER are placed into transition vesicles by the smooth ER. The proteins and glycoproteins within the transition vesicle are then transported to the Golgi complex as the transition vesicles fuse with the Golgi complex membrane. Here the proteins and glycoproteins may be further modified and sorted. Finally the Golgi complex will package these molecules in membrane-bound vesicles for secretion from the cell or transport to lysosomes. The vesicles involved in secretion are called secretion vesicles. These form around the molecules to be secreted as they pinch off of the Golgi complex. The secretion vesicles then fuse with the cytoplasmic membrane to release the proteins and glycoproteins from the cell (see Figure 7.3C.33).

(def) (see Figure 7.3C.31, Figure 7.3C.30, and Figure 7.3C.33)

Flash animation showing the endomembrane system.

html5 version of animation for iPad showing the endomembrane system.

- Electron micrograph of a Golgi apparatus courtesy of Dennis Kunkel's Microscopy.

Concept map for Eukaryotic Cell Structure

Summary

1. The Golgi complex or Golgi apparatus consists of 3-20 flattened and stacked saclike structures called cisternae. A complex network of tubules and vesicles is located at the edges of the cisternae.
2. The Golgi complex functions to sort proteins and lipids received from the ER, modify certain proteins and glycoproteins, and

sort and package these molecules into vesicles for transport to other parts of the cell or secretion from the cell.

Questions

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the Golgi complex and state its functions. (ans)
2. Briefly describe how the Golgi complex packages materials for secretion from the cell. *(ans)*

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7.4: OTHER INTERNAL MEMBRANE-BOUND ORGANELLES

The cell is the basic unit of life. Based on the organization of their cellular structures, all living cells can be divided into two groups: prokaryotic and eukaryotic (also spelled procaryotic and eucaryotic). Animals, plants, fungi, protozoans, and algae all possess eukaryotic cell types. Only bacteria have prokaryotic cell types. Eukaryotic cells are generally much larger and more complex than prokaryotic. Because of their larger size, they require a variety of specialized internal membrane-bound organelles to carry out metabolism, provide energy, and transport chemicals throughout the cell. Eukaryotic cells contain a variety of internal membrane-bound organelles that are not a part of the endomembrane system. These include mitochondria, chloroplasts, lysosomes, peroxisomes, vacuoles, and vesicles. We will now look at the various membrane-bound organelles.



- Topic hierarchy

7.4A: Mitochondria

7.4B: Chloroplasts

7.4C: Lysosomes, Peroxisomes, Vacuoles, and Vesicles

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7.4A: Mitochondria

Briefly describe mitochondria and state their function.

- State where in the mitochondria the electron transport chain is located.
- State where in the mitochondria the enzymes for the citric acid cycle (Krebs cycle) are located.



Figure 7.4A.4.1.1: Two mitochondria from mammalian lung tissue displaying their matrix and membranes as shown by electron microscopy. from Louisa Howard (public domain.

Mitochondria function during aerobic respiration to produce ATP through oxidative phosphorylation. The respiratory enzymes and electron carriers for the electron transport system are located within the inner mitochondria membrane. The enzymes for the citric acid cycle (Krebs cycle) are located in the matrix.

- Electron micrograph of mitochondria courtesy of Dennis Kunkel's Microscopy.
- Electron micrograph of a mitochondrion from the Biology Department at the University of New Mexico.

Concept map for Eukaryotic Cell Structure

Summary

1. Mitochondria are rod-shaped structures ranging from 2 to 8 micrometers in length surrounded by two membranes.
2. Mitochondria are located throughout the cytoplasm.
3. Mitochondria function during aerobic respiration to produce ATP through oxidative phosphorylation.
4. The respiratory enzymes and electron carriers for the electron transport system are located within the inner mitochondria membrane. The enzymes for the citric acid cycle (Krebs cycle) are located in the matrix.
5. Mitochondria replicate giving rise to new mitochondria as they grow and divide. They also have their own DNA and ribosomes.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe mitochondria and state their function.
2. State where in the mitochondria the electron transport chain is located.

3. State where in the mitochondria the enzymes for the citric acid cycle (Krebs cycle) are located.

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7.4B: Chloroplasts

Briefly describe chloroplasts and state their function.

- State where in the chloroplasts the pigments and the electron transport chains needed to convert light energy into ATP are located.

Chloroplasts (see Figure 7.4*B*.41) are disk-shaped structures ranging from 5 to 10 micrometers in length. Like mitochondria, chloroplasts are surrounded by an inner and an outer membrane. The inner membrane encloses a fluid-filled region called the stroma that contains enzymes for the light-independent reactions of photosynthesis. Infolding of this inner membrane forms interconnected stacks of disk-like sacs called thylakoids, often arranged in stacks called grana. The thylakoid membrane, that encloses a fluid-filled thylakoid interior space, contains chlorophyll and other photosynthetic pigments as well as electron transport chains. The light-dependent reactions of photosynthesis occur in the thylakoids. The outer membrane of the chloroplast encloses the intermembrane space between the inner and outer chloroplast membranes (see Figure 7.4*B*.41).

The thylakoid membranes contain several pigments capable of absorbing visible light. Chlorophyll is the primary pigment of photosynthesis. Chlorophyll absorbs light in the blue and red region of the visible light spectrum and reflects green light. There are two major types of chlorophyll, chlorophyll *a* that initiates the light-dependent reactions of photosynthesis, and chlorophyll *b*, an accessory pigment that also participates in photosynthesis. The thylakoid membranes also contain other accessory pigments. Carotenoids are pigments that absorb blue and green light and reflect yellow, orange, or red. Phycocyanins absorb green and yellow light and reflect blue or purple. These accessory pigments absorb light energy and transfer it to chlorophyll.

They are found in plant cells and algae. Like Mitochondria, chloroplasts are surrounded by two membranes. The outer membrane forms the exterior of the organelle while the inner membrane folds to form a system of interconnected disclike sacs called thylakoids. The thylakoids are arranged in stacks called grana. The space enclosed by the inner chloroplast membrane is called the stroma. Chloroplasts replicate giving rise to new chloroplasts as they grow and divide. They also have their own DNA and ribosomes.

The thylakoid membranes contain the pigments chlorophyll and carotenoids, as well as enzymes and the electron transport chains used in photosynthesis *(def)*, a process that converts light energy into the chemical bond energy of carbohydrates. Energy trapped from sunlight by chlorophyll is used to excite electrons in order to produce ATP by photophosphorylation. The light-dependent reactions that trap light energy and produce the ATP and NADPH needed for photosynthesis occur in the thylakoids. The light-independent reactions of photosynthesis use this ATP and NADPH to produce carbohydrates from carbon dioxide and water, a series of reactions that occur in the stroma of the chloroplast.

For More Information: Photosynthesis from Unit 6

Concept map for Eukaryotic Cell Structure

Summary

1. Chloroplasts are disk-shaped structures ranging from 5 to 10 micrometers in length. Like mitochondria, chloroplasts are surrounded by an inner and an outer membrane.
2. Chloroplasts carry out photosynthesis, the process of converting light energy to chemical energy stored in the bonds of sugar.
3. Chloroplasts replicate giving rise to new chloroplasts as they grow and divide. They also have their own DNA and ribosomes.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe chloroplasts and state their function. (ans)
2. State where in the chloroplasts the pigments and the electron transport chains needed to convert light energy into ATP are

located. *(ans)*

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7.4C: Lysosomes, Peroxisomes, Vacuoles, and Vesicles

Describe the structure and state the funtion of the following:

a. lysosomes
b. peroxisomes
c. proteasomes
d. vacuoles

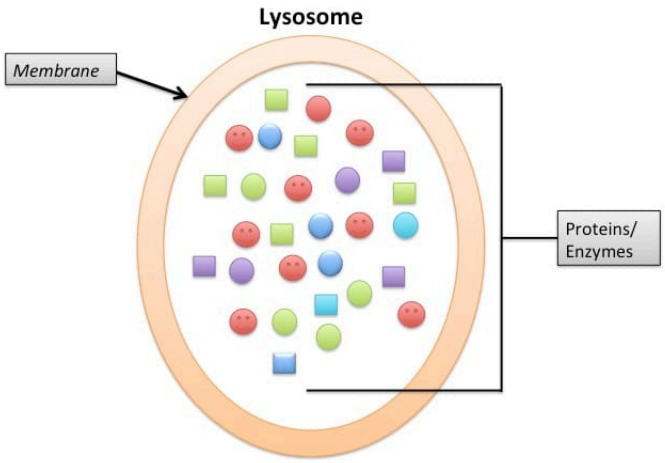


Figure $7.4C.32$A) are often used to store materials used for energy production such as starch, fat, or glycogen. Plant cells often contain large vacuoles filled with water. Vacuoles and vesicles also transport materials within the cell and form around particles that enter by endocytosis *(def)*.

Summary

1. Lysosomes, synthesized by the endoplasmic reticulum and the the Golgi complex, are membrane-enclosed spheres typically about 500 nanometers in diameter that contain powerful digestive enzymes that function to digest materials that enter by endocytosis.
2. Peroxisomes are membrane-bound organelles containing an assortment of enzymes that catalyze a variety of metabolic reactions.
3. Proteasomes are cylindrical complexes that use ATP to digest proteins into peptides and play a critical role in enabling the body to kill infected cells and cancer cells during adaptive immunity.
4. Vacuoles are large membranous sacs; vesicles are smaller. Vacuoles are often used to store materials used for energy production such as starch, fat, or glycogen. Vacuoles and vesicles also transport materials within the cell and form around particles that enter by endocytosis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. ____ Membrane-enclosed spheres that contain powerful digestive enzymes to digest materials that enter by endocytosis. (ans)

_____ Membrane-bound organelles containing an assortment of enzymes that catalyze a variety of metabolic reactions. *(ans)*

a. lysosomes
b. peroxisomes
c. proteasomes
d. vacuoles
e. vesicles

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7.5: Ribosomes

Briefly describe and state the function of eukaryotic ribosomes.

Ribosomes are composed of rRNA and protein and consist of 2 subunits. In eukaryotic cells, the subunits have densities of 60S and 40S ("S" refers to a unit of density called the Svedberg unit) and are composed of longer rRNA molecules and more proteins than the 50S and 30S subunits found in prokaryotic ribosomes. When the two ribosomal subunits join together during translation, they form a complete ribosome having a density of 80S.

The ribosomes are both attached to the endoplasmic reticulum and free in the cytoplasm. They serve as a workbench for protein synthesis, that is, they receive and translate genetic instructions for the formation of specific proteins or polypeptides.

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7.6: The Cytoskeleton

State 4 different functions associated with the cytoskeleton of eukaryotic cells.

The cytoskeleton is a network of microfilaments, intermediate filaments, and microtubules. The cytoskeleton functions to:

1. give shape to cells lacking a cell wall;
2. allow for cell movement,e.g. , the crawling movement of white blood cells and amoebas or the contraction of muscle cells;
3. movement of organelles within the cell and endocytosis;
4. cell division, i.e., the movement of chromosomes during mitosis and meiosis and the constriction of animal cells during cytokinesis.

We will now take a closer look at microtubules, microfilaments, intermediate filaments, centrioles, flagella, and cilia.

Microtubules

Microtubules are hollow tubes made of subunits of the protein tubulin. They provide structural support for the cell and play a role in cell division, cell movement, and movement of organelles within the cell. Microtubules are components of centrioles, cilia, and flagella (see below).

Microfilaments

Microfilaments are solid, rodlike structures composed of actin. They provide structural support, and play a roll in phagocytosis, cell and organelle movement, and cell division.

Intermediate filaments

Intermediate filaments are tough fibers made of polypeptides. They help to strengthen the cytoskeleton and stabilize cell shape.

Centrioles

Centrioles are located near the nucleus and appear as cylindrical structures consisting of a ring of nine evenly spaced bundles of three microtubules. Centrioles play a role in the formation of cilia and flagella. During animal cell division, the mitotic spindle forms between centrioles.

Summary

1. The cytoskeleton is a network of microfilaments, intermediate filaments, and microtubules.
2. The cytoskeleton has a variety functions including, giving shape to cells lacking a cell wall, allowing for cell movement, enabling movement of organelles within the cell, endocytosis, and cell division.

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7.7: Flagella and Cilia

State the difference between eukaryotic flagella and cilia.

- Briefly describe and state the function of eukaryotic flagella and cilia.

Flagellar arrangement schemes

Different species of bacteria have different numbers and arrangements of flagella (Figure 7.7.7.7.1).

- Monotrichous bacteria have a single flagellum (e.g., *Vibrio cholerae*).
- Lophotrichous bacteria have multiple flagella located at the same spot on the bacteria's surfaces which act in concert to drive the bacteria in a single direction. In many cases, the bases of multiple flagella are surrounded by a specialized region of the cell membrane, the so-called *polar organelle*.
- Amphitrichous bacteria have a single flagellum on each of two opposite ends (only one flagellum operates at a time, allowing the bacteria to reverse course rapidly by switching which flagellum is active).
- Peritrichous bacteria have flagella projecting in all directions (e.g., *E. coli*).

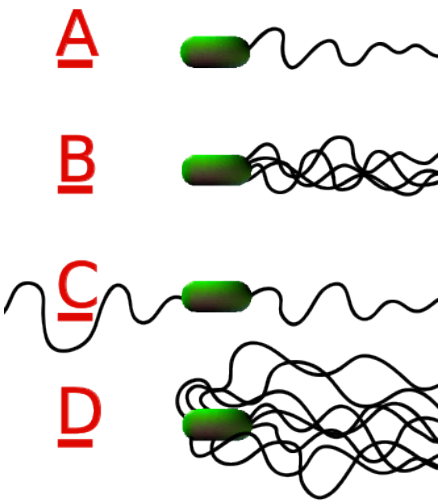


Figure 7.7.7**.7.1:** Examples of bacterial flagella arrangement schemes. A-Monotrichous; B-Lophotrichous; C-Amphitrichous; D-Peritrichous.

Internal Structure

Flagella are long and few in number whereas cilia are short and numerous. Both consist of 9 fused pairs of protein microtubules with side arms of the motor molecule dynein that originate from a centriole. These form a ring around an inner central pair of microtubules that arise from a plate near the cell surface (Figure 7.7.7.2). The arrangement of microtubules is known as a 2X9+2 arrangement. This complex of microtubules is surrounded by a sheath continuous with the cytoplasmic membrane.

Figure 7.7.7.7.3: A cilium (plural cilia) is an organelle found in eukaryotic cells. Cilia are slender protuberances typically extending some 5–10 microm outwards from the cell body. There are two types of cilia: motile cilia, which constantly beat directionally, and non-motile—or primary—cilia, which typ serve as sensory organelles

Flagella and cilia consist of 9 fused pairs of protein microtubules with side arms of the motor molecule dynein that originate from a centriole. These form a ring around an inner central pair of microtubules that arise from a plate near the cell surface. The arrangement of microtubules is known as a 2X9+2 arrangement. This complex of microtubules is surrounded by a sheath continuous with the cytoplasmic membrane.

Summary

1. Flagella are long and few in number whereas cilia are short and numerous.
2. Both flagella and cilia consist of 9 fused pairs of protein microtubules with side arms of the motor molecule dynein that originate from a centriole. These form a ring around an inner central pair of microtubules that arise from a plate near the cell surface. This complex of microtubules is surrounded by a sheath continuous with the cytoplasmic membrane.
3. Flagella and cilia function in locomotion. Cilia also function to move various materials that may surround a cell.

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7.8: The Endosymbiotic Theory

Learning Objectives

- Briefly describe what is meant by the endosymbiotic theory.
- Give some evidence supporting the theory that mitochondria and chloroplasts may have arisen from prokaryotic organisms.

It is thought that life arose on earth around four billion years ago. The endosymbiotic theory states that some of the organelles in today's eukaryotic cells were once prokaryotic microbes. In this theory, the first eukaryotic cell was probably an amoeba-like cell that got nutrients by phagocytosis and contained a nucleus that formed when a piece of the cytoplasmic membrane pinched off around the chromosomes. Some of these amoeba-like organisms ingested prokaryotic cells that then survived within the organism and developed a symbiotic relationship. Mitochondria formed when bacteria capable of aerobic respiration were ingested; chloroplasts formed when photosynthetic bacteria were ingested. They eventually lost their cell wall and much of their DNA because they were not of benefit within the host cell. Mitochondria and chloroplasts cannot grow outside their host cell.

Evidence for this is based on the following:

1. Chloroplasts are the same size as prokaryotic cells, divide by binary fission, and, like bacteria, have Fts proteins at their division plane. The mitochondria are the same size as prokaryotic cells, divide by binary fission, and the mitochondria of some protists have Fts homologs at their division plane.
2. Mitochondria and chloroplasts have their own DNA that is circular, not linear.
3. Mitochondria and chloroplasts have their own ribosomes that have 30S and 50S subunits, not 40S and 60S.
4. Several more primitive eukaryotic microbes, such as *Giardia* and *Trichomonas* have a nuclear membrane but no mitochondria.

Although evidence is less convincing, it is also possible that flagella and cilia may have come from spirochetes.

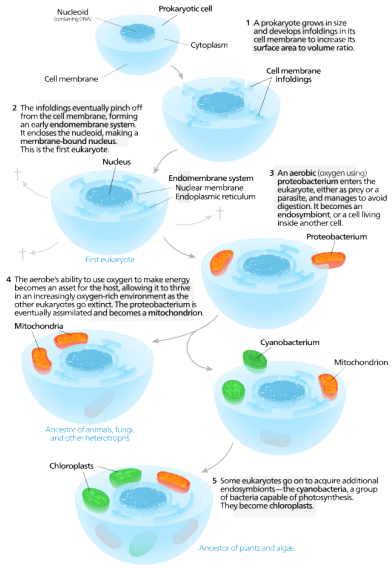


Figure 7.8.1: One model for the origin of mitochondria and plastids. This model has an amitochondriate eukaryote engulfing an aerobe and then a cyanobacterium. from Kelvinsong

Example 7.8.1

1. Briefly describe what is meant by the endosymbiotic theory.

2. Give three points of evidence supporting the theory that mitochondria and chloroplasts may have arisen from prokaryotic organisms.

Solutions

1. The endosymbiotic theory states that some of the organelles in eukaryotic cells were once prokaryotic microbes.
2.
   - Mitochondria and chloroplasts are the same size as prokaryotic cells and divide by binary fission.
   - Mitochondria and chloroplasts have their own DNA which is circular, not linear.
   - Mitochondria and chloroplasts have their own ribosomes which have 30S and 50S subunits, not 40S and 60S.

Summary

The endosymbiotic theory states that mitochondria and chlopoplasts in today's eukaryotic cells were once separate prokaryotic microbes.

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7.E: The Eukaryotic Cell (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

7.1: The Cytoplasmic Membrane

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following descriptions with the best answer.

   _____ The movement of water across a membrane from an area of higher water concentration (lower solute concentration) to lower water concentration (higher solute concentration).

   _____ The net movement of gases or small uncharge polar molecules across a phospholipid bilayer membrane from an area of higher concentration to an area of lower concentration. No metabolic energy is required.

   _____ A transport where the cell uses transport proteins such as antiporters or symporters and metabolic energy to transport substances across the membrane against the concentration gradient.

   _____ If the net flow of water is out of a cell, the cell is in _____ environment.

   _____ If the net flow of water is into a cell, the cell is in _____ environment.

   _____ Theingestion of dissolved materials by endocytosis whereby the cytoplasmic membrane invaginates and pinches off placing small droplets of fluid in a vesicle.

   ____ The process by which a cell releases waste products or specific secretion products by the fusion of a vesicle with the cytoplasmic membrane.

   A. active transport
   B. passive diffusion
   C. osmosis
   D. exocytosis
   E. pinocytosis
   F. phagocytosis
   G. a hypotonic
   H. a hypertonic
   I. an isotonic

7.2: The Cell Wall

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State which eukaryotic organisms possess a cell wall and which lack a cell wall.
2. The function of the cell wall in those eukaryotic cells that possess one is to _____.

7.3: The Endomembrane System

7.4: Other Internal Membrane-Bound Organelles

7.5: Ribosomes

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe and state the function of eukaryotic ribosomes.

7.6: The Cytoskeleton

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State 3 different functions associated with the cytoskeleton of eukaryotic cells.

7.7: Flagella and Cilia

7.8: The Endosymbiotic Theory

1. Parallel membranous tubules and flattened sacs with ribosomes attached. Functions in protein synthesis, production of new membrane, and transport of these proteins and membrane to other locations within the cell. This best describes the:
   A. the Golgi apparatus.
   B. smooth endoplasmic reticulum.
   C. rough endoplasmic reticulum.
   D. the nucleus.
2. Consists of 3-20 flattened and stacked saclike structures called cisternae. Modifies certain proteins and lipids received from the ER and packages these molecules into vesicles for transport to other parts of the cell or secretion from the cell. This best describes:
   A. the Golgi apparatus.
   B. smooth endoplasmic reticulum.
   C. rough endoplasmic reticulum.
   D. the nucleus.
3. Surrounded by two membranes. The outer membrane forms the exterior of the organelle while the inner membrane is arranged in a series of folds called cristae . Produces ATP through oxidative phosphorylation . This describes:
   A. the Golgi apparatus.
   B. mitochondria.
   C. chloroplasts.
   D. the endoplasmic reticulum.
4. Membrane-enclosed spheres that contain powerful digestive enzymes that function to digest materials that enter by endocytosis. This best describes:
   A. peroxisomes.
   B. mitochondria.
   C. proteasomes.
   D. lysosomes.
5. A fluid phospholipid bilayer embedded with proteins and glycoproteins. Determines what goes in and out of the cell. This best describes the:
   A. cell wall.
   B. cytoplasmic membrane.
   C. endomembranesystem.
   D. cytoskeleton.

6. Long and few in number and consisting of 9 fused pairs of protein microtubuleswith side arms of the motor molecule dynein. Originate from a centrioleand function in locomotion. This best describes:
   A. cilia.
   B. flagella.
   C. the cytoskeleton.

Solution

1=C; 2=A; 3=B; 4=D; 5=B; 6=B

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8.1: Overview of Fungi

Name 3 groups of fungi.

- Define mycosis.

Mycology is the study of fungi. Fungi include yeasts, molds, and fleshy fungi. They:

1. are eukaryotic;
2. have a rigid cell wall;
3. are chemoheterotrophs (organisms that require organic compounds for both carbon and energy sources);
4. obtain their nutrients by absorption;
5. obtain nutrients as saprophytes, organisms that live off of decaying matter, or as parasites, organisms that live off of living matter.

Of the over 100,000 species of fungi, only about 100 species are pathogenic for animals. They play a major role in the recycling of nutrients by their ability to cause decay and are used by industry to produce a variety of useful products. However, they also cause many undesirable economic effects such as the spoilage of fruits, grains, and vegetables, as well as the destruction of unpreserved wood and leather products. We will be concerned mainly with the yeasts and molds, especially those causing mycoses (fungal infections).

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8.2: Yeasts

Briefly describe yeasts and state how they reproduce asexually.

- Briefly describe pseodohypae, hyphae, blastoconidia (blastospores), and chlamydoconidia (chlamydospores) and name a yeast producing these structures.
- Name three potentially pathogenic yeasts and state an infection each causes.

Yeast Morphology

1. Yeast (see Figure 8.2.1) are unicellular fungi which usually appear as oval cells 1-5 µm wide by 5-30 µm long.
2. They have typical eukaryotic structures (see Figure 8.2.2 and Figure 8.2.3).
3. They have a thick polysaccharide cell wall.
4. They are facultative anaerobes.
5. The yeast *Candida* is said to be dimorphicin that it can grow as an oval, budding yeast, but under certain culture conditions, the budding yeast may elongate and remain attached producing filament-like structures called pseudohyphae. *C. albicans* may also produce true hyphae similar to molds (see Figure 8.2.4). In this case long, branching filaments lacking complete septa form. The pseudohyphae and hyphae help the yeast to invade deeper tissues after it colonizes the epithelium. Asexual spores called blastoconidia (blastospores) develop in clusters along the hyphae, often at the points of branching. Under certain growth conditions, thick-walled survival spores called chlamydoconidia (chlamydospores) may also form at the tips or as a part of the hyphae (see Figure 8.2.5.)

For More Information: A Comparison of Prokaryotic and Eukaryotic Cells from Unit 1

The Role of Fungal Cell Wall Components in Initiating Body Defense

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Components of the yeast cell wall that function as PAMPs include lipoteichoic acids, and zymosan. In addition, bacteria and other microorganisms also possess mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar) that function as PAMPs. These mannose-rich glycans are common in microbial glycoproteins and glycolipids but rare in those of humans. These PAMPs bind to pattern-recognition receptors on a variety of defense cells of the body and triggers innate immune defenses such as inflammation, fever, and phagocytosis.

Flash animation showing the release of fungal mannans from the cell walls of yeast and their subsequent binding to pattern-recognition receptors on a macrophage.

For More Information: Review of Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Review of Pattern-Recognition Receptors from Unit 5

For More Information: Review of Inflammation from Unit 5

Yeast cell wall components also activate the alternative complement pathway and the lectin pathway, defense pathways that play a variety of roles in body defense. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

Reproduction of yeasts

1. Yeasts reproduce asexually by a process called budding (see Figure 8.2.1 and Figure 8.2.6). A bud is formed on the outer surface of the parent cell as the nucleus divides. One nucleus migrates into the elongating bud. Cell wall material forms between the bud and the parent cell and the bud breaks away.

- Scanning electron micrograph of *Saccharomyces*; courtesy of Dennis Kunkel's Microscopy.
- Movie of *Saccharomyces cerevisiae* reproducing by budding. Movie of Growth and Division of Budding Yeast (*Saccharomyces cerevisiae*) . © Phillip Meaden, author. Licensed for use, ASM MicrobeLibrary.

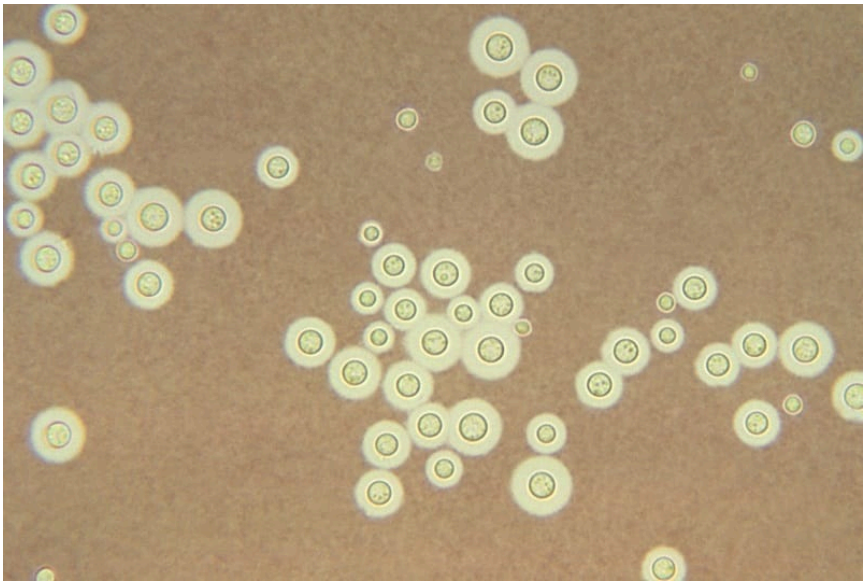


Figure 8.2.8) is thought to be transmitted from person to person by the respiratory route and is almost always asymptomatic. However, in persons with highly depressed immune responses, such as people with leukemias or infected with the Human Immunodeficiency Virus (HIV), *P. jiroveci* can cause a severe pneumonia called PCP (*Pneumocystis* pneumonia).

P. jiroveci can be found in three distinct morphologic stages:

- The trophozoite (trophic form), a haploid amoeboid form 1-4 µm in diameter that replicates by mitosis and binary fission. The trophic forms are irregular shaped and often appears in clusters.
- A precystic form or early cyst. Haploid trophic forms conjugate and produce a zygote or sporocyte (early cyst).
- The cyst form, which contains several intracystic bodies or spores are 5-8 µm in diameter. It has been postulated that in formation of the cyst form (late phase cyst), the zygote undergoes meiosis and subsequent mitosis to typically produce eight haploid ascospores (sporozoites) See Figure 8.2.7. As the haploid ascospores are released the cysts often collapse forming crescent-shaped bodies (see Figure 8.2.8). *P. jiroveci* is usually transmitted by inhalation of the cyst form. Released ascospores then develop into replicating trophic forms that attach to the wall of the alveoli and replicate to fill the alveoli.

In biopsies from lung tissue or in tracheobronchial aspirates, both a trophic form about 1-4 µm in diameter with a distinct nucleus and a cyst form between 5-8 µm in diameter with 6-8 intracystic bodies (ascospores) can be seen.

Malassezia globosa

Malassezia globosa is a dimorphic yeast that is the most frequent cause of a superficial skin infection called tinea versicolor that commonly appears as a hypopigmentation of the infected skin. *M. globosa* is also the most common cause of dandruff and seborrheic dermatitis. The yeast is naturally found on the skin. To view additional photomicrographs of *Candida*, *Cryptococcus*, and *Pneumocystis*, see the AIDS Pathology Tutorial at the University of Utah.

Concept Map for Fungi, Part-1: Yeasts

A woman has taken broad spectrum antibiotics for two weeks to treat a bacterial infection. She subsequently develops vaginitis.

a. Explain what might account for this.
b. Why didn't the antibiotics prevent the vaginitis?

A young child with an immunosuppressive disorder and living in an urban area routinely played in a park with a large pigeon population. The child subsequently developed a respiratory infection followed by symptoms of meningitis.

a. What infection might be expected and why?
b. What might the lab look for in the spinal fluid to help confirm this?

Summary

1. Yeasts are eukaryotic unicellular fungi
2. Some yeast are dimorphic in that they can grow as an oval, budding yeast, but under certain culture conditions, they may produce filament-like structures called hyphae similar to molds.
3. Components of the yeast cell wall that function as pathogen-associated molecular patterns or PAMPs include lipoteichoic acids, zymosan, and mannose-rich glycans.
4. These PAMPs bind to pattern-recognition receptors or PRRs on a variety of body defense cells and triggers innate immune defenses.
5. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens.
6. Yeasts reproduce asexually by a process called budding.
7. Candida albicans is found as normal flora on the mucous membranes and in the gastrointestinal tract but is usually held in check by the body's normal microbiota and normal body defenses.
8. Candida can cause a variety of opportunistic infections in people who are debilitated, immunosuppressed, or have received prolonged antibacterial therapy, and infect the lungs, blood, heart, and meninges, especially in the compromised or immunosuppressed host.
9. Cryptococcus neoformans infections are usually mild or subclinical but, when symptomatic, usually begin in the lungs after inhalation of the yeast in dried bird feces.
10. Pneumocystis jiroveci can cause a severe pneumonia called PCP (Pneumocystis pneumonia).
11. Malassezia globosa is the most frequent cause of a superficial skin infection called tinea versicolor and also the most common cause of dandruff.

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8: FUNGI

Yeasts are eukaryotic microorganisms classified as members of the fungus kingdom with 1,500 species currently identified and are estimated to constitute 1% of all described fungal species.

8.1: Overview of Fungi

8.2: Yeasts

8.3: Molds

8.4: Fungal Pathogenicity

8.5: Chemotherapeutic Control of Fungi

8.E: Fungi (Exercises)

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8.3: Molds

Define:

a. mold
b. hyphae
c. mycelium
d. vegetative mycelium
e. aerial mycelium.

- Briefly describe the following fungal asexual reproductive spores:

a. conidiospores
b. macroconidia,
c. microconidia
d. sporangiospores
e. arthrospores

- Define dermatophyte, list 2 genera of dermatophytes, and name three dermatophytic infections.
- Describe what is meant by the term "dimorphic fungus", name two systemic infections caused by dimorphic fungi, and state how they are initially contracted.

Mold Morphology

Molds are multinucleated, filamentous fungi composed of hyphae. A hypha is a branching tubular structure approximately 2-10 µm in diameter which is usually divided into cell-like units by crosswalls called septa. The total mass of hyphae is termed a mycelium. The portion of the mycelium that anchors the mold and absorbs nutrients is called the vegetative mycelium , composed of vegetative hyphae; the portion that produces asexual reproductive spores is the aerial mycelium , composed of aerial hyphae (Figure 8.3.1).

Molds have typical eukaryotic structures (Figure 8.3.2) and have a cell wall usually composed of chitin, sometimes cellulose, and occasionally both. Furthermore, molds are obligate aerobes *and* grow by elongation at apical tips of their hyphae and thus are able to penetrate the surfaces on which they begin growing.

For More Information: A Comparison of Prokaryotic and Eukaryotic Cells from Unit 1

Reproduction of Molds

1. Molds reproduce primarily by means of asexual reproductive spores (Figure 8.3.1). These include the following.

a. conidiospores (conidia) See Figure 8.3.3.

Spores borne externally on an aerial hypha called a conidiophore ; see Figure 8.3.4 and Figure 8.3.5.

- Scanning electron micrographs of the conidiospores of *Penicillium* and of *Aspergillus*; courtesy of Dennis Kunkel's Microscopy.

b. sporangiospores See Figure 8.3.6.

Spores borne in a sac or sporangium on an aerial hypha called a sporangiophore ; see Figure 8.3.7.

- Scanning electron micrograph of the conidiospores of *Rhizopus*; courtesy of Dennis Kunkel's Microscopy.

c. arthrospores See Figure 8.3.8.

spores produced by fragmentation of a vegetative hypha (Figure 8.3.9).

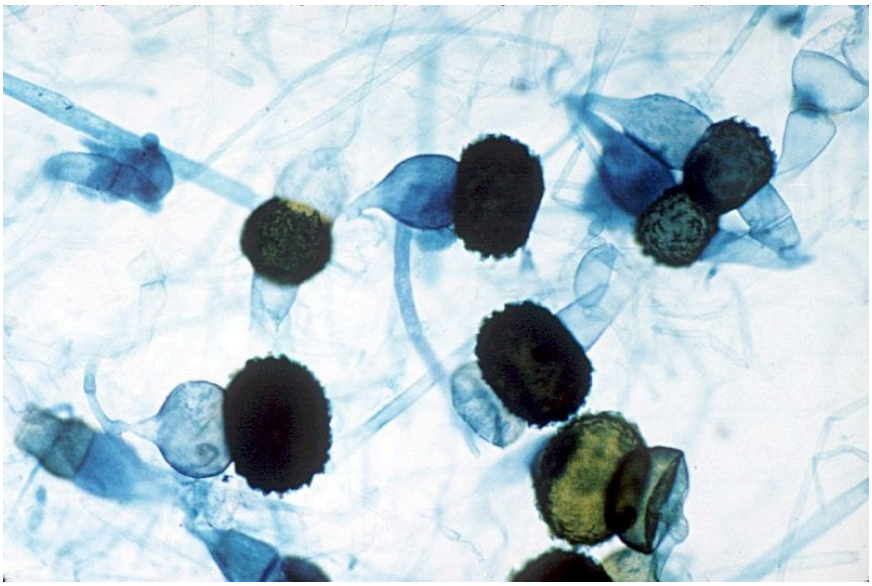


Figure 8.3.8.3.1: Light micrograph of a whole-mount slide of zygospores of Rhizopus. from Wikipedia (Curtis Clark)

Pathogenic Molds

Dermatophytes

The dermatophytes are a group of molds that cause superficial mycoses of the hair, skin, and nails and utilize the protein keratin, that is found in hair, skin, and nails, as a nitrogen and energy source. Infections are commonly referred to as ringworm or tinea infections and include:

- tinea capitis (infection of the skin of the scalp, eyebrows, and eyelashes)
- tinea barbae (infection of the bearded areas of the face and neck)
- tinea faciei (infection of the skin of the face)
- tinea corporis (infection of the skin regions other than the scalp, groin, palms, and soles)
- tinea cruris (infection of the groin; jock itch)
- tinea unguium (onchomycosis; infection of the fingernails and toenails)
- tinea pedis (athlete's foot; infection of the soles of the feet and between the toes).

The three most common dermatophytes are *Microsporum, Trichophyton*, and *Epidermophyton*. They produce characteristic asexual reproductive spores called macroconidia and microconidia (Figure 8.3.10 and Figure 8.3.11).

- Scanning electron micrograph of the macroconidia of *Epidermophyton*; courtesy of Dennis Kunkel's Microscopy.

Another tinea infection of the skin is tinea versicolor caused by the yeast *Malassezia globosa*. Tinea versicolor appears as a hypopigmentation of the infected skin. *M. globosa* is also the most common cause of dandruff.

Dimorphic Fungi

Dimorphic fungi may exhibit two different growth forms. Outside the body they grow as a mold, producing hyphae and asexual reproductive spores, but in the body they grow in a non-mycelial yeast form. These infections appear as systemic mycoses and usually begin by inhaling spores from the mold form. After germination in the lungs, the fungus grows as a yeast. Factors such as body temperature, osmotic stress, oxidative stress, and certain human hormones activate a dimorphism-regulating histidine kinase enzyme in dimorphic molds, causing them to switch from their avirulent mold form to their more virulent yeast form.

For example:

a. Coccidioides *immitis* causes coccidioidomycosis (Figure 8.3.12), a disease endemic to the southwestern United States. An estimated 100,000 infections occur annually in the United States, but one to two thirds of these cases are subclinical.

The mold form of the fungus grows in arid soil and produces thick-walled, barrel-shaped asexual spores called arthrospores (Figure 8.3.8) by a fragmentation of its vegetative hyphae.

After inhalation, the arthrospores germinate and develop into endosporulating spherules (Figure 8.3.13) in the terminal bronchioles of the lungs. The spherules reproduce by a process called endosporulation, where the spherule produces numerous endospores (yeast-like particles), ruptures, and releases viable endospores that develop into new spherules.

b. *Histoplasma capsulatum* (Figure 8.3.14)is a dimorphic fungus that causes histoplasmosis, a disease commonly found in the Great Lakes region and the Mississippi and Ohio River valleys. Approximately 250,000 people are thought to be infected annually in the US, but clinical symptoms of histoplasmosis occur in less than 5% of the population. Most individuals with histoplasmosis are asymptomatic. Those who develop clinical symptoms are typically either immunocompromised or are exposed to a large quantity of fungal spores.

The mold form of the fungus often grows in bird or bat droppings or soil contaminated with these droppings and produces large tuberculate macroconidia and small microconidia (Figure 8.3.15). Although birds cannot be infected by the fungus and do not transmit the disease, bird excretions contaminate the soil and enrich it for mycelial growth. Bats, however, can become infected and transmit histoplasmosis through their droppings. After inhalation of the fungal spores and their germination in the lungs, the fungus grows as a budding, encapsulated yeast (Figure 8.3.16).

- Chest X-ray of a person with histoplasmosis.

c. Blastomycosis, caused by *Blastomyces dermatitidis*, is common around the Great Lakes region and the Mississippi and Ohio River valleys.Infection can range from an asymptomatic, self-healing pulmonary infection to widely disseminated and potentially fatal disease. Pulmonary infection may be asymptomatic in nearly 50% of patients. *Blastomyces dermatitidis* can also sometimes infect the skin.

Blastomyces dermatitidis produces a mycelium with small conidiospores (Figure 8.3.17) and grows actively in bird droppings and contaminated soil. When spores are inhaled or enter breaks in the skin, they germinate and the fungus grows as a yeast (Figure 8.3.18).having a characteristic thick cell wall. It is diagnosed by culture and by biopsy examination.

These infections usually remains localized in the lungs, but in rare cases may spread throughout the body.

As mentioned earlier, the yeast *Candida albicans* can also exhibit dimorphism.

- To view additional photomicrographs of *Coccidioides* and *Histoplasma*, see the AIDS Pathology Tutorial at the University of Utah.

Opportunistic Molds

Certain molds once considered as non-pathogenic have recently become a fairly common cause of opportunistic lung and wound infections in the debilitated or immunosuppressed host. These include the common molds *Aspergillus* (Figure 8.3.4) and *Rhizopus* (Figure 8.3.6). Although generally harmless in most healthy individuals, *Aspergillus* species do cause allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing *Aspergillus* pneumonia (or chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma (a mycetoma or fungus ball in a body cavity such as the lung), and invasive aspergillosis. In highly immunosuppressed individuals, however, *Aspergillus* may disseminate beyond the lung via the blood.

Mucormycoses are infections caused by fungi belonging to the order of Mucorales. *Rhizopus* species are the most common causative organisms. The most common infection is a severe infection of the facial sinuses, which may extend into the brain. Other mycoses include pulmonary, cutaneous, and gastrointestinal.

A patient infected with HIV and living in the southwestern US frequently takes walks in a dry, arid area that was once a ranch. On a particular windy and dusty day, he hikes near an area where bulldozers are excavating the area for a housing development. A couple of weeks later he develops severe respiratory symptoms. A microscopic examination of lung tissue in the lab shows spherical bodies filled with yeast like particles.

a. What infection does he most likely have?
b. How specifically did he contract this infection?

- A woman notices an intense itching between her toes. The skin appears red and inflamed with some cracking of the skin. A scraping of the skin is viewed under a microscope and fungal hyphae and large leaf-shaped spores are evident.

  What infection does this person most likely have and how can you tell from this information?

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8.4: Fungal Pathogenicity

- Name at least three fungal virulence factors that promote fungal colonization.
- Name at least two fungal virulence factors that damage the host.

As with the bacteria, fungal virulence factors can be divided into two categories: virulence factors that promote fungal colonization of the host; and virulence factors that damage the host.

Virulence Factors that Promote Fungal Colonization

Virulence factors that promote fungal colonization of the host include the ability to:

1. adhere to host cells and resist physical removal;
2. invade host cells;
3. compete for nutrients;
4. resist innate immune defenses such as phagocytosis and complement; and
5. evade adaptive immune defenses.

Examples of virulence factors that promote fungal colonization include:

1. A compromised immune system is the primary predisposing factor for serious fungal infections. A person highly immunosuppressed, such as a person taking immunosuppressive drugs to suppress transplant rejection, or a person with advancing HIV infection, or a person with other immunosuppressive disorders, becomes very susceptible to infections by fungi generally considered not very harmful to a healthy person with normal defenses.

2. As with bacteria, the ability to adhere to host cells with cell wall adhesins seems to play a role in fungal virulence.

3. Some fungi produce capsules allowing them to resist phagocytic engulfment, such as the yeast *Cryptococcus neoformans* and the yeast form of *Histoplasma capsulatum* (Figure 8.4.1).

4. *Candida albicans* stimulates the production of a cytokine called GM-CSF and this cytokine can suppress the production of complement by monocytes and macrophages. This may decrease the production of the opsonin C3b as well as the complement proteins that enhance chemotaxis of phagocytes.

5. *C. albicans* also appears to be able to acquire iron from red blood cells.

6. *C. albicans* produces acid proteases and phospholipases that aid in the penetration and damage of host cell membranes.

7. Some fungi are more resistant to phagocytic destruction, e.g., *Candida albicans, Histoplasma capsulatum*, and *Coccidioides immitis*.

8. There is evidence that when the yeast form of *Candida* enters the blood it activates genes allowing it to switch from its budding form to its hyphal form. In addition, when engulfed by macrophages, it starts producing the tubular germ tubes which penetrate the membrane of the macrophage thus causing its death.

   A movie of *Candida* killing a macrophage from within from the Theriot Lab Website at Stanford University Medical School: *Candida albicans* killing macrophages from inside out.

9. Factors such as body temperature, osmotic stress, oxidative stress, and certain human hormones activate a dimorphism-regulating histidine kinase enzyme in dimorphic molds, such as *Histoplasma capsulatum, Blastomyces dermatitidis*, and *Coccidioides immitis,* causing them to switch from their avirulent mold form to their virulent yeast form. It also triggers the yeast *Candida albicans* to switch from its yeast form to its more virulent hyphal form.

Virulence Factors that Damage the Host

Like bacteria, fungal PAMPs binding to PRRs can trigger excessive cytokine production leading to a harmful inflammatory response that damages tissues and organs. As fungi grow in the body, they can secrete enzymes to digest cells. These include proteases, phospholipases, and elastases. In response to both the fungus and to cell injury, cytokines are released. As seen earlier under Bacterial Pathogenesis, this leads to an inflammatory response and extracellular killing by phagocytes that leads to further destruction of host tissues.

Many molds secrete mycotoxins , especially when growing on grains, nuts and beans. These toxins may cause a variety of effects in humans and animals if ingested including loss of muscle coordination, weight loss, and tremors. Some mycotoxins are mutagenic and carcinogenic. Aflatoxins, produced by certain *Aspergillus* species, are especially carcinogenic. A mold called *Stachybotrys chartarum* is a mycotoxin producer that has been implicated as a potential serious problem in homes and buildings as one of the causes of "sick building syndrome." Mycotoxin symptoms in humans include dermatitis, inflammation of mucous membranes, , cough, fever, headache, and fatigue.

Summary

Many of the same factors that enable bacteria to colonize the body also enable fungi to colonize. Many of the same factors that enable bacteria to harm the body also enable fungi to cause harm.

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8.5: Chemotherapeutic Control of Fungi

Briefly describe 3 different ways antifungal chemotherapeutic agents may affect fungi and give an example of an antibiotic for each way.

Remember that like human cells, fungal cells are eukaryotic. Since fungal cells, unlike prokaryotic bacterial cells, are not that different from human cells, it is more difficult to find a chemotherapeutic agent that is selectively toxic for fungi, that is, will inhibit or kill fungal cells without also inhibiting or killing human cells. Some of the common antifungal chemotherapeutic agents are listed below.

1. One antibiotic, griseofulvin (*Fulvicin, Grifulvin, Gris-PEG*), interferes with nuclear division by preventing the aggregation of microtubules needed for mitosis in superficial mycelial fungi. It is used only for severe dermatophyte infections.
2. The antimetabolites trimethoprim + sulfomethoxazole , trimetrexate, atovaquone, and flucytosine interfere with normal nucleic acid synthesis. Trimethoprim/sulfomethoxazole (*Septra, Bactrim*), atovaquone (*Mepron*), and trimetrexate (*Neutrexin*) are used to treat *Pneumocystis* pneumonia. Flucytosine (*Ancobon*) is used for more serious *Candida* infections.
3. Polyene antibiotics such as amphotericin B, pimaricin, and nystatin are fungicidal drugs that bind to ergosterol in the fungal cytoplasmic membrane thus altering its structure and function and causing leakage of cellular needs. Nystatin (*Mycostatin*) is used to treat superficial *Candida* infections (thrush, vaginitis, cutaneous infections), amphotericin B (*Abelcet, Fungizone*) is used for systemic *Candida* infections, *Cryptococcus* infections, and dimorphic fungal infections.
4. The azole derivative antibiotics such as clotrimazole, miconazole, itraconazole, fluconazole, and ketoconazole, are fungistatic drugs used to treat many fungal infections. They interfere with ergosterol biosynthesis and thus alter the structure of the cytoplasmic membrane as well as the function of several membrane-bound enzymes like those involved in nutrient transport and chitin synthesis. Clotrimazole (*Lotramin, Mycelex*), miconazole (*Monistat*), and econazole (*Spectazole*) are used to treat superficial *Candida* and dermatophyte infections; oxiconazole (*Oxistat*) and sulconazole (*Exelderm*) are used for dermatophyte infections; butaconazole (*Femstat-3*), terconazole (*Terazole*), and tioconazole (*Vagistat-1*) are used for *Candida* vaginitis; ketoconazole (*Nizoral*) and itraconazole (*Sporanox*) are used for systemic *Candida, Cryptococcus*, and dimorphic fungal infections; and fluconazole (*Diflucan*) is used for *Candida* infections. Voriconazole (*VFEND*) is a triazole is used to treat *Candida* infections such as candidemia, disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds. It is also used for invasive aspergillosis.
5. Echinocandins, including caspofungin (*Cancidas*) and micafungin (*Mycamine*) are intravenous antifungals that inhibits glucan synthesis in fungal cell walls. It is used in the treatment of candidemia , *Candida* intra-abdominal abscesses, peritonitis, esophageal candidiasis, and pleural space infections.
6. Naftifine (*Naftin*) and terbinafine (*Lamisil*) are allylamines that block synthesis of ergosterol as does the topical thiocarbonate tolnaftate. They are used to treat dermatophyte infections.

Why are there so few antifungal chemotherapeutic agents compared to the number of antibacterial agents?

- Most of the antifungal agents interfere with the synthesis of ergosterol in the fungal cytoplasmic membrane.

  a. How does this harm the fungus?
  b. Why don't these agents work on bacterial and viral infections?

For a more detailed description of any specific antimicrobial agent, see the website of RxList - The Internet Drug Index.

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8.E: Fungi (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

8.1: Overview of Fungi

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. A fungal infection is termed a _____.

8.2: Yeasts

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe a typical yeast and state how it reproduces asexually.
2. Match the following:

   _____ Reproductive spores produced by yeast by budding.

   _____ Thick walled survival spores produced by the yeast *Candida*.

   _____Long, continuous fungal filaments produced by dimorphic yeast.

   a. hyphae
   b. blastoconidia (blastospores)
   c. chlamydoconidia (chlamydospores)
3. Name 3 potentially pathogenic yeasts and state an infection each causes.
   a.
   b.
   c.

8.3: Molds

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define mold.
2. Match the following:

   _____ The hyphae that grow up in the air and produce asexual reproductive spores.

   _____ Large asexual reproductive mold spores coming of of vegetative hyphae and often produced by dermatophytes.

   _____ Asexual reproductive mold spores produced inside a sac or sporangium at the end of an aerial hypha.

_____ The hyphae that anchor a mold and absorb nutrients.

_____ Asexual reproductive mold spores produced in chains at the end of an aerial hypha.

_____ A branching tubular structure of a mold that is usually divided into cell-like units by crosswalls called septa.

_____ Asexual reproductive mold spores produced by fragmentation of vegetative hyphae.

A. hypha
B. macroconidia
C. vegetative mycelium
D. aerial mycelium
E. sporangiospores
F. arthrospores
G. conidiospores

3. Define dermatophyte.
4. List 2 genera of dermatophytes.
   a.
   b.
5. Name 3 dermatophytic infections.
6. Describe what is meant by the term "dimorphic fungus", name 2 systemic infections caused by dimorphic fungi, and state how they are initially contracted.

8.4: Fungal Pathogenicity

1. Name at least 3 fungal virulence factors that promote fungal colonization.
   a.
   b.
   c.
2. Name 2 fungal virulence factors that damage the host.
   a.
   b.

8.5: Chemotherapeutic Control of Fungi

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe 2 different ways antifungal chemotherapeutic agents may affect fungi and give an example of an antibiotic for each way.
   a.
   b.

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9.1: Characteristics of Protozoa

Learning Objectives

After completing this section you should be able to perform the following objectives.

1. Briefly describe protozoa.
2. Briefly describe 3 ways protozoans may reproduce asexually.
3. Define the following:
   A. trophozoite
   B. protozoan cyst.

Protozoa are unicellular eukaryotic microorganisms lacking a cell wall and belonging to the Kingdom Protista. Although there are nearly 20,000 species of protozoa, relatively few cause disease; most inhabit soil and water. Protozoa reproduce asexually by the following means:

1. **fission**: One cell splits into two.
2. **schizogony**: A form of asexual reproduction characteristic of certain protozoa, including sporozoa, in which daughter cells are produced by multiple fission of the nucleus of the parasite followed by segmentation of the cytoplasm to form separate masses around each smaller nucleus.
3. **budding**: Buds form around a nucleus and pinch off of the parent cell.

Some protozoa also reproduce sexually by fusion of gametes (Figure 9.1.1).

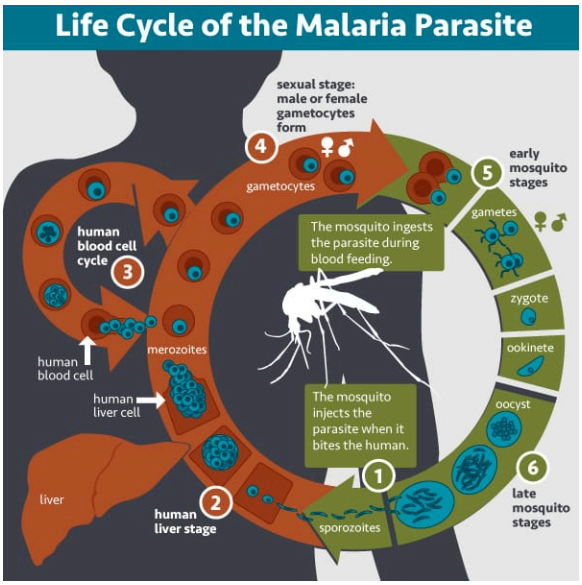


Figure 9.1.1**:** Life Cycle of Plasmodium, the Protozoan that causes Malaria. (1) A female Anopheles mosquito carrying malaria-causing parasites feeds on a human and injects the parasites in the form of sporozoites into the bloodstream. The sporozoites travel to the liver and invade liver cells. (2) Over 5-16 days*, the sporozoites grow, divide, and produce tens of thousands of haploid forms, called merozoites, per liver cell. Some malaria parasite species also produce hypnozoites in the liver that remain dormant for extended periods, causing relapses weeks or months later. (3) The merozoites exit the liver cells and re-enter the bloodstream, beginning a cycle of invasion of red blood cells, known as asexual replication. In the red blood cells they develop into mature schizonts, which rupture, releasing newly formed merozoites that then reinvade other red blood cells. This cycle of invasion and cell rupture repeats every 1-3 days* and can result in thousands of parasite-infected red blood cells in the host bloodstream, leading to illness and complications of malaria that can last for months if not treated. (4) Some of the merozoite-infected blood cells leave the cycle of asexual replication. Instead of replicating, the merozoites in these cells develop into sexual forms of the parasite, called male and female gametocytes. In some malaria species, young gametocytes sequester in the bone marrow and some organs while late stage (stage V) gametocytes, circulate in the bloodstream. (5) When a mosquito bites an infected human, it ingests the gametocytes. In the mosquito midgut, the infected human red blood cells burst, releasing the gametocytes, which develop further into mature sexual forms called gametes. Male and female gametes fuse to form diploid zygotes, which develop into actively moving ookinetes that burrow through the mosquito midgut wall and form oocysts on the other side. (6) Growth and division of each oocyst produces thousands of active haploid forms called sporozoites. After 8-15 days*, the oocyst bursts, releasing sporozoites into the body cavity of the mosquito, from which they travel to and invade the mosquito salivary glands. The cycle of human infection re-starts when the mosquito takes a blood meal, injecting the sporozoites from its salivary glands into the human bloodstream. (7) The vegetative, reproducing, feeding form of a protozoan is called a trophozoite. Under certain conditions, some protozoa produce a protective form called a cyst that enable them to survive harsh environments. Cysts allow some pathogens to survive outside their host. *from* NIAID .

Exercise: Think-Pair-Share Questions

1. Protozoa that cause gastrointestinal infections are capable of producing cyst forms as well as trophozoites. State why this is essential to these pathogens.

The Role of Protozoan Cytoplasmic Membrane Components in Initiating Body Defense

Initiation of Innate Immunity

In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Components of protozoa that function as PAMPs include GPI-anchored proteins (GPI = Glycosylphosphatidylinositol) and mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar) that function as

PAMPs. These mannose-rich glycans are common in microbial glycoproteins and glycolipids but rare in those of humans. These PAMPs bind to pattern-recognition receptors or PRRs on a variety of defense cells of the body and triggers innate immune defenses such as inflammation, fever, and phagocytosis.

Initiation of Adaptive Immunity

Proteins associated with protozoa function as antigens and initiate adaptive immunity. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response. The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR). This will be discussed in greater detail in Unit 6.

We will now briefly look at some medically important protozoa classified into phyla based on their motility. Illustrations can be found in your Lab Manual in Lab 20.

Summary

Protozoa are unicellular eukaryotic microorganisms lacking a cell wall and belonging to the Kingdom Protista. Protozoa reproduce asexually by fission, schizogony, or budding. Some protozoa can also reproduce sexually. Relatively few protozoa cause disease. The vegetative, reproducing, feeding form of a protozoan is called a trophozoite. Under certain conditions, some protozoa produce a protective form called a cyst. Components of protozoa that function as PAMPs include GPI-anchored proteins and mannose-rich glycans. These PAMPS bind to PRRs on various defense cells and trigger innate immunity. Protozoan molecules can also trigger adaptive immunity such as the production of antibody molecules against protozoan antigens.

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9.2: Medically Important Protozoa

State a disease caused by each of the following protozoans and indicate their means of motility and how they are transmitted to humans:

a. *Entamoeba histolytica*
b. *Acanthamoeba*
c. *Giardia lamblia*
d. *Trichomonas vaginalis*
e. *Trypanosoma brucei-gambiens*
f. *Balantidium coli*
g. *Plasmodium* species
h. *Toxoplasma gondii*
i. *Cryptosporidium*

The Sarcomastigophora (Amoeboflagellates)

The amoebas (subphylum Sarcodina) move by extending lobelike projections of their cytoplasm called pseudopodia .

- Photomicrograph of an amoeba.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Video YouTube movie an amoeba moving by forming pseudopodia (https://www.youtube.com/embed/7pR7TNzJ_pA).

a. *Entamoeba histolytica* (see photomicrograph) which causes a gastrointestinal infection called amoebic dysentery. The organism produces protective cysts which pass out of the intestines of the infected host and are ingested by the next host. It is transmitted by the fecal-oral route.

b. *Acanthamoeba* can cause rare, but severe infections of the eye, skin, and central nervous system. *Acanthamoeba* keratitis is an infection of the eye that typically occurs in healthy persons and can result in blindness or permanent visual impairment. Granulomatous amebic encephalitis (GAE) is an infection of the brain and spinal cord typically occurring in persons with a compromised immune system. *Acanthamoeba* is found in soil, dust, and a variety of water sources including lakes, tap water, swimming pools, and heating and air conditioning units. It typically enters the eyes and most cases are associated with contact lens use, but it can also enter cuts or wounds and be inhaled.

c. *Naegleria fowleri* (sometimes called the"brain-eating amoeba"), is another amoeba that can cause a rare but devastating infection of the brain called primary amebic meningoencephalitis (PAM). The amoeba is commonly found in warm freshwater rivers, lakes, rivers, and hot springs, as well as in the soil. It typically causes infections when contaminated water enters the body through the nose where it can subsequently travel to the brain.

YouTube movie of *Acanthamoeba*

The flagellates (subphylum Mastigophora) move by means of flagella. Some also have an undulating membrane .

a. *Giardia lamblia* (see photomicrograph) can cause a gastrointestinal infection called giardiasis. Cysts pass out of the intestines of the infected host and are ingested by the next host. It is transmitted by the fecal-oral route.

YouTube animation illustrating giardiasis

- Scanning electron micrograph of *Giardia* in the intestines; courtesy of Dennis Kunkel's Microscopy.
- Scanning electron micrograph of *Giardia*;courtesy of CDC.

b. *Trichomonas vaginalis* (see photomicrograph) infects the vagina and the male urinary tract causing an infection called genitourinary trichomoniasis. It does not produce a cysts stage and is usually transmitted by sexual contact.

YouTube movie *Trichomonas vaginalis*.

YouTube movie showing motility of *Trichomonas vaginalis*.

c. *Trypanosoma brucei gambiens* (see photomicrograph) causes African sleeping sickness and is transmitted by the bite of an infected Tsetse fly. The disease primarily involves the lymphatic and nervous systems of humans.

YouTube movie of *Trypanosoma*

The Ciliophora

The ciliates move by means of cilia.

- Scanning electron micrograph of *Paramecium*, a ciliated protozoan; courtesy of Dennis Kunkel's Microscopy.

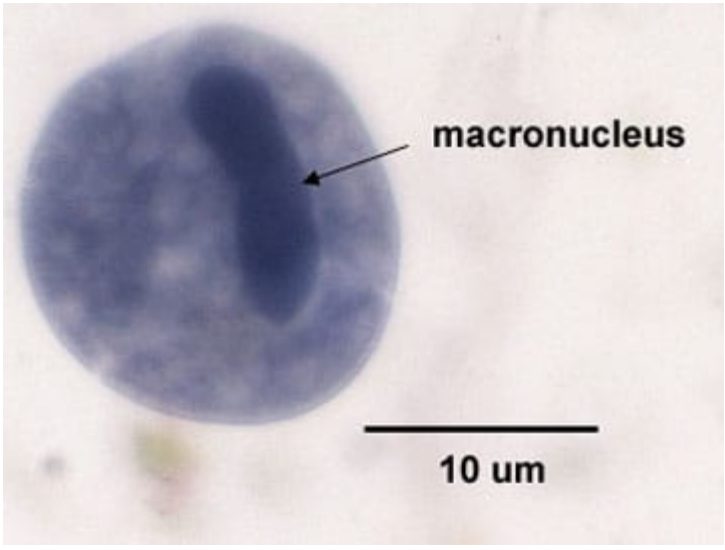
YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

YouTube movie showing motility of Balantidium coli.

a. The only pathogenic ciliate is *Balantidium coli* (see photomicrograph) which causes a diarrhea-type infection called balantidiasis. Cysts pass out of the intestines of the infected host and are ingested by the next host. It is transmitted by the fecal-oral route.



Balantidium coli in a Fecal Smear

The Apicomplexans

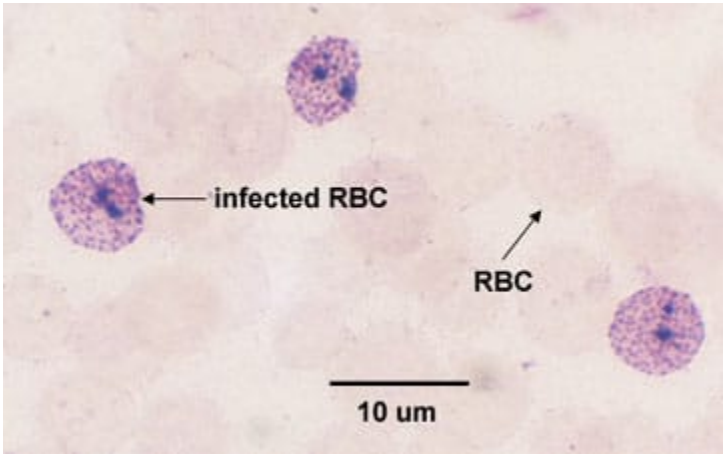


Figure 9.2.5: Plasmodium-Infected Red Blood Cells (arrows)

Toxoplasma gondii is another intracellular apicomplexan and causes toxoplasmosis (see the AIDS pathology tutorial at the University of Utah). It can infect most mammals and is contracted by inhaling or ingesting cysts from the feces of infected domestic cats, where the protozoa reproduce both asexually and sexually, or by ingesting raw meat of an infected animal. Toxoplasmosis is usually mild in people with normal immune responses but can infect the brain, heart, or lungs of people who are immunosuppressed. It can also be transmitted congenitally and infect the nervous system of the infected child.

Cryptosporidium is an intracellular parasite that causes a gastrointestinal infection called cryptosporidiosis, although in people who are immunosuppressed it can also cause respiratory and gallbladder infections. It is transmitted by the fecal-oral route.

> Movie of motile *Cryptosporidium*, courtesy of the Sibly Lab, Washington University in St. Louis School of Medicine.
>
> Movie of *Cryptosporidium* entering an epithelial cell, courtesy of the Sibly Lab, Washington University in St. Louis School of Medicine.

Virulence Factors that Promote Colonization of Protozoans

Virulence factors that promote protozoal colonization of the host include the ability to:

1. contact host cells;
2. adhere to host cells and resist physical removal;
3. invade host cells;
4. compete for nutrients;
5. resist innate immune defenses such as phagocytosis and complement; and
6. evade adaptive immune defenses.

Examples of virulence factors that promote protozoal colonization include:

1. Some protozoa, such as *Entamoeba histolytica*,*Trichomonas vaginalis*, *Giardia lamblia*, and *Balantidium coli* use pseudopodia, flagella or cilia to swim through mucus and contact host cells.
2. Protozoa use adhesins associated with their cytoplasmic membrane to adhere to host cells, colonize, and resist flushing.
3. Some protozoa, such as the apicomplexans (*Plasmodium (inf)*, *Toxoplasma gondii (inf),* and *Cryptosporidium (inf)*) possess a complex of organelles called apical complexes at their apex that contain enzymes used in penetrating host tissues and cells.
4. Protozoans such as Trypanosoma *brucei gambiens (inf)* and *Plasmodium* species *(inf)* are able to change their surface antigens during their life cycle in the human. As the protozoa change the amino acid sequence and shape of their surface antigens, antibodies and cytotoxic T-lymphocytes made against a previous shape will no longer fit and the body has to start a new round of adaptive immunity against the new antigen shape.
5. Some protozoa, such as *Entamoeba histolytica (inf)* shed their surface antigens so that antibodies made by the body against these surface antigens are tied up by the shed antigens.

To view a Quicktime movie of *Cryptosporidium* and electron micrographs of *Giardia* and *Entamoeba*, see the Parasites section of the CELL'S ALIVE web page.

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9: PROTOZOA

9.1: Characteristics of Protozoa
9.2: Medically Important Protozoa
9.E: Protozoa (Exercises)

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9.E: Protozoa (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

9.1: Characteristics of Protozoa

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

   _____ Multiple fission. The nucleus divides many times before the cell divides. The single cell then separates into numerous daughter cells.

   _____ Division in which one cell splits in two.

   _____ Division in which a cell pinches off of the parent cell.

   _____ The vegetative, reproducing, feeding form of a protoaoan.

   _____ A protective form that enables protozoa to survive harsh environments.

   A. trophozoite
   B. cyst
   C. fission
   D. schizogony
   E. budding

9.2: Medically Important Protozoa

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching

   ____ Moves by flagella; transmitted by ingesting cysts via the fecal-oral route; causes an intestinal infection.

   ____ Moves by cilia; transmitted by ingesting cysts via the fecal-oral route; causes an intestinal infection.

   ____ Moves by flagella; transmitted by an infected tsetse fly; causes African sleeping sickness.

   _____ Nonmotile in the body; reproduces sexually and asexually; transmitted by an infecteded *Anopheles* mosquito; causes malaria.

   _____ Moves by flagella; transmitted sexually; causes vaginitis.

   _____ Nonmotile in the body; reproduces sexually and asexually; transmitted by eating infected meat or inhaling or ingesting cysts from cat feces.

   a. *Entamoeba histolytica*
   b. *Acanthamoeba*
   c. *Giardia lamblia*

d. *Trichomonas vaginalis*
e. *Trypanosoma brucei-gambiens*
f. *Balantidium coli*
g. *Plasmodium* species
h. *Toxoplasma gondii*
i. *Cryptosporidium*

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10.1: General Characteristics of Viruses

Learning Objectives

1. State 2 living and 2 nonliving characteristics of viruses.
2. List 3 criteria used to define a virus.
3. Discuss why bacteria can be cultivated on synthetic media such as nutrient broth whereas viruses cannot.
4. Define bacteriophage.

Viruses are infectious agents with both living and nonliving characteristics. They can infect animals, plants, and even other microorganisms. Viruses that infect only bacteria are called bacteriophages and those that infect only fungi are termed mycophages . There are even some viruses called virophages that infect other viruses.

Living Characteristics of Viruses	Nonliving Characteristics of Viruses
a. They reproduce at a fantastic rate, but only in living host cells. b. They can mutate.	a. They are acellular, that is, they contain no cytoplasm or cellular organelles. b. They carry out no metabolism on their own and must replicate using the host cell's metabolic machinery. In other words, viruses don't grow and divide. Instead, new viral components are synthesized and assembled within the infected host cell. c. The vast majority of viruses possess either DNA or RNA but not both.

Recently, viruses have been declared as living entities based on the large number of protein folds encoded by viral genomes that are shared with the genomes of cells. This indicates that viruses likely arose from multiple ancient cells.

The vast majority of viruses contain only one type of nucleic acid: DNA or RNA, but not both. Virus are totally dependent on a host cell for replication (i.e., they are strict intracellular parasites.) Furthermore, viral components must assemble into complete viruses (virions) to go from one host cell to another. Since viruses lack metabolic machinery of their own and are totally dependent on their host cell for replication, they cannot be grown in synthetic culture media. Animal viruses are normally grown in animals, embryonated eggs, or in cell cultures where in animal host cells are grown in a synthetic medium and the viruses are then grown in these cells.

Summary

1. Viruses are infectious agents with both living and nonliving characteristics.
2. Living characteristics of viruses include the ability to reproduce – but only in living host cells – and the ability to mutate.
3. Nonliving characteristics include the fact that they are not cells, have no cytoplasm or cellular organelles, and carry out no metabolism on their own and therefore must replicate using the host cell's metabolic machinery.
4. Viruses can infect animals, plants, and even other microorganisms.
5. Since viruses lack metabolic machinery of their own and are totally dependent on their host cell for replication, they cannot be grown in synthetic culture media.

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10.2: Size and Shapes of Viruses

Learning Objectives

1. Compare the size of most viruses to that of bacteria.
2. List 4 shapes of viruses.

Size

Viruses are usually much smaller than bacteria with the vast majority being submicroscopic. While most viruses range in size from 5 to 300 nanometers (nm) , in recent years a number of giant viruses, including Mimiviruses and Pandoraviruses with a diameter of 0.4 micrometers (μm) , have been identified. For a comparison of the size of a virus, a bacterium, and a human cell, scroll down to how big is... on the Cell Size and Scale Resource at the University of Utah webpage (see Figure 10.2.1A, Figure 10.2.1B, and Figure 10.2.1C),

Shapes

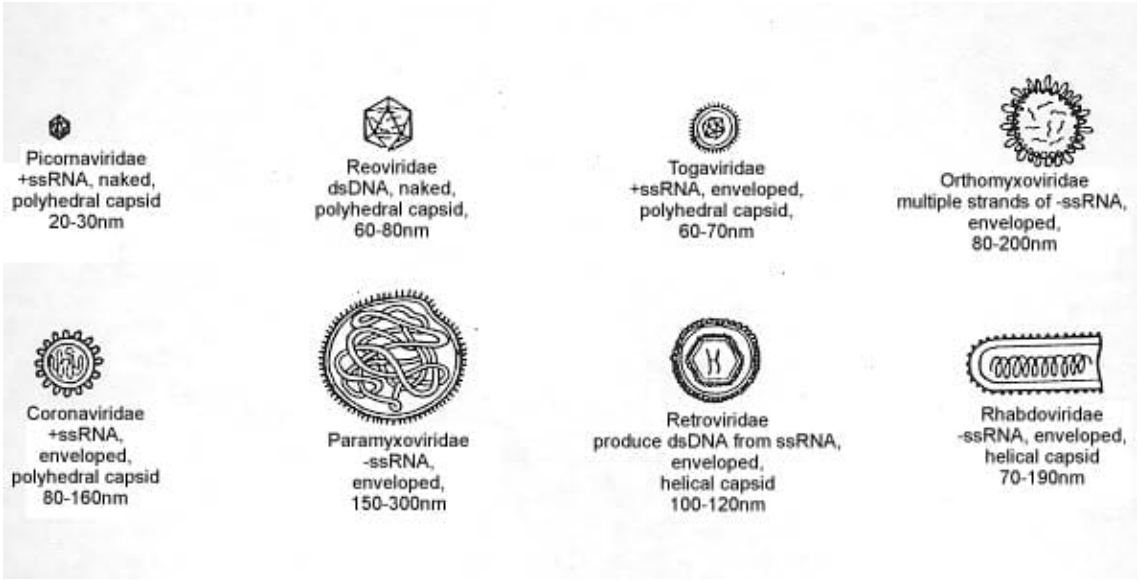


Figure 10.2.1A: Sizes and Shapes of Viruses (Animal RNA Viruses)

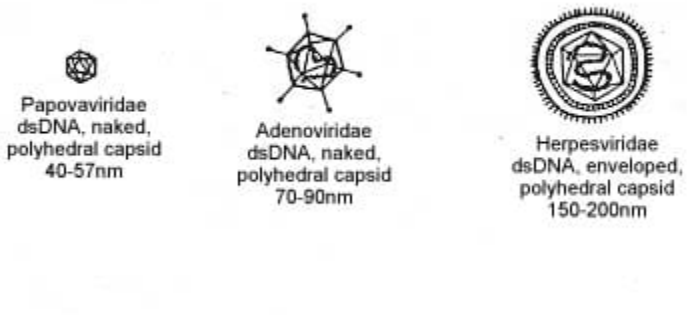


Figure 10.2.1B: Sizes and Shapes of Viruses (Animal DNA Viruses)

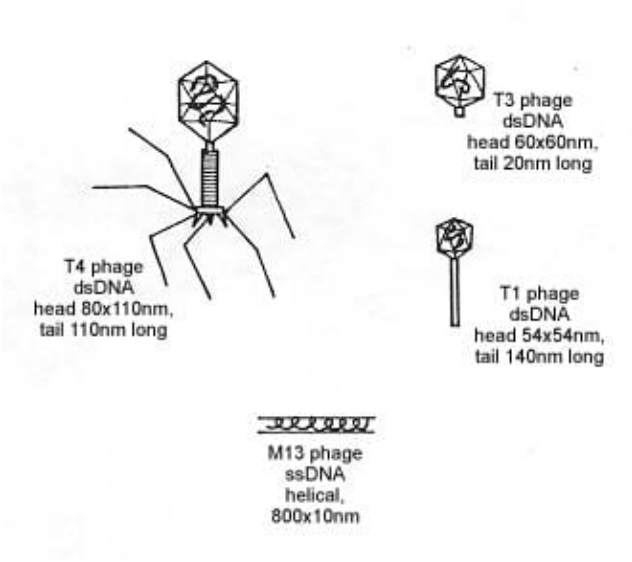
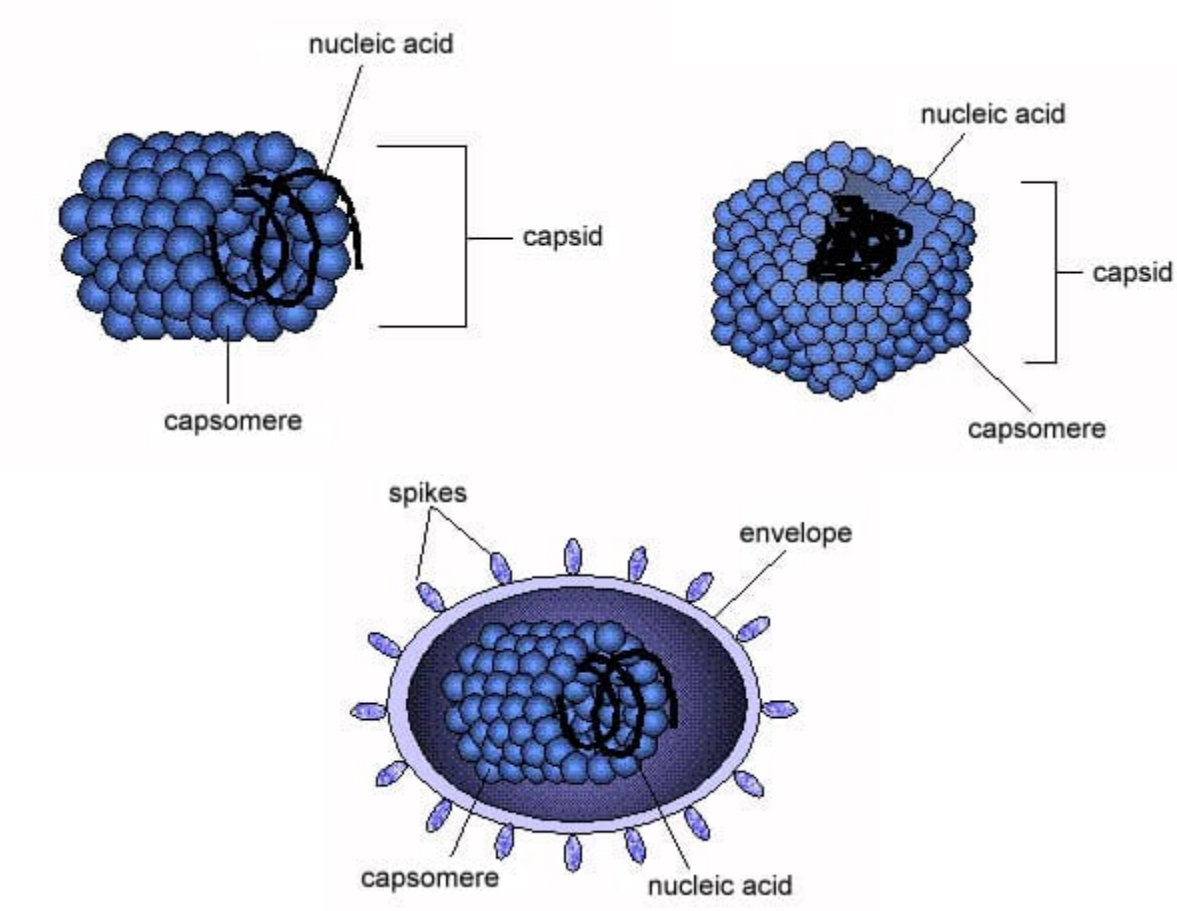


Figure 10.2.1*C: Sizes and Shapes of Viruses (Bacteriophages)*

a. Helical viruses consist of nucleic acid surrounded by a hollow protein cylinder or capsid and possessing a helical structure (Figure 10.2.2A).



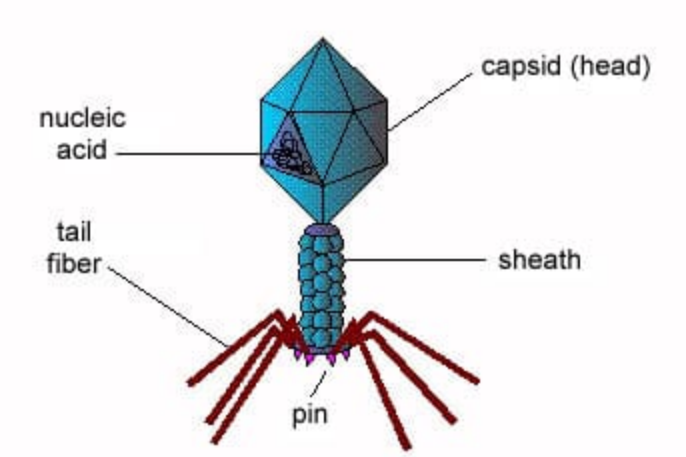


Figure 10.2.2: Viral Structure (Helical Virus). (B) Viral Structure (Polyhedral Virus), (C) Viral Structure (Enveloped Helical Virus), D: Viral Structure (Enveloped Polyhedral Virus), (F) Viral Structure (Binal) Illustration of a T-even bacteriophage consisting of a head, sheath, and tail.

b. Polyhedral viruses consist of nucleic acid surrounded by a polyhedral (many-sided) shell or capsid, usually in the form of an icosahedron (Figure 10.2.2B).

- Transmission electron micrograph of Adenoviruses; courtesy of CDC.
- Transmission electron micrograph of poliomyelitis viruses; courtesy of CDC.
- Transmission electron micrograph of poliomyelitis viruses; courtesy of Dennis Kunkel's Microscopy.

c. Enveloped viruses consist of nucleic acid surrounded by either a helical or polyhedral core and covered by an envelope (see Figure 10.2.2C and Figure 10.2.2D).

- Transmission electron micrograph of Hepatitis B viruses; courtesy of CDC.
- Transmission electron micrograph of an Influenza A virus; courtesy of CDC.
- Transmission electron micrograph of HIV; courtesy of CDC.
- Transmission electron micrograph showing envelope and glycoprotein spikes Coronaviruses; courtesy of CDC.
- Transmission electron micrograph of herpes simplex viruses; courtesy of Dennis Kunkel's Microscopy.

d. Binal (complex) viruses have neither helical nor polyhedral forms, are pleomorphic or irregular shaped (Figure 10.2.3), or have complex structures (Figure 10.2.2F).



Figure 10.2.3: Electron Micrograph of Filamentous Ebola Viruses Budding from an Infected Host Cell Filamentous, enveloped Ebola visuses (red). Courtesy of National Institute of Allergy and Infectious Diseases (NIAID).

- Transmission electron micrograph of the bacteriophage coliphage T4; courtesy of Dennis Kunkel's Microscopy.

Exercise: Think-Pair-Share Questions

We just learned that most viruses are much smaller than bacteria.

1. Compare the sizes of viruses and bacteria.
2. Why are viruses able to be so much smaller than bacteria

Summary

1. Viruses are usually much smaller than bacteria with the vast majority being submicroscopic, generally ranging in size from 5 to 300 nanometers (nm).
2. Helical viruses consist of nucleic acid surrounded by a hollow protein cylinder or capsid and possessing a helical structure.
3. Polyhedral viruses consist of nucleic acid surrounded by a polyhedral (many-sided) shell or capsid, usually in the form of an icosahedron.
4. Enveloped viruses consist of nucleic acid surrounded by either a helical or polyhedral core and covered by an envelope.
5. Binal (complex) viruses have neither helical nor polyhedral forms, have irregular shapes, or have complex structures.

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10.3: Viral Structure

Learning Objectives

1. Describe what an animal virus consists of structurally.
2. Define the following:
   a. capsid
   b. capsomere
   c. nucleocapsid.
3. Describe how most animal viruses obtain their envelope.
4. State why some bacteriophages are more complex than typical polyhedral or helical viruses.

Since viruses are not cells, they are structurally much simpler than bacteria. An intact infectious viral particle is called a virion and consists of: a genome, a capsid, and often an envelope.

Viral Genome

The viral genome is a single or segmented, circular or linear molecule of nucleic acid functioning as the genetic material of the virus. It can be single-stranded or double-stranded DNA or RNA (but almost never both), and codes for the synthesis of viral components and viral enzymes for replication. It is also becoming recognized that viruses may play a critical role in evolution of life by serving as shuttles of genetic material between other organisms.

Viral Capsid

The capsid, or core, is a protein shell surrounding the genome and is usually composed of protein subunits called capsomeres. The capsid serves to protect and introduce the genome into host cells. Some viruses consist of no more than a genome surrounded by a capsid and are called *nucleocapsid* or *nucleocapsid* (Figure 10.3.1). Attachment proteins project out from the capsid and bind the virus to susceptible host cells.

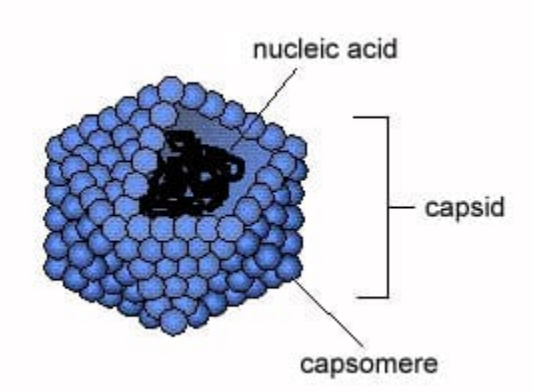


Figure 10.3.1: (A) Viral Structure (Helical Virus) and (B) Viral Structure (Polyhedral Virus).

The Adenovirus and Poliomyelitis viruses are examples of naked viruses (Figure 10.3.2); both exhibit polyhedral structures.

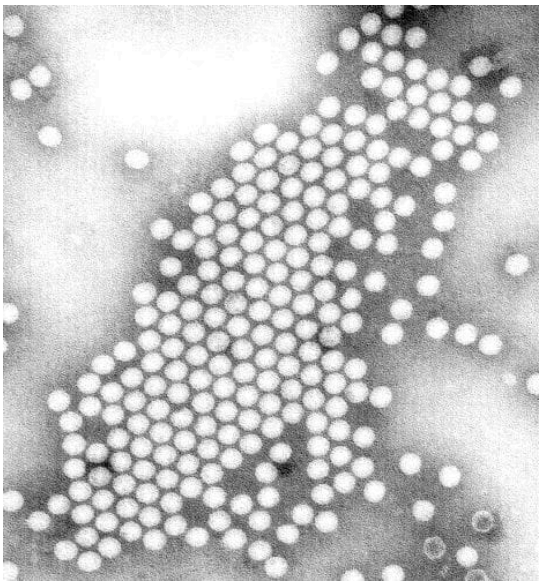


Figure 10.3.2: Naked Viruses (left) Transmission electron micrograph of Adenoviruses. Image provided by Dr. G. William Gary, Jr. (right) Transmission electron micrograph of poliomyelitis viruses; Image provided by J. J. Esposito and F. A. Murphy. Courtesy of the Centers for Disease Control and Prevention.

Viral Envelope

Most animal viruses also have an envelope surrounding a polyhedral or helical nucleocapsid, in which case they are called enveloped viruses (Figure 10.3.3). The envelope may come from the host cell's nuclear membrane, vacuolar membranes (packaged by the Golgi apparatus), or outer cytoplasmic membrane.

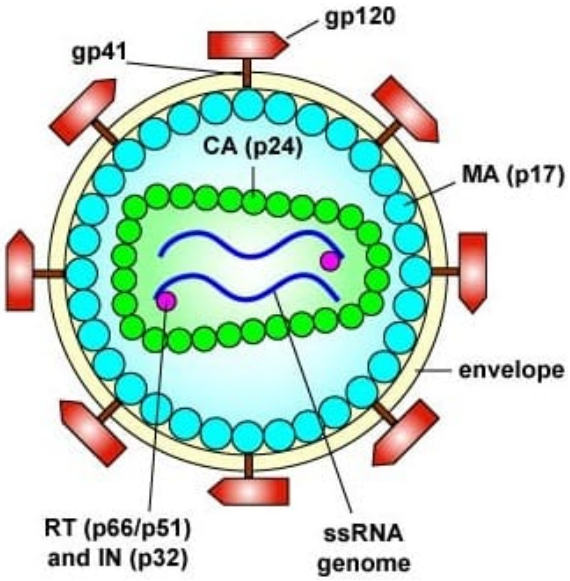


Figure 10.3.3: Viral Structure (left) Enveloped Helical Virus, (center) Enveloped Polyhedral Virus, (right) Structure of HIV.

- Transmission electron micrograph of Rubella viruses budding from an infected host cell; courtesy of CDC.
- Transmission electron micrograph of an Influenza A virus; courtesy of CDC.
- Transmission electron micrograph of HIV; courtesy of CDC.

Although the envelope is usually of host cell origin, the virus does incorporate proteins of its own, often appearing as glycoprotein spikes, into the envelope. These glycoprotein spikes function in attaching the virus to receptors on susceptible host cells.

- Transmission electron micrograph showing envelope and glycoprotein spikes (gp120) of HIV; courtesy of CDC.

- Transmission electron micrograph showing envelope and glycoprotein spikes Coronaviruses; courtesy of CDC.

Viral Activation of Innate Immunity

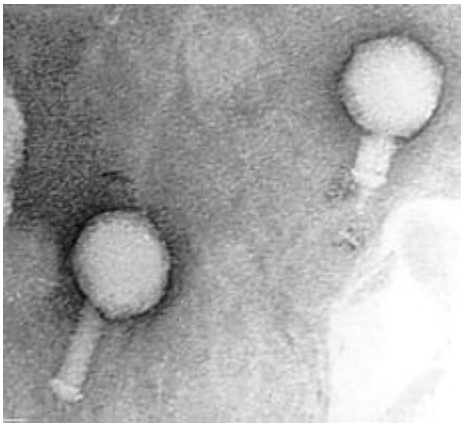
To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called *pathogen-associated molecular patterns* or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

For example, most viral genomes contain a high frequency of unmethylated cytosine-guanine dinucleotide sequences (a cytosine lacking a methyl or CH_3 group and located adjacent to a guanine). Mammalian DNA has a low frequency of cytosine-guanine dinucleotides and most are methylated. In addition, most viruses produce unique double-stranded viral RNA, and some viruses produce uracil-rich single-stranded viral RNA during portions of their life cycle. These forms of viral nucleic acids are common PAMPs associated with viruses. These PAMPs bind to *pattern-recognition receptors* or PRRs called toll-like receptors or TLRs found within the endosomes of phagocytic cells. Viral RNA can also bind to cytoplasmic PRRs called RIG-1 (retinoic acid-inducible gene-1)and MDR-5 (melanoma differentiation-associated gene-5).

Most of the PRRs that bind to viral components trigger the synthesis of cytokines called Type-I interferons that block viral replication within infected host cells. The TLRs for viral components are found in the membranes of the phagosomes used to degrade viruses during phagocytosis. As viruses are engulfed by phagocytes, the viral PAMPS bind to TLRs located within the phagolysosomes (endosomes). The TLRs for viral components include:

1. TLR-3 binds double-stranded viral RNA;
2. TLR-7 binds uracil-rich single-stranded viral RNA such as in HIV;
3. TLR-8 binds single-stranded viral RNA;
4. TLR-9 binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes.
5. RIG-1 (retinoic acid-inducible gene-1) and MDA-5 (melanoma differentiation-associated gene-5), are cytoplasmic sensors that both viral double-stranded and single-stranded RNA molecules produced in viral-infected cells

Bacteriophages are viruses that only infect bacteria. Some bacteriophages are structurally much more complex than typical nucleocapsid or enveloped viruses and may possess a unique tail structure composed of a base plate, tail fibers, and a contractile sheath (also see Figure 10.3.1C and Figure 10.3.2E). Other bacteriophages, however, are simple icosahedrals or helical (see Figure 10.3.1C).



Electron Micrograph of a Bacteriophage with a Contractile Sheath. A = normal bacteriophage and B = bacteriophage after contraction of sheath

- Transmission electron micrograph of the bacteriophage coliphage T4 courtesy of Dennis Kunkel's Microscopy.

Exercise: Think-Pair-Share Questions

1. Discuss why viruses can only replicate inside living cells.
2. Most of the PRRs for viral PAMPs are found in the membranes of the phagosomes, not on the surface of the cell.
   a. Why do you think this is?
   b. Name the primary cytokines produced in response to viral PAMPs and state how they function to protect against viruses.

Summary

1. Since viruses are not cells, they are structurally much simpler than bacteria.
2. An intact infectious viral particle - or virion - consists of a genome, a capsid, and maybe an envelope.
3. Viruses possess either DNA or RNA as their genome.
4. The genome is typically surrounded by a protein shell called a capsid composed of protein subunits called capsomeres.
5. Some viruses consist of no more than a genome surrounded by a capsid and are called nucleocapsid or naked viruses.
6. Most animal viruses also have an envelope surrounding a polyhedral or helical nucleocapsid that is typically derived from host cell membranes by a budding process and are called enveloped viruses.
7. Specific proteins or glycoproteins on the viral surface are used to attach viruses to the surface of its host cell.
8. The viral nucleic acid functions as a pathogen-associated molecular pattern (PAMP).
9. Binding of viral PAMPs to host cell pattern-recognition receptors (PRRs) triggers the synthesis and secretion of anti-viral cytokines called type-1 interferons that block viral replication within infected host cells.

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10.4: Classification of Viruses

Learning Objectives

1. State what criteria are used in viral classification.
2. Regarding the naming of enzymes involved in the replication of viral nucleic acid, state what the "dependent" part of the name refers to and what the "polymerase" part of the name refers to.

Viruses can store their genetic information in six different types of nucleic acid which are named based on how that nucleic acid eventually becomes transcribed to the viral mRNA (Figure 10.4.1) capable of binding to host cell ribosomes and being translated into viral proteins.

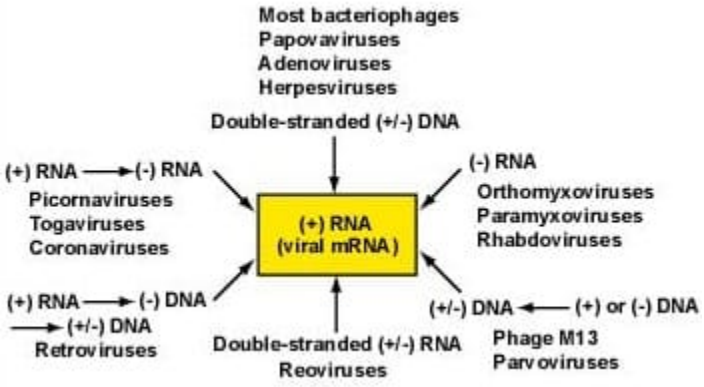


Figure 10.4.1: Transcription of Viral Nucleic Acid into Viral mRNA. A (+) RNA can be translated into viral protein. (+) and (-) strands are complementary.

In the diagrams below, (+) and (-) represent complementary strands of nucleic acid. Copying of a (+) strand by complementary base pairing forms a (-) strand. Only a (+) viral mRNA strand can be translated into viral protein. Regarding the enzymes involved in nucleic acid replication, the "dependent" part of the name refers what type of nucleic acid is being copied. The "polymerase" part of the name refers what type of nucleic acid is being synthesized, e.g., DNA-dependent RNA-polymerase would synthesize a strand of RNA complementary to a strand of DNA. These six forms of viral nucleic acid are:

1. **(+/-) double-stranded DNA (Figure 10.4.2).** To replicate the viral genome, DNA-dependent DNA polymerase enzymes copy both the (+) and (-) DNA strands producing dsDNA viral genomes. To produce viral mRNA molecules, DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Examples include most bacteriophages, Papovaviruses, Adenoviruses, and Herpesviruses.

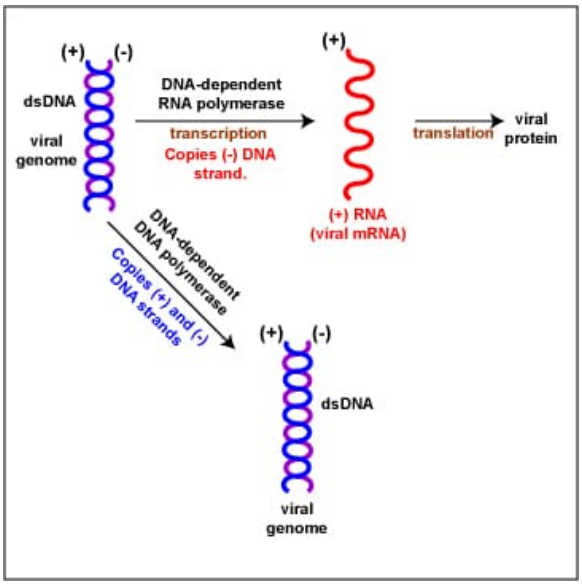


Figure 10.4.2: Replication of a Double-Stranded DNA Viral Genome and production of Viral mRNA. To replicate the viral genome, DNA-dependent DNA polymerase enzymes copy both the (+) and (-) DNA strands producing dsDNA viral genomes. To produce viral mRNA molecules. DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be transtated into viral proteins by host cell ribosomes.

- **(+) single-stranded DNA (Figure 10.4.2).** To replicate the viral genome, DNA-dependent DNA polymerase enzymes copy the (+) DNA strand of the genome producing a dsDNA intermediate. DNA-dependent DNA polymerase enzymes then copy the (-) DNA strand into ss (+) DNA genomes. To produce viral mRNA molecules, DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Examples include Phage M13 and Parvoviruses.

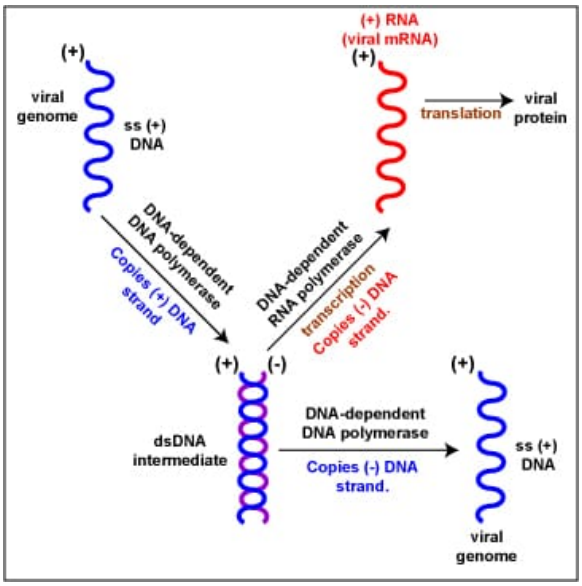


Figure 10.4.3: Replication of a Single-Stranded DNA Viral Genome and Production of Viral mRNA. To replicate the viral genome, DNA-dependent DNA polymerase enzymes copy the (+) DNA strand of the genome producing a dsDNA intermediate. DNA-dependent DNA polymerase enzymes then copy the (-) DNA strand into ss (+) DNA genomes. To produce viral mRNA molecules. DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be transtated into viral proteins by host cell ribosomes.

- **(+/-) double-stranded RNA (Figure 10.4.4).** To replicate the viral genome, RNA-dependent RNA polymerase enzymes copy both the (+) RNA and (-) RNA strands of the genome producing a dsRNA genomes. To produce viral mRNA molecules, RNA-dependent RNA polymerase enzymes copy the (-) RNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Reoviruses are an example.

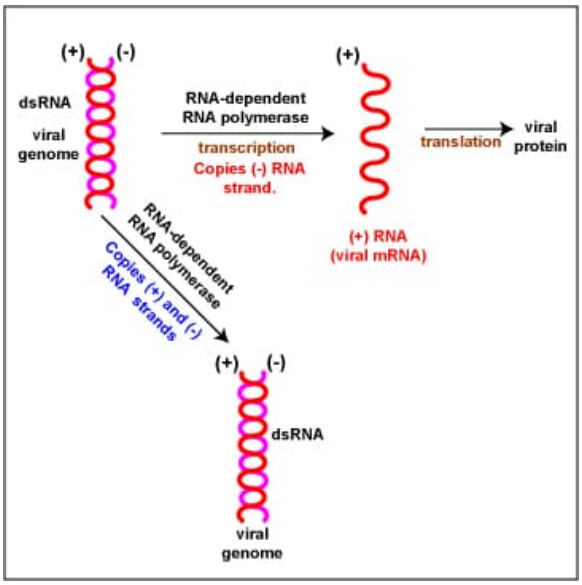


Figure 10.4.4: Replication of a Double-Stranded RNA Viral Genome and Production of Viral mRNA. To replicate the viral genome, RNA-dependent RNA polymerase enzymes copy both the (+) RNA and (-) RNA strands of the genome producing a dsRNA genomes. To produce viral mRNA molecules. RNA-dependent RNA polymerase enzymes copy the (-) RNA strand into (+) viral mRNA. The (+) viral mRNA can then be transtated into viral proteins by host cell ribosomes.

- **(-) RNA (Figure 10.4.5).** To replicate the viral genome, RNA-dependent RNA polymerase enzymes copy the (-) RNA genome producing ss (+) RNA. RNA-dependent RNA polymerase enzymes then copy the (+) RNA strands producing ss (-) RNA viral genome. The (+) mRNA strands also function as viral mRNA and can then be translated into viral proteins by host cell ribosomes. Examples include Orthomyxoviruses, Paramyxoviruses, Rhabdoviruses.

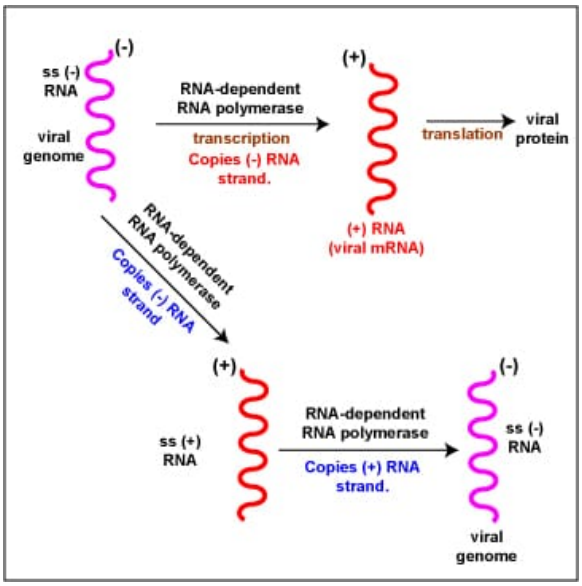


Figure 10.4.5: Replication of a Single-Stranded Minus RNA Viral Genome and Production of Viral mRNA. To replicate the viral genome, RNA-dependent RNA polymerase enzymes copy the (-) RNA genome producing ss (+) RNA. RNA-dependent RNA polymerase enzymes then copy the (+) RNA strands producing ss (-) RNA viral genome. The (+) mRNA strands also function as viral mRNA and can then be transtated into viral proteins by host cell ribosomes.

- **(+) RNA (Figure 10.4.6).** To replicate the viral genome, RNA-dependent RNA polymerase enzymes copy the (+) RNA genome producing ss (-) RNA. RNA-dependent RNA polymerase enzymes then copy the (-) RNA strands producing ss (+) RNA viral genome. To produce viral mRNA molecules. RNA-dependent RNA polymerase enzymes copy the (-) RNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Examples include Picornaviruses, Togaviruses, and Coronaviruses.

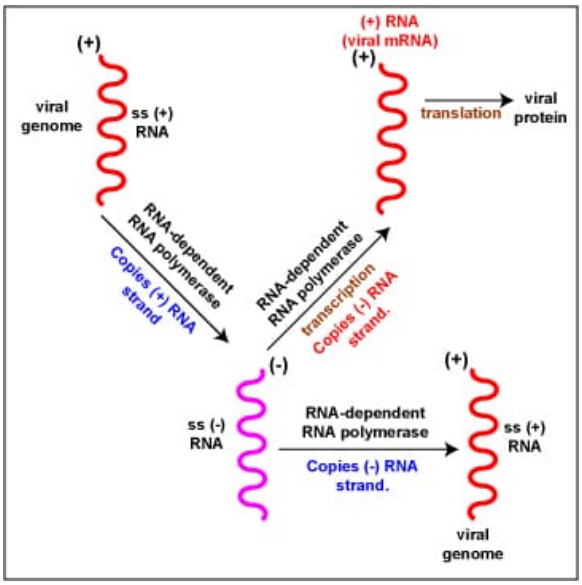


Figure 10.4.6: Replication of a Single-Stranded Plus RNA Viral Genome and Production of Viral mRNA. To replicate the viral genome, RNA-dependent RNA polymerase enzymes copy the (+) RNA genome producing ss (-) RNA. RNA-dependent RNA polymerase enzymes then copy the (-) RNA strands producing ss (+) RNA viral genome. To produce viral mRNA molecules. RNA-dependent RNA polymerase enzymes copy the (-) RNA strand into (+) viral mRNA. The (+) viral mRNA can then be transtated into viral proteins by host cell ribosomes.

- **(+) RNA Retroviruses (Figure 10.4.7).** To replicate the viral genome, reverse transcriptase enzymes (RNA-dependent DNA polymerases) copy the (+) RNA genome producing ss (-) DNA strands. DNA-dependent DNA polymerase enzymes then copy the (-) DNA strands to produce a dsDNA intermediate. DNA-dependent RNA polymerase enzymes then copy the (-) DNA strands to produce ss (+) RNA genomes. To produce viral mRNA molecules, DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Retroviruses, such as HIV-1, HIV-2, and HTLV-1 are examples.

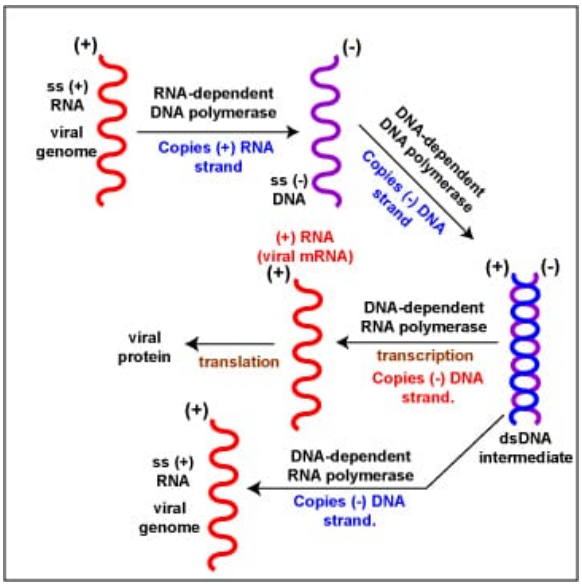


Figure 10.4.7: Replication of a Single-Stranded Plus RNA Viral Genome and Production of Viral mRNA by way of Reverse Transcriptase. To replicate the viral genome, reverse transcriptase enzymes (RNA-dependent DNA polymerases) copy the (+) RNA genome producing ss (-) DNA strands. DNA-dependent DNA polymerase enzymes then copy the (-) DNA strands to produce a dsDNA intermediate. DNA-dependent RNA polymerase enzymes then copy the (-) DNA strands to produce ss (+) RNA genomes. To produce viral mRNA molecules. DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be transtated into viral proteins by host cell riboso

Exercise: Think-Pair-Share Questions

A viral enzyme that synthesizes a complementary RNA copy of an RNA would be called what?

Table 10.4.1 below describes some of the medically important viruses.

Table 10.4.1: Classification of Viruses

Properties	Viral Family	Size	Example
single-stranded DNA; naked; polyhedral capsid	Parvoviridae	18-25 nm	parvoviruses (roseola, fetal death, gastroenteritis; some depend on coinfection with adenoviruses)
double-stranded, DNA; naked; polyhedral capsid	Papovaviridae; circular dsDNA	40-57 nm	human papilloma viruses (HPV; benign warts and genital warts; genital and rectal cancers)
	Adenoviridae; dsDNA	70-90 nm	adenoviruses (respiratory infections, gastroenteritis, infectious pinkeye, rashes, meningoencephalitis)
double-stranded, circular DNA; enveloped; complex	Poxviridae	200-350 nm	smallpox virus (smallpox), vaccinia virus (cowpox), molluscipox virus (molluscum contagiosum-wartlike skin lesions)
double-stranded DNA; enveloped; polyhedral capsid	Herpesviridae	150-200 nm	herpes simplex 1 virus (HSV-1; most oral herpes; herpes simplex 2 virus (HSV-2; most genital herpes), herpes simplex 6 virus (HSV-6; roseola), varicella-zoster virus (VZV; chickenpox and shingles), Epstein-Barr virus (EBV; infectious mononucleosis and lymphomas), cytomegalovirus (CMV; birth defects and infections of a variety of body systems in immunosuppressed individuals)
	Hepadnaviridae	42 nm	hepatitis B virus (HBV; hepatitis B and liver cancer)
(+)single-stranded RNA; naked; polyhedral capsid	picornaviridae	28-30 nm	enteroviruses (poliomyelitis), rhinoviruses (most frequent cause of the common cold), Noroviruses (gastroenteritis), echoviruses (meningitis), hepatitis A virus (HAV; hepatitis A)
(+)single-stranded RNA; enveloped; usually a polyhedral capsid	Togaviridae	60-70 nm	arboviruses (eastern equine encephalitis, western equine encephalitis), rubella virus (German measles)
	Flaviviridae	40-50 nm	flaviviruses (yellow fever, dengue fever, St. Louis encephalitis), hepatitis C virus (HCV; hepatitis C)
	Coronaviridae	80-160 nm	coronaviruses (upper respiratory infections and the common cold; SARS)
(-)single-stranded RNA; enveloped; pleomorphic	Rhabdoviridae; bullet-shaped	70-189 nm	rabies virus (rabies)
	Filoviridae; long and filamentous	80-14,000 nm	Ebola virus, Marburg virus (hemorrhagic fevers)
	Paramyxoviridae; pleomorphic	150-300 nm	paramyxoviruses (parainfluenza, mumps); measles virus (measles)
(-) strand; multiple strands of RNA; enveloped	Orthomyxoviridae	80-200 nm	influenza viruses A, B, and C (influenza)
	Bunyaviridae	90-120 nm	California encephalitis virus (encephalitis); hantaviruses (Hantavirus pulmonary syndrome, Korean hemorrhagic fever)
	Arenaviridae	50-300 nm	arenaviruses (lymphocytic choriomeningitis, hemorrhagic fevers)

Properties	Viral Family	Size	Example
produce DNA from (+) single-stranded RNA using reverse transcriptase; enveloped; bullet-shaped or polyhedral capsid	Retroviridae	100-120 nm	HIV-1 and HIV-2 (HIV infection/AIDS); HTLV-1 and HTLV-2 (T-cell leukemia)
dsRNA; naked; polyhedral capsid	Reoviridae	60-80 nm	reoviruses (mild respiratory infections, infant gastroenteritis); Colorado tick fever virus (Colorado tick fever)

Summary

1. Viruses can store their genetic information in six different types of nucleic acid which are named based on how that nucleic acid eventually becomes transcribed to the viral mRNA.
2. (+) and (-) strands of nucleic acid are complementary. Copying a (+) stand gives a (-) strand; copying a (-) stand gives a (+) strand.
3. Only (+) strands of viral RNA can be translated into viral protein.
4. Regarding the enzymes involved in nucleic acid replication, the "dependent" part of the name refers what type of nucleic acid is being copied. The "polymerase" part of the name refers what type of nucleic acid is being synthesized.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what criteria are used in viral classification. *(ans)*
2. What would a DNA-dependent RNA-polymerase enzyme do? *(ans)*

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10.5: Other Acellular Infectious Agents: Viroids and Prions

Learning Objectives

1. Define viroid and name an infection caused by a viroid.
2. Define prion and name 3 protein misfolding diseases that apprear to be initiated by prions.

Viroids and Prions

Viroids are even more simple than viruses. They are small, circular, single-stranded molecules of infectious RNA lacking even a protein coat. They are the cause of a few plant diseases such as potato spindle-tuber disease,cucumber pale fruit, citrus exocortis disease, and cadang-cadang (coconuts).

Prions are infectious protein particles responsible for a group of transmissible and/or inherited neurodegenerative diseases including Creutzfeldt-Jakob disease, kuru, and Gerstmann-Straussler-syndrome in humans, as well as scrapie in sheep and goats, and bovine spongiform encephalopathy (mad cow disease) in cattle and in humans (where it is called new variant Creutzfeldt–Jakob disease humans). The infections are often referred to as transmissible spongiform encephalopathies.

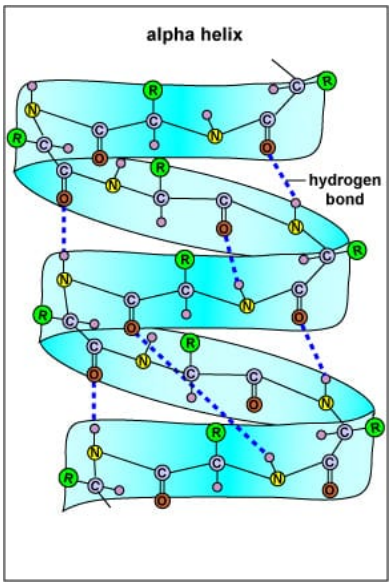


Figure 10.5.1: Secondary Structure of a Protein or Polypeptide Alpha Helix. The secondary structure of a protein or polypeptide is due to hydrogen bonds forming between an oxygen atom of one amino acid and a nitrogen atom of another. There are two possible types of secondary structure: an alpha helix and a beta sheet. In the case of an alpha helix, the hydrogen bonding causes the polypeptide to twist into a helix. With a beta sheet the hydrogen bonding enables the polypeptide to fold back and forth upon itself like a pleated sheet.

Most evidence indicates that the infectious prion proteins are modified (misfolded) forms of normal proteins coded for by a host gene in the brain. It is thought that the normal prion protein, expressed on stem cells in the bone marrow and on cells that will become neurons, plays a role in the maturation of neurons. In the case of the disease scrapie, the normal prion protein in an animal without the disease has alpha-helices in the proteins secondary structure (Figure 10.5.1) while the scrapie prion protein in diseased animals has beta-sheets for the secondary structure (Figure 10.5.2). When the scrapie prion protein contacts the normal protein it causes it to change its configuration to the scrapie beta-sheet form. This suggests that the conversion of a normal prion protein into an infectious prion protein may be catalyzed by the prion protein itself upon entering the brain. Inherited forms may be a result of point mutations that make the prion protein more susceptible to a change in its protein structure.

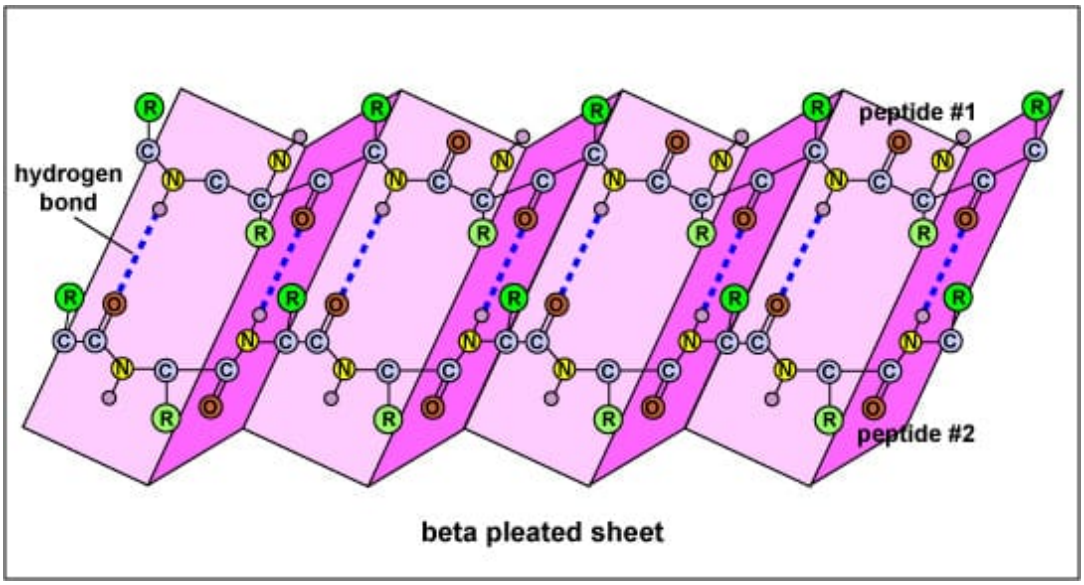


Figure 10.5.2: Secondary Structure of a Protein or Polypeptide Beta Pleated Sheet. The secondary structure of a protein or polypeptide is due to hydrogen bonds forming between an oxygen atom of one amino acid and a nitrogen atom of another. There are two possible types of secondary structure: an alpha helix and a beta sheet. In the case of an alpha helix, the hydrogen bonding causes the polypeptide to twist into a helix. With a beta sheet the hydrogen bonding enables the polypeptide to fold back and forth upon itself like a pleated sheet.

There is growing evidence that other probable protein misfolding diseases initiated by prions include Alzheimer's disease, Hunington's disease, Parkinson's disease, frontotemporal dementias, amyotrophic lateral sclerosis, and certain cancers.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Summary

1. Viroids are small, circular, single-stranded molecules of infectious RNA that cause several plant diseases.
2. Prions are infectious protein particles responsible for a group of transmissible and/or inherited neurodegenerative diseases as a result of prion protein misfolding.
3. Diseases including Creutzfeldt-Jakob disease Gerstmann-Straussler-syndrome, and mad cow disease.
4. There is growing evidence that other probable protein misfolding diseases initiated by prions include Alzheimer's disease, Hunington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and certain cancers.

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10: VIRUSES

A virus is a small infectious agent that replicates only inside the living cells of other organisms. Viruses can infect all types of life forms, from animals and plants to microorganisms, including bacteria and archaea.

10.1: General Characteristics of Viruses

10.2: Size and Shapes of Viruses

10.3: Viral Structure

10.4: Classification of Viruses

10.5: Other Acellular Infectious Agents: Viroids and Prions

10.6: Animal Virus Life Cycles

10.6A: The Productive Life Cycle of Animal Viruses

10.6B: Productive Life Cycle with Possible Latency

10.6C: The Life Cycle of HIV

10.6D: Natural History of a Typical HIV Infection

10.6E: The Role of Viruses in Tumor Production

10.7: Bacteriophage Life Cycles: An Overview

10.7A: The Lytic Life Cycle of Bacteriophages

10.7B: The Lysogenic Life Cycle of Bacteriophages

10.8: Pathogenicity of Animal Viruses

10.9: Bacteriophage-Induced Alterations of Bacteria

10.10: Antiviral Agents

10.11: General Categories of Viral Infections

10.E: Viruses (Exercises)

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10.6: ANIMAL VIRUS LIFE CYCLES

Viruses that infect animal cells replicate by what is called the productive life cycle. The productive life cycle is also often referred to as the lytic life cycle, even though not all viruses cause lysis of their host cell during their replication. Some viruses, such as HIV and the herpes viruses are able to become latent in certain cell types. A few viruses increase the risk of certain cancers. We will now look at the life cycles of viruses that infect animal cells.



-  Topic hierarchy 

10.6A: The Productive Life Cycle of Animal Viruses

10.6B: Productive Life Cycle with Possible Latency

10.6C: The Life Cycle of HIV

10.6D: Natural History of a Typical HIV Infection

10.6E: The Role of Viruses in Tumor Production

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10.6A: The Productive Life Cycle of Animal Viruses

Learning Objectives

1. When given information about a virus in terms of how it penetrates the host cell, whether it has a DNA or RNA genome, and how it is released, describe how an enveloped virus accomplishes each of the steps of the productive life cycle listed below. (Tailor the life cycle to that virus.)
   A. viral attachment or adsorption to the host cell
   B. viral entry into the host cell
   C. viral movement to the site of replication within the host cell
   D. viral replication within the host cell
   E. viral assembly or maturation within the host cell
   F. viral release from the host cell
2. When given information about a virus in terms of how it penetrates the host cell, whether it has a DNA or RNA genome, and how it is released, describe how a naked virus accomplishes each of the steps of the productive life cycle listed below. (Tailor the life cycle to that virus.)
   A. viral attachment or adsorption to the host cell
   B. viral entry into the host cell
   C. viral movement to the site of replication within the host cell
   D. viral replication within the host cell
   E. viral assembly or maturation within the host cell
   F. viral release from the host cell

For many animal viruses, the details of each step in their life cycle have not yet been fully characterized, and among the viruses that have been well studied there is great deal of variation. What follows is a generalized productive life cycle for animal viruses consisting of the following steps: adsorption, viral entry, viral movement to the site of replication and release of the viral genome from the remainder of the virus, viral replication, viral assembly, and viral release.

Viral Attachment or Adsorption to the Host Cell

Adsorption (Figures 1) involves the binding of attachment sites on the viral surface with receptor sites on the host cell cytoplasmic membrane.

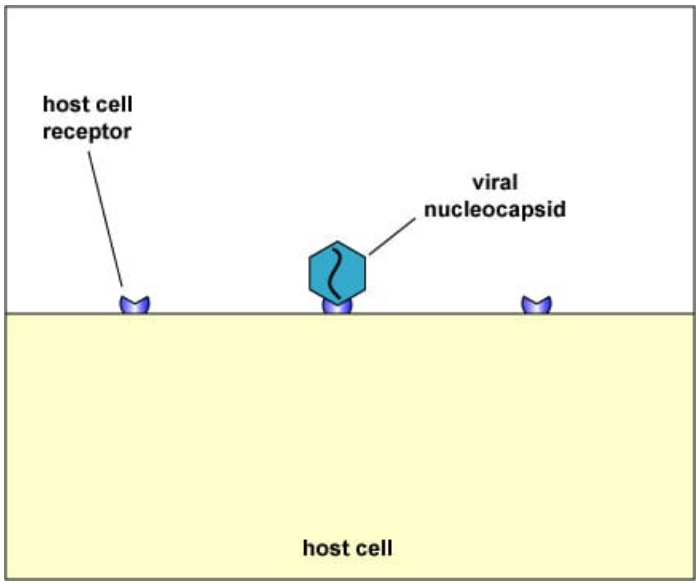


Figure 10.6A.1: (A) Adsorption of an Enveloped Virus to a Susceptible Host Cell. Attachment sites on the viral envelope bind to corresponding host cell receptors. (B) Adsorption of an Enveloped Virus to a Susceptible Host Cell. Attachment sites on the viral capsid bind to corresponding host cell receptors.

For a virus to infect a host cell, that cell must have receptors for the virus on its surface and also be capable of supporting viral replication. These host cell receptors are normal surface molecules involved in routine cellular function, but since a portion of a molecule on the viral surface resembles the chemical shape of the body's molecule that would normally bind to the receptor, the virus is able to attach to the host cell's surface.

For example:

- Most human rhinoviruses that cause the common cold bind to intercellular adhesion molecules (ICAM-1) found on cells of the nasal epithelium. These ICAM-1 molecules are used normally for the recruitment of leukocytes into the respiratory tract.
- The human immunodeficiency viruses (HIV) adsorbs to first CD4 molecules and then chemokine receptors found on the surface of human T4-lymphocytes and macrophages . CD4 molecules are normally involved in immune recognition while chemokine receptors play a role in initiating inflammation and recruiting leukocytes.
- Human cytomegaloviruses (CMV) adsorb to MHC-I molecules . MHC-I molecules on human cells enable T8-lymphocytes to recognize antigens during adaptive immunity.
- The hepatitis B virus (HBV) adsorbs to IgA receptors on human cells. These receptors normally bind the antibody isotype IgA for transport across cells.

Flash animation showing adsorption of an enveloped virus.	Flash animation showing adsorption of a naked virus.

html5 version of animation for iPad showing adsorption of an enveloped virus.

html5 version of animation for iPad showing adsorption of a naked virus.

Viral Entry into the Host Cell

a. Enveloped viruses

Enveloped viruses enter the host cell in one of two ways:

1. In some cases, the viral envelope may fuse with the host cell cytoplasmic membrane and the nucleocapsid is released into the cytoplasm (see Figs. 2A, Figure 10.6A.2B and Figure 10.6A.2C).

Flash animation showing entry of an enveloped virus by envelope fusion.

html5 version of animation for iPad showing entry of an enveloped virus by envelope fusion.

2. Usually they enter by endocytosis , whereby the host cell cytoplasmic membrane invaginates and pinches off, placing the virus in an endocytic vesicle (see Figure 10.6A.3A, Figure 10.6A.3B, Figure 10.6A.3C, and Figure 10.6A.3D).

Flash animation showing entry of an enveloped virus by endocytosis.

html5 version of animation for iPad showing entry of an enveloped virus by endocytosis.

3D animation illustrating adsorption and penetration of the dengue fever virus.

Janet Iwasa, Gaël McGill (Digizyme) & Michael Astrachan (XVIVO). This animation takes some time to load.

b. Naked viruses

Naked viruses enter the cell in one of two ways:

1. In some cases, interaction between the viral capsid and the host cell cytoplasmic membrane causes a rearrangement of capsid proteins allowing the viral nucleic acid to pass through the membrane into the cytoplasm (see Figure 10.6A.4A, Figure 10.6A.4B, Figure 10.6A.4C, and Figure 10.6A.4D).

Flash animation showing entry of a naked virus by capsid reconfiguration.

html5 version of animation for iPad showing entry of a naked virus by capsid reconfiguration.

2. Most naked viruses enter by receptor-mediated endocytosis whereby the host cell cytoplasmic membrane invaginates and pinches off, placing the virus in an endocytic vesicle (see Figure 10.6A.5A, Figure 10.6A.5B, Figure 10.6A.5C, and Figure 10.6A.5D).

Flash animation showing penetration of a naked virus by endocytosis.

html5 version of animation for iPad showing penetration of a naked virus by endocytosis.

3. Viral Movement to the Site of Replication within the Host Cell and Release of the Viral Genome from the Remainder of the Virus.

In the case of viruses that enter by endocytosis, the endocytic vesicles containing the virus move within the host cell. During this process the pH of the endocytic vesicle typically decreases and this enables the virus to leave the endocytic vesicle. Viruses exit the endocytic vesicle through a variety of mechanisms, including:

a. Fusion of the viral envelope with the membrane of the endocytic vesicle enabling the viral nucleocapsid to enter the cytoplasm of the host cell (see Figure 10.6A.7A, Figure 10.6A.7B, and Figure 10.6A.7C).

Flash animation showing fusion of the viral envelope with the membrane of the endocytic vesicle.

html5 version of animation for iPad showing fusion of the viral envelope with the membrane of the endocytic vesicle.

b. Lysis of the endocytic vesicle releasing the viral nucleocapsid into the cytoplasm of the host cell (see Figure 10.6A.7D , and Figure 10.6A.7E).

Flash animation showing lysis of the endocytic vesicle.

html5 version of animation for iPad showing lysis of the endocytic vesicle.

c. The viral capsid undergoing conformational changes that forms pores in the endocytic vesicle enabling the virial genome to enter the cytoplasm of the host cell (see Figure 10.6A.9A, Figure 10.6A.9B, and Figure 10.6A.9C).

Flash animation showing viral capsid undergoing conformational changes that forms pores in the endocytic vesicle and enable the virial genome to enter the cytoplasm.

html5 version of animation for iPad showing viral capsid undergoing conformational changes that forms pores in the endocytic vesicle and enable the virial genome to enter the cytoplasm.

Before viruses can replicate within the infected host cell, the viral genome needs to released from the remainder of the virus. This process is sometimes referred to as uncoating.

In the case of most viruses with an RNA genome, the viral RNA genome is released from the capsid and enters the cytoplasm of the host cell (see Figure 10.6A.8A , and Figure 10.6A.8B) where replication generally occurs.

Flash animation showing release of the viral genome from the capsid (uncoating).

html5 version of animation for iPad showing release of the viral genome from the capsid (uncoating).

In the case of most viruses with a DNA genome, the viral genome enters the nucleus of the host cell through one the mechanisms shown below. Most larger DNA viruses use either a or b to enter the nucleus. Method c is used by some very small DNA whose capsid is small enough to be carried through the nuclear pores.

a. The viral DNA genome is released from the capsid, enters the cytoplasm of the host cell, and subsequently enters the nucleus of the host cell through the pores in the nuclear membrane (see Figure 10.6A.9D and Figure 10.6A.9E).

Flash animation showing a viral DNA genome entering the nucleus of the host cell through the pores in the nuclear membrane.

html5 version of animation for iPad showing a viral DNA genome entering the nucleus of the host cell through the pores in the nuclear membrane.

b. The capsid of the viruses interacts with the nuclear membrane of the host cell enabling the viral DNA genome to enter the nucleus of the host cell via the pores in the nuclear membrane (see Figure 10.6A.9F and Figure 10.6A.9G).

Flash animation showing a viral capsid interacting with the nuclear membrane of the host cell enabling the viral DNA to enter the nucleus.

html5 version of animation for iPad showing a viral capsid interacting with the nuclear membrane of the host cell enabling the viral DNA to enter the nucleus.

c. The nucleocapsid of a small DNA virus enters the nucleus of the host cell and the capsid is subsequently removed releasing the viral DNA genome into the nucleoplasm (see Figure 10.6A.9H and Figure 10.6A.9I).

Flash animation showing a viral nucleocapsid entering the nuclear membrane of the host cell .

html5 version of animation for iPad showing a viral nucleocapsid entering the nuclear membrane of the host cell.

This uncoating begins the eclipse period , the period during which no intact virions can be detected within the cell. After uncoating

and during the replication stage the virus is not infectious.

4. Viral Replication within the Host Cell

The viral genome directs the host cell's metabolic machinery (ribosomes, tRNA, nutrients, energy, enzymes, etc.) to synthesize viral enzymes and viral parts. The viral genome has to both replicate itself and become transcribed into viral mRNA molecules. The viral mRNA can then be translated by the host cell's ribosomes into viral structural components and enzymes need for replication and assembly of the virus.

As mentioned earlier under Viral Classification, viruses can store their genetic information in six different types of nucleic acid which are named based on how that nucleic acid eventually becomes transcribed to the viral mRNA:

a. (+/-) double-stranded DNA (see Figure $10.6A.10$A). To replicate the viral genome, DNA-dependent DNA polymerase enzymes (usually provided by the cell) copy both the (+) and (-) DNA strands producing dsDNA viral genomes. To produce viral mRNA molecules, host cell-DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Examples include most bacteriophages, Papovaviruses, Adenoviruses, and Herpesviruses.

b. (+) single-stranded DNA (see Figure $10.6A.10$B). To replicate the viral genome, DNA-dependent DNA polymerase enzymes (usually provided by the cell) copy the (+) DNA strand of the genome producing a dsDNA intermediate. DNA-dependent DNA polymerase enzymes (again, usually provided by the cell) then copy the (-) DNA strand into ss (+) DNA genomes. To produce viral mRNA molecules, host cell-DNA-dependent RNA polymerase enzymes copy the (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Examples include Phage M13 and Parvoviruses.

c. (+/-) double-stranded RNA (see Figure $10.6A.10$C) . To replicate the viral genome, viral RNA-dependent RNA polymerase enzymes (replicase) copy both the (+) RNA and (-) RNA strands of the genome producing a dsRNA genomes. To produce viral mRNA molecules, viral RNA-dependent RNA polymerase enzymes (transcriptase) copy the (-) RNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Reoviruses are an example.

d. (-) RNA (see Figure $10.6A.10$D). To replicate the viral genome, viral RNA-dependent RNA polymerase enzymes (transcriptase) copy the (-) RNA genome producing ss (+) RNA. Transcriptase must be carried into the cell with the virion. Viral RNA-dependent RNA polymerase enzymes (replicase) then copy the (+) RNA strands producing ss (-) RNA viral genome. The (+) mRNA strands also function as viral mRNA and can then be translated into viral proteins by host cell ribosomes. Examples include Orthomyxoviruses, Paramyxoviruses, Rhabdoviruses.

e. (+) RNA (see Figure $10.6A.10$E). To replicate the viral genome, viral RNA-dependent RNA polymerase enzymes (replicase) copy the (+) RNA genome producing ss (-) RNA. Viral RNA-dependent RNA polymerase enzymes (replicase) then copy the (-) RNA strands producing ss (+) RNA viral genome. To produce viral mRNA molecules. RNA-dependent RNA polymerase enzymes (replicase) copy the (-) RNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Examples include Picornaviruses, Togaviruses, and Coronaviruses.

f. (+) RNA Retroviruses (see Figure $10.6A.10$F). To replicate the viral genome, viral reverse transcriptase enzymes (RNA-dependent DNA polymerases) copy the (+) RNA genome producing ss (-) DNA strands. Viral reverse transcriptase can also function as a DNA-dependent DNA polymerase enzymes and will copy the (-) DNA strands to produce a dsDNA intermediate. Reverse transcriptase must be carried into the cell with the virion. The viral DNA will move to the nucleus where it integrates into the cell's DNA using the viral enzyme integrase which also must be carried into the host cell with the virion. Once in the host cell's DNA, host cell DNA-dependent RNA polymerase enzymes then copy the ds (-) DNA strands to produce ss (+) RNA genomes. To produce viral mRNA molecules, host cell DNA-dependent RNA polymerase enzymes copy the ds (-) DNA strand into (+) viral mRNA. The (+) viral mRNA can then be translated into viral proteins by host cell ribosomes. Retroviruses, such as HIV-1, HIV-2, and HTLV-1 are examples.

As the host cell's ribosomes attach to the viral mRNA molecules, the mRNAs are translated into viral structural proteins and viral enzymes. During the early phase of replication, proteins needed for the replication of the viral genome are made and the genome makes thousands of replicas of itself. During the late phase of replication, viral structural proteins (capsid and matrix proteins, envelope glycoproteins, etc.) and the enzymes involved in maturation are produced.

Some viral mRNAs are monocistronic, that is, they contain genetic material to translate only a single protein or polypeptide. Other

viral mRNAs are polycistronic. They contain transcripts of several genes and are translated into one or more large polyproteins. These polyproteins are subsequently cut into individual functional proteins by viral enzymes called proteases.

In the case of most RNA viruses, replication and assembly occurs in the host cell's cytoplasm. With DNA viruses, most replication and assembly occurs in the nucleus of the host cell. The viral genome enters the nucleus of the host cell and here is transcribed into viral mRNA. The viral mRNA molecules then leave the nucleus through the pores in the nuclear membrane and are translated into viral proteins by the host cell's ribosomes in the cytoplasm. Most of these viral proteins then re-enter the nucleus where the virus assembles around the replicated genomes.

- Transmission electron micrograph of Herpes simplex viruses in the nucleus of an infected host cell; courtesy of CDC.

Also during replication, viral envelope proteins and glycoproteins coded by the viral genome are incorporated into the host cell's cytoplasmic membrane (see Figure $10.6A.11$A and Figure $10.6A.11$B) or nuclear membrane.

Flash animation showing viral replication.

html5 version of animation for iPad showing showing viral replication.

For More Information: Transcription from Unit 7

For More Information: Translation from Unit 7

Whether a virus has an RNA or a DNA genome is significant when it comes to developing antiviral agents to control viruses. In the case of RNA viruses, all of the enzymes used in genome replication and transcription are viral encoded enzymes different from those of the host cell so these enzymes can potentially be targeted. On the other hand, DNA viruses use the host cell's RNA transcription machinery and DNA replication machinery so these enzymes, shared by the virus and the host cell, cannot be targeted without killing the host cell. Since all viruses use the host cell's translation machinery regardless of genome type, translation can not be targeted in any viruses.

For More Information: Control of Viruses from Unit 3

5. Viral Assembly or Maturation within the Host Cell

During maturation, the capsid is assembled around the viral genome .

- Maturation of an enveloped virus: see Figure $10.6A.12$A.
- Maturation of a naked virus: see Figure $10.6A.12$B.

Flash animation showing maturation of an enveloped virus that will be released by budding.

html5 version of animation for iPad showing maturation of an enveloped virus that will be released by budding.

Flash animation showing maturation of an enveloped virus that will be released by exocytosis.

html5 version of animation for iPad showing maturation of an enveloped virus that will be released by exocytosis.

Flash animation showing maturation of a naked virus.

html5 version of animation for iPad showing maturation of a naked virus.

Viral Release from the Host Cell

a. Naked viruses

Naked viruses are predominantly released by host cell lysis (see Figure 10.6A.13 C). While some viruses are cytolytic and lyse the host cell more or less directly, in many cases it is the body's immune defenses that lyse the infected cell.

Flash animation showing release of a naked virus by cell lysis.

html5 version of animation for iPad showing release of a naked virus by cell lysis.

b. Enveloped viruses

With enveloped viruses, the host cell may or may not be lysed. The viruses obtain their envelopes from host cell membranes by budding. As mentioned above, prior to budding, viral proteins and glycoproteins are incorporated into the host cell's membranes. During budding the host cell membrane with incorporated viral proteins and glycoproteins evaginates and pinches off to form the viral envelope. Budding occurs either at the outer cytoplasmic membrane, the nuclear membrane, or at the membranes of the Golgi apparatus .

1. Viruses obtaining their envelope from the cytoplasmic membrane are released during the budding process (see Figure 10.6A.14A and Figure 10.6A.14B).

Flash animation showing release of an enveloped virus by budding.

html5 version of animation for iPad showing release of an enveloped virus by budding.

- Transmission electron micrograph of Rubella viruses budding from an infected host cell; courtesy of CDC.

2. Viruses obtaining their envelopes from the membranes of the nucleus, the endoplasmic reticulum, or the Golgi apparatus are then released by exocytosis via transport vesicles (see Figure 10.6A.15A and Figure 10.6A.15B).

Flash Animation showing release of an enveloped virus by exocytosis.

html5 version of animation for iPad showing release of an enveloped virus by exocytosis.

- Transmission electron micrograph of Coronaviruses in the endoplasmic reticulum of an infected host cell; courtesy of CDC.

Some viruses, capable of causing cell fusion, may be transported from one cell to adjacent cells without being released, that is, they are transmitted by cell-to-cell contact whereby an infected cell fuses with an uninfected cell (see Figure 10.6A.16A, Figure 10.6A.16B, and Figure 10.6A.16C).

Reinfection

As many as 10,000 to 50,000 animal viruses may be produced by a single infected host cell.

- Transmission electron micrograph showing envelope and glycoprotein spikes Coronaviruses; courtesy of CDC.

Exercise: Think-Pair-Share Questions

1. Animal viruses adsorb to receptors on the cytoplasmic membrane of host cells.

   Why would our cells possess receptors that viruses could adsorb too?

2. When we vaccinate against viral infections such as measles, mumps, rubella, poliomyelitis, and chickenpox, we inject an attenuated or inactivated form of the virus. The body responds by making antibodies that coat the surface of that virus by binding to its surface proteins or glycoproteins.

Briefly describe two ways this may prevent future infections with this virus.

Flash Animation showing a summary animation of the life cycle of an enveloped virus.

html5 version of animation for iPad showing a summary animation of the life cycle of an enveloped virus.

Flash Animation showing a summary animation of the life cycle of a naked virus.

html5 version of animation for iPad showing a summary animation of the life cycle of a naked virus.

Flash Animation Showing All Viral Life Cycle Animations
on this Page.

Nice Animation with Simplistic Explanation of the Replication of Influenza Viruses.

created for NPR by medical animator, David Bolinsky

Great animation of the productive live cycle of the dengue virus.

The dengue virus is an RNA virus that enters by endocytosis, gets its envelope by budding into the endoplasmic reticulum, and is packaged by the Golgi apparatus and released by exocytosis.

Dengue fever is a mosquito-borne viral infection found mainly in tropical areas. Often asymptomatic and self-limiting but when symptoms do appear, they can include joint and muscle pain, headache, and a rash that may become hemorrhagic. The virus replicates in macrophages.

Courtesy of HHMI's Biointeractive.

Concept Map for Productive Life Cycle of a Naked Animal Virus

Concept Map for Productive Life Cycle of an Enveloped Animal Virus

Summary

1. For a virus to infect a host cell, that cell must have receptors for the virus on its surface and also be capable of supporting viral replication.
2. Adsorption involves the binding of attachment sites on the viral surface with receptor sites on the host cell cytoplasmic membrane.
3. Once adsorbed, many viruses enter the host cell by endocytosis, whereby the host cell cytoplasmic membrane invaginates and pinches off, placing the virus in an endocytic vesicle. Some viruses enter by a fusion process whereby part of the virus fuses with the host cell enabling the remainder of the virus to enter the host cell's cytoplasm.
4. Following entry, the virus moves to the site of replication within the host cell. Most RNA viruses replicate in the host cell's cytoplasm; most DNA viruses replicate in the host cell's nucleus.
5. During replication, the viral genome directs the host cell's metabolic machinery (ribosomes, tRNA, nutrients, energy, enzymes, etc.) to synthesize viral enzymes and viral parts. The viral genome has to both replicate itself and become transcribed into viral mRNA molecules. The viral mRNA can then be transcribed by the host cell into viral structural components and enzymes need for replication and assembly of the virus.

6. During maturation, the capsid is assembled around the viral genome.
7. Prior to or during release, enveloped viruses obtain their envelopes from host cell membranes by budding. Budding occurs either at the outer cytoplasmic membrane, the nuclear membrane, or at the membranes of the Golgi apparatus.
8. Viruses obtaining their envelopes from the membranes of the nucleus, the endoplasmic reticulum, or the Golgi apparatus are then released by exocytosis via transport vesicles; viruses obtaining their envelope from the cytoplasmic membrane are released during the budding process.
9. Naked viruses are predominantly released by host cell lysis.
10. As many as 10,000 to 50,000 animal viruses may be produced by a single infected host cell.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. An enveloped virus enters by fusion, has an RNA genome, and is released by budding. Describe how it accomplishes each of the following steps during its productive life cycle.
   A. viral attachment or adsorption to the host cell *(ans)*
   B. viral entry into the host cell *(ans)*
   C. viral movement to the site of replication within the host cell *(ans)*
   D. viral replication within the host cell *(ans)*
   E. viral assembly or maturation within the host cell *(ans)*
   F. viral release from the host cell *(ans)*
2. When a virus infects the body, the body responds by producing antibodies that coat the virion. Discuss briefly how this might offer protection to the body. *(ans)*
3. Why are viruses generally very specific as to the types of hosts, tissues, and cells they are able to infect? *(ans)*
4. Multiple Choice *(ans)*

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10.6B: Productive Life Cycle with Possible Latency

State the major difference between the productive life cycle of animal viruses and the latent life cycle.

- Define provirus.
- Name 3 herpes viruses that may have a latent cycle, state in what cell types they become latent, and name the diseases each cause.

Some animal viruses, such as the herpes viruses and a group of viruses known as the retroviruses, are able to remain latent within infected host cells for long periods of time without replicating or causing harm. Some of these viruses remain latent within the cytoplasm of the host cell while others are able to insert or integrate their DNA into the host cell's chromosomes. When the viral DNA is incorporated into the host cell's DNA, it is called a provirus.

In many instances, viral latency, as well as viral persistence, is thought to be due to a process called RNA interference (RNAi) where small non-coding regulatory RNAs (ncRNAs) such as microRNAs (miRNAs) regulate gene expression. Certain viruses that infect humans are able to establish persistent infection by using their own miRNAs and/or miRNAs produced by their human host.

For example, viral and/or host miRNAs may bind to certain viral messenger RNA (mRNA) molecules and block translation of viral proteins required for rapid viral replication, or they may bind to the mRNA of human genes that produce proteins used in viral replication. The resulting low viral levels may then minimize immune responses against that virus. In addition, these miRNAs may directly affect host immune defenses by turning off the production of antiviral cytokinesor by blocking apoptosisof infected host cells. Examples include the herpesviruses, retroviruses, and anelloviruses.

Herpes viruses, for example, are often latent in some cell types but productive in others. Herpes viruses include herpes simplex type 1 (HSV-1) which usually causes fever blisters or oral herpes, herpes simplex type 2 (HSV-2) which usually causes genital herpes, Epstein-Barr virus (EBV) which causes infectious mononucleosis and plays a role in certain cancers, varicella-zoster virus (VZV) which causes chickenpox and shingles, and cytomegalovirus (CMV) which causes a variety of infections in immunosuppressed persons and is also a leading cause of birth defects.

For more on HSV and CMV, see the AIDS Pathology Tutorial at the University of Utah.

Herpesviruses use both host and viral miRNAs to switch between the productive life cycle in infected epithelial cells whereby large numbers of viruses are produced and the infected host cells are killed (as in the case of fever blisters) and the persistent latent state in nerve cells where low levels of viruses are produced and the infected host cells are not killed by apoptosis.

With EBV, the virus is productive in epithelial cells but latent in B-lymphocytes.

In the case of HSV-1, HSV-2, and VZV, primary infection causes the virus to replicate within epithelial cells. However, some of the viruses enter and migrate down neurons where they become latent in the body of sensory neurons. Subsequent activation of the latently infected neurons by a variety of extracellular stimuli enables the viruses to migrate back up the nerve cell and replicate again in the epithelial cells. With EBV, the virus is productive in epithelial cells but latent in B-lymphocytes.

- Scanning electron micrograph of HSV; courtesy of Dennis Kunkel's Microscopy.

In the case of HIV, the viral genome eventually becomes a provirus. After integration, the HIV proviral DNA can exist in either a latent or productive state, which is determined by genetic factors of the viral strain, the type of cell infected, and the production of specific host cell proteins.

The majority of the proviral DNA is integrated into the chromosomes of activated T4-lymphocytes. These generally comprise between 93% and 95% of infected cells and are productively infected, not latently infected. However, a small percentage of HIV-infected memory T4-lymphocytes persists in a resting state because of a latent provirus. Subsequent activation of the host cell by extracellular stimuli, however, causes the needed proteins to be made and the virus again replicates via the productive life cycle.

These memory T4-lymphocytes, along with infected monocytes, macrophages, and dendritic cells, provide stable reservoirs of HIV capable of escaping host defenses and antiretroviral chemotherapy.

In the next section we will now look at the life cycle of HIV.

Summary

1. For a virus to infect a host cell, that cell must have receptors for the virus on its surface and also be capable of supporting viral replication.
2. Adsorption involves the binding of attachment sites on the viral surface with receptor sites on the host cell cytoplasmic membrane.
3. Once adsorbed, many viruses enter the host cell by endocytosis, whereby the host cell cytoplasmic membrane invaginates and pinches off, placing the virus in an endocytic vesicle. Some viruses enter by a fusion process whereby part of the virus fuses with the host cell enabling the remainder of the virus to enter the host cell's cytoplasm.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define provirus. *(ans)*
2. Name 4 herpes viruses that may have a latent cycle, state in what cell types they become latent, and name the diseases each cause.
   A. (ans)
   B. *(ans)*
   C. *(ans)*
3. Multiple Choice *(ans)*

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10.6C: The Life Cycle of HIV

Learning Objectives

1. Describe how the retrovirus HIV-1 accomplishes each of the following steps during its life cycle. (Include the following key words in your description: gp120, CD4, chemokine receptors, gp41, capsid, RNA genome, reverse transcriptase, double-stranded DNA intermediate, provirus, polyproteins, proteases, and budding.)
   A. viral attachment or adsorption to the host cell
   B. viral entry into the host cell
   C. viral movement to the site of replication within the host cell and production of a provirus.
   D. viral replication within the host cell
   E. viral assembly or maturation within the host cell and release from the host cell
2. Name 3 types of cells HIV primarily infects and briefly explain why.

The Structure of the Human Immunodeficiency Virus (HIV)

HIV (see HIV A, HIV B and HIV C) has an envelope derived from host cell membranes during replication. Associated with the envelope are two HIV-encoded glycoproteins, gp120 and gp41. Underneath the envelope is a protein matrix composed of p17. Inside the virus is a capsid or core made of the protein p24. The nucleocapsid also contains p6, p7, reverse transcriptase (p66/p51), integrase (p32), protease (p10), and 2 molecules of single-stranded RNA, the viral genome (see Figure $10.6C.3$).

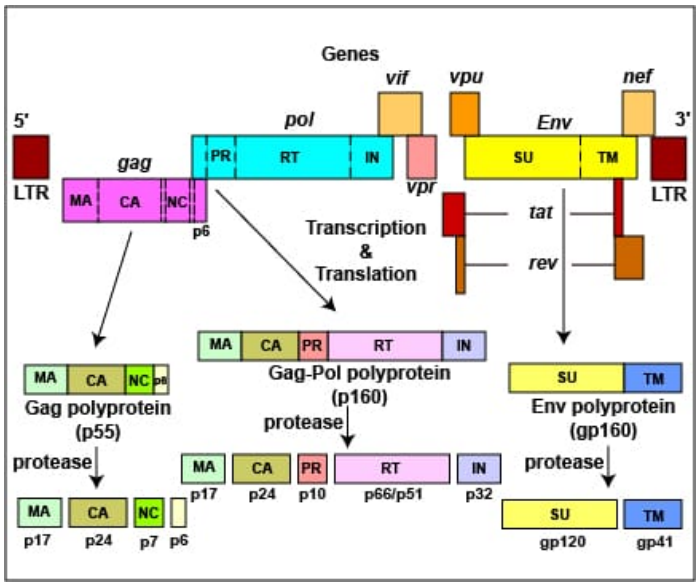


Figure $10.6C.3$: Transcription and Translation of the Genome of HIV. The gag and pol genes are transcribed as a unit and translated into two polyproteins Gag-Pol (p160) and Gag (p55). HIV proteases then cleave the Gag polyprotein (p55) into HIV matrix proteins (MA; p17), capsid proteins (CA; p24), and nucleocapsid proteins (NC, p7). The Gag-Pol polyprotein (p160) will be cleaved by HIV proteases to become HIV matrix proteins (MA; p17), capsid proteins (CA; p24), proteinase molecules (protease or PR; p10), reverse transcriptase molecules (RT; p66/p51), and integrase molecules (IN; p32). Likewise, the env gene is transcribed and translated into ENV polyprotein (gp160) that is cleaved by proteases into SU (surface glycoprotein; gp120) and TM (transmembrane glycoprotein; gp41). HIV Genes: Gag (group antigen; codes for matrix antigen p17, capsid antigen p24, and nucleocapsid antigen); Pol (polymerase; codes for reverse transcriptase, protease, and integrase); Env (envelope; codes for surface glycoprotein gp120 and transmembrane glycoprotein gp41); Tat (transactivating protein; regulates transcription of integrated DNA of HIV); Rev (regulator of viral expression; passage of RNA transcripts out of the nucleus); Nef (negative factor; needed for full pathogenecity of HIV); Vif (viral infectivity gene; may play a role in viral assembly); Vpu (blocks transport of CD4 to the host cell surface to aid in viral release); vpr (assists transport of dsDNA intermediate into host and arrests infected cells in the G2 phase of the cell cycle).

To view further electron micrographs of HIV, see the AIDS Pathology Tutorial at the University of Utah.

The Life Cycle for the Human Immunodeficiency Virus (HIV)

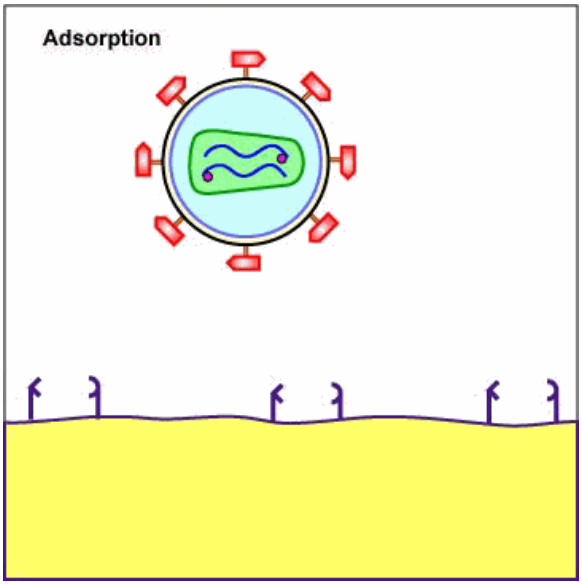
1. Attachment or Adsorption to the Host Cell

Initially, HIV uses a cellular protein called cyclophilin that is a component of its envelope to bind a low affinity host cell receptor called heparin. This first interaction (not shown in the illustrations or animations) enables the virus to initially make contact with the host cell. In order to infect a human cell, however, an envelope glycoprotein on the surface of HIV called gp120 must adsorbs to both a CD4 molecule and then a chemokine receptor found on the surface of only certain types of certain human cells.

Human cells possessing CD4 molecules include:

- T4-helper lymphocytes (also called T4-cells and $CD4^+$ cells)
- monocytes
- macrophages
- dendritic cells

Chemokines are cytokines that promote an inflammatory response by pulling white blood cells out of the blood vessels and into the tissue to fight infection. Different white blood cells have receptors on their surface for different chemokines. The chemokine receptors are now thought to determine the type of $CD4^+$ cell HIV is able to infect. First, a portion or domain of the HIV surface glycoprotein gp120 binds to its primary receptor, a CD4 molecule on the host cell. This induces a change in shape that enables the chemokine receptor binding domains of the gp120 to interact with a host cell chemokine receptor. The chemokine receptor functions as the viral co-receptor. This interaction brings about another conformational change that exposes a previously buried portion of the transmembrane glycoprotein gp41 called the fusion peptide that enables the viral envelope to fuse with the host cell membrane (see Figure 10.6C.1A, Figure 10.6C.1B), and Figure 10.6C.1C).



Animation: Adsorption of HIV to a T4-Helper Lymphocyte. The HIV envelope gp120 must attach to both a CD4 molecule and a chemokine receptor on the surface of such cells as macrophages and T4-helper lymphocytes in order to enter the cell. The gp120 first binds to a CD4 molecule on the plasma membrane of the host cell. The interaction between the gp120 and the CD4 molecule on the host cell induces a change in shape that brings the chemokine receptor binding domains of the gp120 into proximity with the host cell chemokine receptor

- Transmission electron micrograph showing envelope and glycoprotein spikes (gp120) of HIV; courtesy of CDC.
- Scanning electron micrograph showing HIV infecting a T4-lymphocyte; courtesy of CDC.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

YouTube animation illustrating adsorption and penetration of HIV.

Most strains of HIV are referred to as M-tropic or T-tropic. The gp120 of M-tropic HIV (see Figure 10.6C.2) is able to adsorb to the CD4 molecules and the CCR5 chemokine receptors found on $CD4^+$ macrophages, immature dendritic cells, and memory T4-lymphocytes. (M-tropic HIV are also called R5 viruses since they adsorb to the chemokine receptor CCR5.) M-tropic HIV require only low levels of CD4 molecules expressed on the surface of the host cell for infection. M-tropic HIV are thought to spread the infection. These strains appear to be slower-replicating and less virulent than the later T-tropic strains and do not cause the formation of syncytias. HIV initially replicates to high levels within macrophages without destroying them. (The T-tropic HIV, found later in HIV infection, are faster-replicating, more virulent, and lead to syncytia formation.)

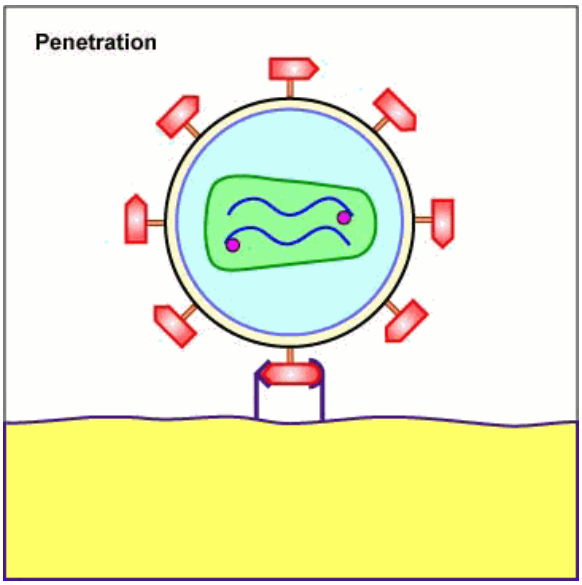
As time goes by, mutation in the gene coding for gp120 enables some of the HIV to become dual tropic and able to infect both macrophages via the CCR5 chemokine receptor found on these cells, and T4-lymphocytes via the CCR5 and CXCR4 chemokine receptors found on these cells. (Duel-tropic HIV are also called R5X4 viruses since they adsorb to both the chemokine receptors CCR5 and CXCR4.)

Later during the course of HIV infection, most of the viruses have mutated their gp120 to become T- tropic (see Figure 10.6C.2) and infect primarily mature dendritic cells and T4-lymphocytes by way of CD4 and the CXCR4 co-receptors found on these cells. (T-tropic HIV are also called X4 viruses since they adsorb to the chemokine receptor CXCR4.) T-tropic HIV require high levels of CD4 molecules expressed on the surface of the host cell for infection. As mentioned, these T-tropic strains of HIV are faster-replicating and more virulent, and cause formation of syncytias and begin the cycles of T4-lymphocyte destruction.

HIV infecting microglia cells in the brain appear to bind to a CD4 molecule and a chemokine receptor called CCR3 found on these macrophage-like cells.

2. Viral Entry into the Host Cell

As mentioned above under adsorption, the binding of a portion or domain of the HIV surface glycoprotein gp120 to a CD4 molecule on the host cell induces a change in shape that brings the chemokine receptor binding domains of the gp120 into proximity with the host cell chemokine receptor. This, in turn, brings about a conformational change that exposes a previously buried portion of the transmembrane glycoprotein gp41 enabling the viral envelope to fuse with the host cell membrane (see Figure 10.6C.5 and Figure 10.6C.6). After fusion of the viral envelope with the host cell cytoplasmic membrane, the genome-containing protein core of the virus enters the host cell's cytoplasm. (Occasionally the virus enters by endocytosis, after which the viral envelope fuses with the endocytic vesicle releasing the genome-containing core into the cytoplasm.)



Animation: Penetration of HIV into Host Cell. The binding of a portion or domain of the HIV surface glycoprotein gp120 to a CD4 molecule on the host cell induces a change in shape that brings the chemokine receptor binding domains of the gp120 into proximity with the host cell chemokine receptor. This, in turn, brings about a conformational change that exposes a previously buried portion of the transmembrane glycoprotein gp41 enabling the viral envelope to fuse with the host cell membrane. After fusion of the viral envelope with the host cell cytoplasmic membrane, the genome-containing protein core of the virus enters the host cell's cytoplasm.

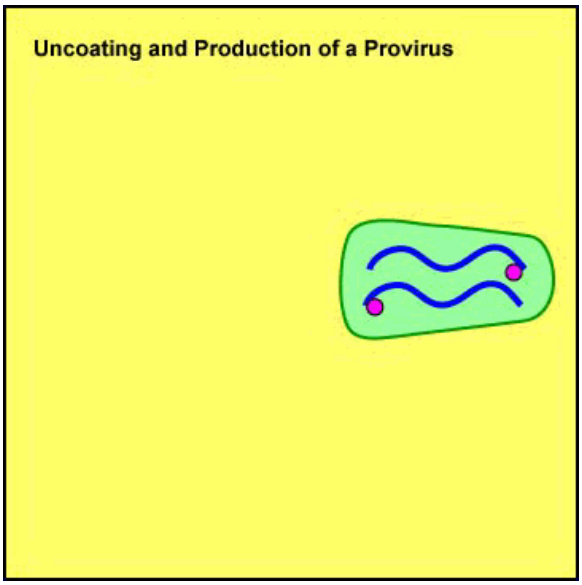
3. Viral Movement to the Site of Replication within the Host Cell and Production of a Provirus

During uncoating, the single-stranded RNA genomes within the core or capsid of the virus are released into the cytoplasm. HIV now uses the enzyme *reverse transcriptase*, associated with the viral RNA genome, to make a DNA copy of the RNA genome. (Normal transcription in nature is when the DNA genome is transcribed into mRNA which is then translated into protein. In HIV reverse transcription, RNA is reverse-transcribed into DNA.)

Reverse transcriptase has three enzyme activities:

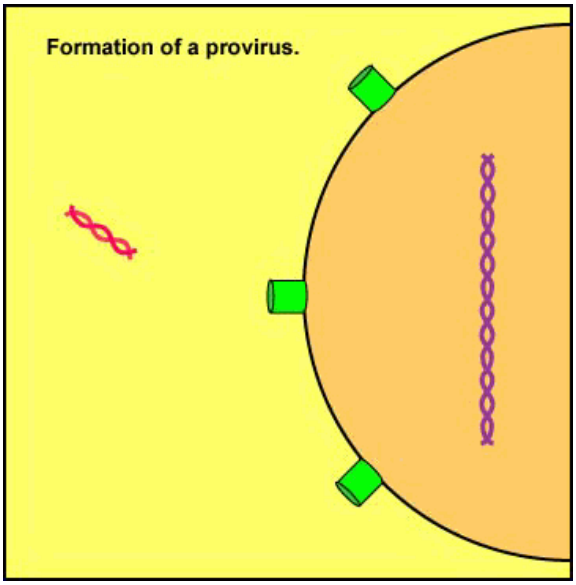
a. It has RNA-dependent DNA polymerase activity that copies the viral (+) RNA into a (-) viral complementary DNA (cDNA);
b. It has ribonuclease activity that degrades the viral RNA during the synthesis of cDNA; and
c. It has DNA-dependent DNA polymerase activity that copies the (-) cDNA strand into a (+) DNA to form a double-stranded DNA intermediate.

As the cDNA is being synthesized off of the RNA template the ribonuclease activity degrades the viral RNA genome (see Figure $10.6C.7$A, Figure $10.6C.7$B, and Figure $10.6C.7$C). The reverse transcriptase then makes a complementary DNA strand to form a double-stranded viral DNA intermediate (see Figure $10.6C.7$D).



Animation: HIV Copying RNA into DNA with Reverse Transcriptase. The single-stranded RNA genomes are released from the capsid. HIV uses the enzyme reverse transcriptase to transcribe its RNA genome into single-stranded DNA. As the DNA is being made, the RNA genome is degraded by an RNase. The reverse transcriptase then synthesizes a complementary DNA strand to produce a double-stranded DNA intermediate that enters the infected host cell's nucleus.

A viral enzyme called integrase then binds to the double-stranded viral DNA intermediate, transports it through the pores of the host cell's nuclear membrane, and inserts into one of the host cell's chromosomes to form a provirus (see Figure $10.6C.8$A and Figure $10.6C.8$B).



Animation: Formation of a Provirus. An HIV enzyme called integrase is used to insert the HIV double-stranded DNA intermediate into the DNA of a host cell's chromosome. HIV is now a provirus.

After integration, the HIV proviral DNA can exist in either a latent or productive state, which is determined by genetic factors of the viral strain, the type of cell infected, and the production of specific host cell proteins.

The majority of the proviral DNA is integrated into the chromosomes of activated T4-lymphocytes. These generally comprise between 93% and 95% of infected cells and are productively infected, not latently infected. However, a small percentage of HIV-infected memory T4-lymphocytes persists in a resting state because of a latent provirus. These, along with infected monocytes, macrophages, and dendritic cells, provide stable reservoirs of HIV capable of escaping host defenses and antiretroviral

chemotherapy.

4. Replication of HIV within the Host Cell

The vast majority of T4-lymphocytes, which are productively infected, immediately begin producing new viruses. In the case of the small percentage of infected, resting memory T4-lymphocytes, before replication can occur, the HIV provirus must become activated. This is accomplished by such means as antigenic stimulation of the infected T4-lymphocytes or their activation by factors such as cytokines, endotoxins, and superantigens.

Following activation of the provirus, molecules of (+) mRNA are transcribed off of the (-) proviral DNA strand by the enzyme RNA polymerase II. Once synthesized,HIV mRNA goes through the nuclear pores into the rough endoplasmic reticulum to the host cell's ribosomes where it is translated into HIV structural proteins, enzymes, glycoproteins, and regulatory proteins(see Figure 10.6C.3).

A 9 kilobase mRNA is formed that is used for three viral functions:

a. Synthesis of Gag polyproteins (p55). These polyproteins will eventually be cleaved by HIV proteases to become HIV matrix proteins (MA; p17), capsid proteins (CA; p24), and nucleocapsid proteins (NC, p7). See Figure 10.6C.9A and Figure 10.6C.9B.

b. Synthesis of Gag-Pol polyproteins (p160). These polyproteins will eventually be cleaved by HIV proteases to become HIV matrix proteins (MA; p17), capsid proteins (CA; p24), proteinase molecules (protease or PR; p10), reverse transcriptase molecules (RT; p66/p51), and integrase molecules (IN; p32). See Figure 10.6C.9C and Figure 10.6C.9D.

c. During maturation, these RNA molecules also become the genomes of new HIV virions.

The 9kb mRNA can also be spliced to form a 4kb mRNA and a 2kb mRNA.

The 4kb mRNA is used to:

a. Synthesize the Env polyproteins (gp160). These polyproteins will eventually be cleaved by proteases to become HIV envelope glycoproteins gp120 and gp41. See Figure 10.6C.9E and Figure 10.6C.9F.

b. Synthesize 3 regulatory proteins called *vif, vpr*, and *vpu*.

The 2kb mRNA is used to synthesize 3 regulatory proteins known as *tat, rev*, and *naf*.

GIF Animation showing translation of HIV mRNA.

For More Information: Transcription from Unit 7

For More Information: Translation from Unit 76

5. Viral Assembly or Maturation within the Host Cell and Release from the Host Cell

Assembly of HIV virions begins at the plasma membrane of the host cell. Maturation occurs either during the budding of the virion from the host cell or after its release from the cell.

- Transmission electron micrograph of HIV budding from a T4-lymphocyte; courtesy of Dennis Kunkel's Microscopy.

Prior to budding, the Env polyprotein (gp160) goes through the endoplasmic reticulum and is transported to the Golgi complex where it is cleaved by a protease (proteinase) and processed into the two HIV envelope glycoproteins gp41 and gp120. These are transported to the plasma membrane of the host cell where gp41 anchors the gp120 to the membrane of the infected cell. See Figure 10.6C.10A, Figure 10.6C.10B, Figure 10.6C.10C, and Figure 10.6C.10D.

GIF animation showing maturation of gp41 and gp120.

The Gag (p55) and Gag-Pol (p160) polyproteins also associate with the inner surface of the plasma membrane along with the HIV genomic RNA as the forming virion begins to bud from the host cell.

During maturation, HIV proteases (proteinases) will cleave the remaining polyproteins into individual functional HIV proteins and enzymes such as matrix proteins (MA; p17), capsid proteins (CA; p24), reverse transcriptase molecules (RT; p66/p51), and integrase molecules (IN; p32).. See Figure 10.6C.10E, Figure 10.6C.10F, Figure 10.6C.10G, and Figure 10.6C.10H.

a. The Gag polyproteins (p55) will be cleaved by HIV proteases to become HIV matrix proteins (MA; p17), capsid proteins (CA; p24), and nucleocapsid proteins (NC, p7 and p6).

b. The Gag-Pol polyproteins (p160) will be cleaved by HIV proteases to become HIV matrix proteins (MA; p17), capsid proteins (CA; p24), proteinase molecules (protease or PR; p10), reverse transcriptase molecules (RT; p66/p51), and integrase molecules (IN; p32).

The various structural components then assemble to produce a mature HIV virion.

GIF animation showing maturation of of HIV.

6. Reinfection

Free viruses now infect new susceptible body cells. HIV can also be transmitted by cell-to-cell contact. This can occur when an infected cell with gp120 on its cytoplasmic membrane attaches to CD4 molecules and chemokine receptors on the surface of an uninfected cell. The cells then fuse (see Figure 10.6C.11 and Figure 10.6C.12).

Excellent Animation Summarizing the Life Cycle of HIV

Courtesy of HHMI's Biointeractive.

YouTube Animation Illustrating Reproduction of HIV.
Courtesy of 3D Medical Animations Library, Dr. Rufus Rajadurai

Exercise: Think-Pair-Share Questions

1. State the role(s) of gp120 and gp41 in the life cycle of HIV.
2. Why does HIV primarily infect T4-lymphocytes, macrophages, and dendritic cells?
3. How do antiretroviral drugs that bind to HIV-encoded protease help to reduce the number of HIV in the body.
4. If one could destroy all of the infected white blood cells in a person infected with HIV and then reconstitute the cells by giving a bone marrow transplant from a person homozygous for a deletion mutation in their gene coding for the chemokine receptor CCR5 (he or she can not make CCR5 molecules), describe how this might prevent HIV infection in the person receiving the transplant.

Concept Map for Life Cycle of HIV

Medscape article on infections associated with organisms mentioned in this Learning Object. Registration to access this website is free.

- HIV Infection and AIDS

Summary

1. During adsorption, an envelope glycoprotein on the surface of HIV called gp120 must adsorbs to both a CD4 molecule and then a chemokine receptor found on the surface of only certain types of certain human cells such as T4-lymphocytes, monocytes, macrophages, and dendritic cells.
2. Following adsorption, glycoprotein gp41 enabling the viral envelope to fuse with the host cell membrane, allowing the nucleocapsid of the virus enters the host cell's cytoplasm.
3. During uncoating, the single-stranded RNA genomes within the capsid of the virus are released into the cytoplasm and HIV now uses the enzyme reverse transcriptase to make a single-stranded DNA copy of its single-stranded RNA genome. The reverse transcriptase then makes a complementary DNA strand to form a double-stranded viral DNA intermediate.
4. A viral enzyme called integrase then binds to the double-stranded viral DNA intermediate, transports it through the pores of the host cell's nuclear membrane, and inserts into one of the host cell's chromosomes to form a provirus.
5. Following activation of the provirus, molecules of mostly polycistronic mRNA are transcribed off of the proviral DNA strand, go through the nuclear pores into the rough endoplasmic reticulum where it is translated by host cell's ribosomes HIV structural proteins, enzymes, glycoproteins, and regulatory proteins.
6. Polyproteins translated from polycistronic mRNAs must be cleaved into function proteins by HIV protease enzymes.
7. The two HIV envelope glycoproteins gp41 and gp120 are transported to the plasma membrane of the host cell where gp41 anchors the gp120 to the membrane of the infected cell. HIV obtains its envelope from the plasma membrane by budding.
8. Most maturation occurs either during the budding of the virion from the host cell or after its release from the cell.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe how the retrovirus HIV-1 accomplishes each of the following steps during its life cycle. (Include the following key words in your description: gp120, CD4, chemokine receptors, gp41, capsid, RNA genome, reverse transcriptase, double-stranded DNA intermediate, provirus, polyproteins, proteases, and budding.)
   A. viral attachment or adsorption to the host cell *(ans)*
   B. viral entry into the host cell *(ans)*
   C. viral movement to the site of replication within the host cell and production of a provirus. *(ans)*
   D. viral replication within the host cell *(ans)*
   E. viral assembly or maturation within the host cell and release from the host cell *(ans)*
2. Name 3 types of cells HIV primarily infects and briefly explain why. *(ans)*
3. HIV possesses a genome of RNA. How then is HIV able to insert into the DNA of host cells and form a provirus? *(ans)*
4. Multiple Choice *(ans)*

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10.6D: Natural History of a Typical HIV Infection

State the median incubation period for AIDS and, in terms of viral load, exhaustion of the lymphopoietic system, and immune responses, briefly describe what marks the progression to AIDS.

- Briefly describe the following:

  a. early or acute HIV infection
  b. chronic HIV infection
  c. AIDS

According to WHO estimates from 2004, HIV has now infected 50 to 60 million people worldwide. The virus has killed over 22 million children adults and has left 14 million children orphaned. Worldwide, over 42 million people are currently living with HIV infection/AIDS - approximately 70% of these live in Africa, 20% in Asia. Around 3 million people die each year of AIDS and it is estimated that each day 14,000 people in the world become newly infected with HIV.

The median incubation period for AIDS is around 10 years. During early or acute HIV infection the virus primarily infects and destroys memory T4-lymphocytes which express the chemokine receptor CCR5 and are very abundant in mucosal lymphoid tissues. Here HIV also encounters the dendritic cells located throughout the epithelium of the skin and the mucous membranes where in their immature form called Langerhans cells they are attached by long cytoplasmic processes. The envelope glycoproteins gp41 and gp120 of HIV contain mannose-rich glycans that bind to mannan-binding proteins (pattern recognition receptors; also called lectin receptors) on the dendritic cells.

Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by pro-inflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, the dendritic cells have matured and are now able to present antigens of HIV to naive T-lymphocytes located in the the lymph nodes in order to induce adaptive immune responses.

At this point the infection has transitioned from the acute phase to the chronic phase. The chronic phase of HIV infection is characterized by viral dissemination, viremia, and induction of adaptive immune responses. The viremia allows the viruses to spread and infect T4-helper lymphocytes, macrophages, and dendritic cells found in peripheral lymphoid tissues.

During the chronic phase of HIV infection, the lymph nodes and the spleen become sites for continuous viral replication and host cell destruction. During most of this phase, the immune system remains active and competent and there are few clinical symptoms. A steady state-infection generally persists where T4-lymphocyte death and T4-lymphocyte replacement by the body are in equilibrium. In a person infected with HIV, somewhere between one and two billion of these T4-cells die each day as a result of HIV infection and must be replaced by the body's lymphopoietic system in the bone marrow. It is estimated that 10 billion virions are produced and cleared in an infected individual each day. However, the enormous turnover of T4-lymphocytes eventually exhausts the lymphopoietic system and it becomes unable to replace the T4-cells being destroyed. A variety of mechanisms then eventually lead to immunodeficiency.

Mechanisms of HIV-induced immunodeficiency include:

- Direct HIV-induced cytopathic effect on infected T4-lymphocytes. This can occur through:
  - Increased cell permeability as a result of gp41 expression in the host cell membrane and viral release by budding;
  - Inhibition of host cell protein synthesis as a result of viral replication within the infected cell; and
  - Fusion of infected T4-cells with numerous uninfected T4-cells resulting in syncytia formation.
- Killing of HIV-infected T4-cells by cytotoxic T-lymphocytes or CTLs.
- Killing of HIV-infected T4-cells by antibody-dependent cytotoxicity or ADCC.
- Apoptosis of T4-cells as a result of chronic activation by HIV and by cytokines.
- Shedding of gp120 molecules by HIV. This subsequently triggers a series of events that cause the adaptive immune system to become less and less effective, primarily by altering the normal balance of immunoregulatory T_H1 and T_H2 cells in the body.
- Impaired function of HIV infected macrophages and dendritic cells.

These mechanisms will be discussed in greater detail in Unit 5 under secondary immunodeficiency.

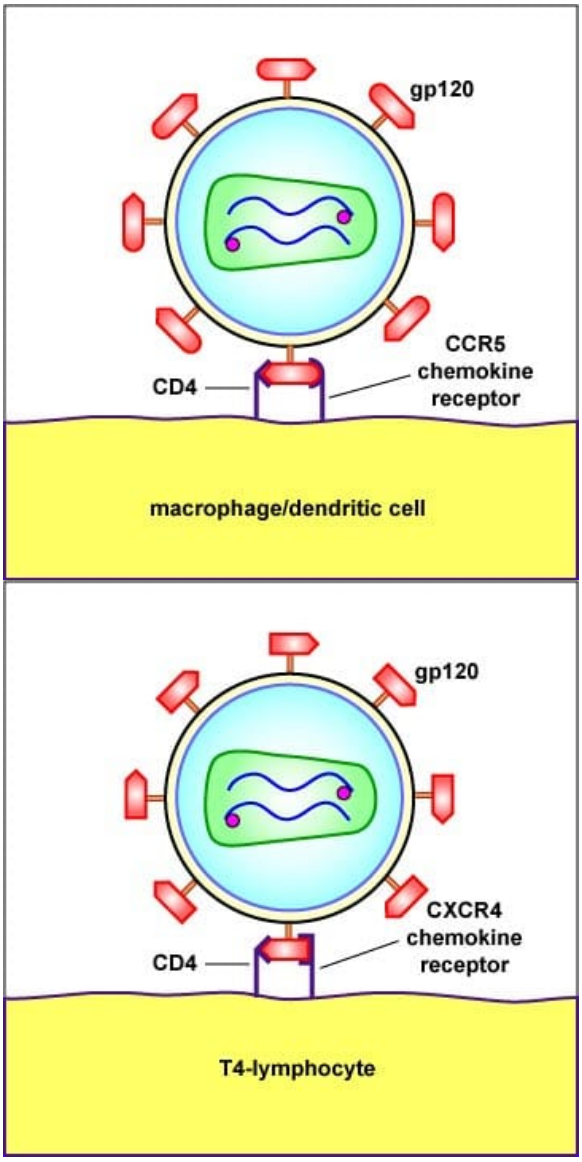


Figure 10.6D.2: Affinity of HIV for Different Immune Cells. (left) In early phase HIV infection, initial viruses are M-tropic. Their envelope glycoprotein gp120 is able to bind to CD4 molecules and chemokine receptors called CCR5 found on macrophages. (right) In late phase HIV infection, most of the viruses are T-tropic, having gp120 capable of binding to CD4 and CXCR4 found on T4-lymphocytes.

Progression to AIDS is marked by a viral load that progressively increases in number while the immune system weakens as a result of the destruction of increasing numbers of T4-lymphocytes and the inability of the body to continually replace these destroyed cells. As will be seen in Unit 5, the loss of T4-helper lymphocytes leads to a marked decline in cells called cytotoxic T-lymphocytes (CTLs), the primary cells the body's immune responses use to destroy virus-infected cells. Once a person progresses to full-blown AIDS he or she becomes susceptible to a variety of opportunistic infections by:

- bacteria such as *Mycobacterium avium* complex (MAC), *Salmonella*, and *Nocardia*;
- protozoa such as *Cryptosporidium* and *Toxoplasma*;
- viruses such as cytomegalovirus (CMV), herpes simplex viruses types 1 and 2 (HSV-1, HSV-2), and varicella zoster virus (VZV);
- *Candida, Cryptococcus, Coccidioides, Histoplasma*, and *Pneumocystis*.

There is also an increased incidence of tumors, such Epstein-Barr virus-associated B-cell lymphomas, other lymphomas, cervical cancer, and Kaposi's sarcoma. Wasting syndrome and encephalopathy are also common.

Why do you think the incubation period between HIV infection and AIDS has typically been 10 years or more?

Highly active anti-retroviral therapy (HAART) with a combination of reverse transcriptase inhibitors and protease inhibitors, as will be discussed later in Unit 4 under "Control of Viruses," has had relatively good success in both improving T4-lymphocyte levels and reducing the levels of HIV in the body - sometimes to undetectable levels. However, even with undetected levels of HIV, most infected persons continue to harbor relatively small amounts of replication-competent HIV, most likely in the resting T4-memory cells produced as a normal part of the immune responses. These infected T4-memory cells probably persist for years after antiretroviral therapy has reduced viral load below the limit of laboratory detection and could represent a pool that can keep HIV infection going or reactivate the infection. Macrophages and dendritic cells may also serve as a reservoir for HIV.

Summary

1. The median incubation period for AIDS is around 10 years.
2. During early or acute HIV infection the virus primarily infects and destroys memory T4-lymphocytes which express the chemokine receptor CCR5 and are very abundant in mucosal lymphoid tissues. Here HIV also encounters the dendritic cellslocated throughout the epithelium of the skin and the mucous membranes.
3. The dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes where they are now able to present antigens of HIV to naive T-lymphocytes in order toinduce adaptive immune responses.
4. The virus transitions from the acute phase to the chronic phase characterized by viral dissemination, viremia, and induction of adaptive immune responses.
5. The viremia allows the viruses to spread and infect T4-helper lymphocytes, macrophages, and dendritic cells found in peripheral lymphoid tissues.
6. During the chronic phase of HIV infection, the lymph nodes and the spleen become sites for continuous viral replication and host cell destruction whereby a steady state-infection generally persists where T4-lymphocyte death and T4-lymphocyte replacement by the body are in equilibrium.
7. The enormous turnover of T4-lymphocytes eventually exhausts the lymphopoietic system and it becomes unable to replace the T4-cells being destroyed eventually leading to immunodeficiency.
8. Progression to AIDS is marked by a viral load that progressively increases in number while the immune system weakens as a result of the destruction of increasing numbers of T4-lymphocytes and the inability of the body to continually replace these destroyed cells.
9. As a result of immunosuppression, the person becomes susceptible to a variety of opportunistic infections and secondary cancers.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State the median incubation period for AIDS. *(ans)*
2. In terms of viral load, exhaustion of the lymphopoietic system, and immune responses, briefly describe what marks the progression to AIDS. (ans)
3. Briefly describe the following:
   a. early or acute HIV infection *(ans)*
   b. chronic HIV infection *(ans)*
4. Multiple Choice *(ans)*

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10.6E: The Role of Viruses in Tumor Production

Describe how certain viruses may contribute to the development of tumors by altering proto-oncogenes or tumor-suppressor genes.

- Name 3 viruses that have been implicated in human cancers.

Some viruses can also play a role in converting normal host cells into tumor cells. These viruses are capable of viral transformation, that is, they transform normal cells into malignant cells. In fact, five viruses, hepatitis B virus (HBV), hepatitis C virus (HCV), human papilloma virus (HPV), Epstein-Barr virus (EBV), and human T-lymphotropic virus type I (HTLV-I) are thought to contribute to over 15% of the world's cancers. Up to 80% of these human viral-associated cancers are cervical cancer (associated with HPV) and liver cancer (associated with HBV and HCV).

The hepatitis B virus (HBV) is a DNA virus that may potentially cause chronic hepatitis in those infected. There is a strong link between chronic infection with HBV and hepatocellular carcinoma, which typically appears after 30-50 years of chronic liver damage and liver cell replacement. Chronic carriers of HBV have a 300 times greater risk of eventually developing liver cancer. Around 90% of individuals infected at birth and 10% of individuals infected as adults become chronic carriers of HBV. There are about one million chronic carriers of HBV in the US. Worldwide, HBV is responsible for 60% of all liver cancer cases.

The hepatitis C virus (HCV) is a RNA virus that may also cause chronic hepatitis in those infected. As with HBV, there is a strong link between chronic infection with HCV and liver cancer, typically appearing after 30-50 years of chronic liver damage and liver cell replacement. Around 85% of individuals infected with HCV become chronic carriers and there are approximately four million chronic carriers of HCV in the US. Worldwide, HCV is responsible for 22 % of all liver cancer cases.

The human papilloma viruses (HPV) are responsible for warts. While warts are generally considered as benign tumors, some sexually-transmitted strains of HPV (HPV-16 and 18 are definitely carcinogenic in humans; HPV-31 and 33 are probably carcinogenic), have been implicated in cervical and vulvar cancer, rectal cancer, and squamous cell carcinoma of the penis. In these tumor cells the viral DNA is usually found integrated in host cell chromosomes. In the US, HPVs are associated with 82% of the deaths due to cervical cancer each year, as well as a million precancerous lesions.

The Epstein-Barr virus (EBV), a herpes virus, normally causes benign proliferations such as infectious mononucleosis and hairy leukoplakia of the tongue. However, it can contribute to non-Hodgkin's lymphoma in AIDS patients and post-transplantation lymphoproliferative diseases, appears to be an essential factor for posterior nasopharyngeal cancer in some individuals, can be a co-factor for Burkitt's lymphoma, and contributes to smooth-muscle tumors in immunosuppressed children.

The retrovirus human T-lymphotropic virus type I (HTLV-I) can induce a rare adult T-lymphocyte leukemia-lymphoma.

The development of tumors is a multistep process depending on the accumulation of mutations altering a number of genes. The altered genes then function collectively to cause malignant growth.

Proliferation of normal cells is regulated by growth-promoting proto-oncogenes and counterbalanced by growth-restricting tumor suppressor genes. Mutations that increase the activities of proto-oncogenes to create oncogenes and/or decrease the activities of tumor suppressor genes can lead to growth of tumors. It is now known that many tumors require both activation of oncogenes from proto-oncogenes and inactivation of tumor suppressor genes for their development.

Viruses are thought to play a role in cancer development both indirectly and directly. Indirectly, the viruses may induce immunosuppression so that cancer cells are not removed by immune responses, as in the case of HIV/AIDS, or they may cause long term damage to tissues resulting in large scale cell regeneration which increases the chances of natural mutation in proto-oncogenes and tumor suppressor genes, as in the case of HBV and HCV. Directly, by integrating into the host cell's chromosomes, some viruses may alter the normal function of the proto-oncogenes and tumor suppressor genes, as is seen with HPV and HBV.

However, most virus-associated cancers have long latency periods of several decades and only a small percentage of the people infected with the virus actually develop the cancer. This indicates other factors promoting changes in cellular genes are also involved. For example, in the case of cervical cancer and HPV, two variants of a tumor suppressor gene known as *p53* are known. One form of the *p53* gene produces a suppressor protein that is much more susceptible to degradation by an oncoprotein

called E6 which is produced by carcinogenic strains of HPV.

Name the three most common viruses associated with cancer in the US and state the cancers with which they are associated.

Summary

1. Viruses are responsible for about 15% of the world's cancers.
2. Up to 80% of these human viral-associated cancers are cervical cancer (associated with human papilloma virus or HPV) and liver cancer (associated with the hepatitis B virus or HBV and the hepatitis C virus or HCV).
3. The Epstein-Barr virus (EBV) and human T-lymphotropic virus type I (HTLV-I) also increase the risk of certain cancers.
4. The development of tumors is a multistep process depending on the accumulation of mutations altering a number of genes.
5. Most virus-associated cancers have long latency periods of several decades and only a small percentage of the people infected with the virus actually develop the cancer. This indicates other factors promoting changes in cellular genes are also involved.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe how certain viruses may contribute to the development of tumors by altering proto-oncogenes or tumor-suppressor genes. (ans)
2. Name 3 viruses that have been implicated in human cancers.
   A. *(ans)*
   B. *(ans)*
   C. *(ans)*
3. People with chronic hepatitis B have a much higher risk of developing liver cancer. This cancer, however, usually appears after decades of chronic infection. Explain the link between HBV and liver cancer and why, if it does develop, it usually takes so long. *(ans)*
4. Multiple Choice *(ans)*

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10.7: BACTERIOPHAGE LIFE CYCLES: AN OVERVIEW

Name the 2 types of bacteriophage life cycles and state what the bacteriophage capable of each is called.

As mentioned in an earlier section, bacteriophages are viruses that only infect bacteria (also see Figure 10.7.1C and Figure 10.7.2 E). There are two primary types of bacteriophages: lytic bacteriophages and temperate bacteriophages. Bacteriophages that replicate through the lytic life cycle are called **lytic bacteriophages**, and are so named because they lyse the host bacterium as a normal part of their life cycle. Bacteriophages capable of a lysogenic life cycle are termed **temperate phages**. When a temperate phage infects a bacterium, it can either replicate by means of the lytic life cycleand cause lysis of the host bacterium, or, it can incorporate its DNA into the bacterium's DNAand become a noninfectious prophage. We will now look at the lytic life cycle and lysogenic life cycle of bacteriophages.

- Topic hierarchy

10.7A: The Lytic Life Cycle of Bacteriophages

10.7B: The Lysogenic Life Cycle of Bacteriophages

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Summary

1. Bacteriophages are viruses that only infect bacteria.
2. Bacteriophages that replicate through the lytic life cycle are called lytic bacteriophages, and are so named because they lyse the host bacterium as a normal part of their life cycle.
3. Bacteriophages capable of a lysogenic life cycle are termed temperate phages. and can either replicate by means of the lytic life cycle and cause lysis of the host bacterium, or, can incorporate their DNA into the bacterium's DNA and become a non-infectious prophage.

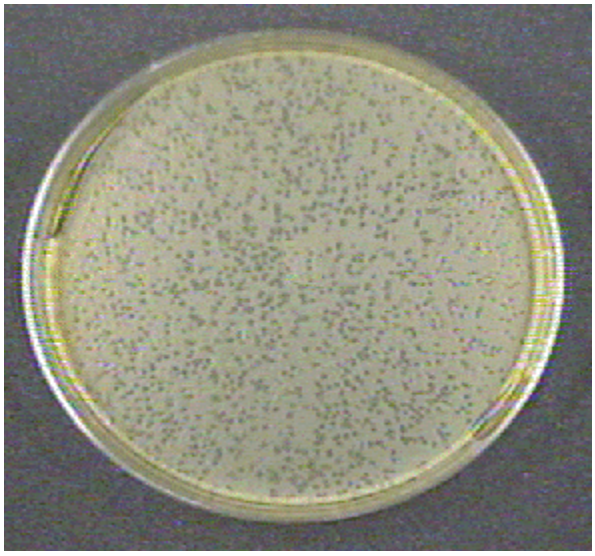
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10.7A: The Lytic Life Cycle of Bacteriophages

Learning Objectives

1. Describe the steps involved in the lytic life cycle of bacteriophages.
2. Define the following:
   a. lytic bacteriophage
   b. eclipse period

As mentioned in an earlier section, bacteriophages are viruses that only infect bacteria (see Figure 10.7A.1C and Figure 10.7A.2 E). Bacteriophages that replicate through the lytic life cycle are called lytic bacteriophages. After infecting bacteria with lytic bacteriophages in the lab, plaques can be seen on the petri plates. Plaques are small clear areas on the agar surface where the host bacteria have been lysed by lytic bacteriophages. The lytic life cycle is somewhat similar to the productive life cycle of animal viruses and consists of the following steps:



Plaques on an agar surface after infecting Escherichia coli with Coliphage T-4

Step 1: Adsorption

Attachment sites on the bacteriophage adsorb to receptor sites on the host bacterium (see Figure 10.7A.1). Most bacteriophages adsorb to the bacterial cell wall, although some are able to adsorb to flagella or pili. Specific strains of bacteriophages can only adsorb to specific strain of host bacteria. This is known as viral specificity.

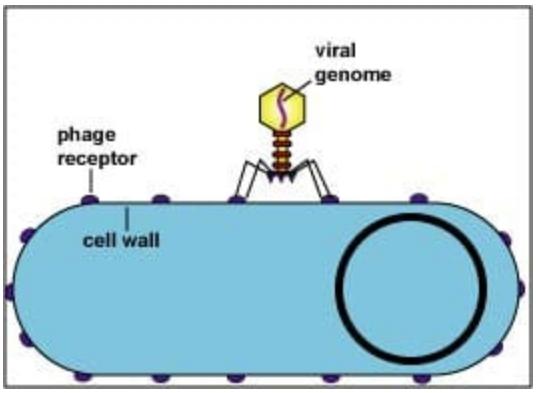


Figure 10.7A.1: Adsorption during the Lytic Life Cycle of a Lytic Bacteriophage. The bacteriophage binds to receptors on the bacterial cell wall.

Step 2: Penetration

In the case of bacteriophages that adsorb to the bacterial cell wall, a bacteriophage enzyme "drills" a hole in the bacterial wall and the bacteriophage injects its genome into the bacterial cytoplasm (Figure 10.7A.2). Some bacteriophages accomplish this by contracting a sheath which drives a hollow tube into the bacterium. This begins the eclipse period. The genomes of bacteriophages which adsorb to flagella or pili enter through these hollow organelles. In either case, only the phage genome enters the bacterium so there is no uncoating stage.

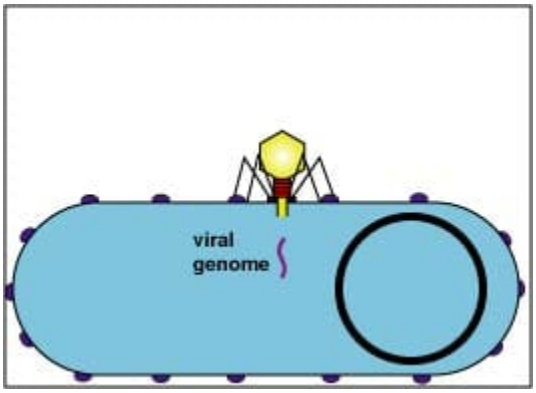


Figure 10.7A.2: Penetration during the Lytic Life Cycle of a Lytic Bacteriophage. The bacteriophage injects its genome into the cytoplasm of the bacterium.

Step 3: Replication

Enzymes coded by the bacteriophage genome shut down the bacterium's macromolecular (protein, RNA, DNA) synthesis. The bacteriophage replicates its genome and uses the bacterium's metabolic machinery to synthesize bacteriophage enzymes and bacteriophage structural components (Figure 10.7A.3 and Figure 10.7A.4).

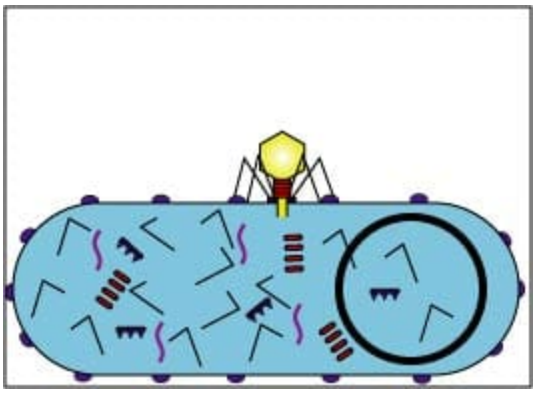


Figure $10.7A.4$: Late Replication during the Lytic Life Cycle of a Lytic Bacteriophage. The production of bacteriophage components and enzymes progresses.

Step 4: Maturation

The phage parts assemble around the genomes (Figure $10.7A.5$).

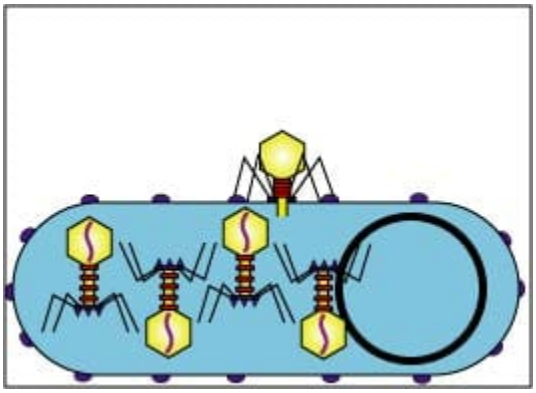


Figure $10.7A.5$: Maturation during the Lytic Life Cycle of a Lytic Bacteriophage. The bacteriophage components assemble.

Step 5: Release

Usually, a bacteriophage-coded lysozyme breaks down the bacterial peptidoglycan causing osmotic lysis and release of the intact bacteriophages (Figure $10.7A.6$).

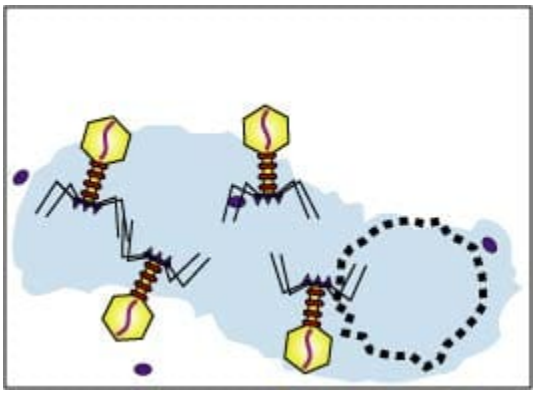
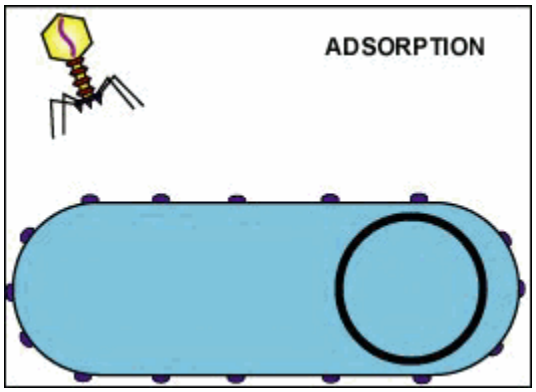


Figure $10.7A.6$: Release during the Lytic Life Cycle of a Lytic Bacteriophage. A bacteriophage-coded enzyme breaks down the peptidoglycan in the bacterial cell wall causing osmotic lysis.

Step 6: Reinfection

From 50 to 200 bacteriophages may be produced per infected bacterium.



Adsorption of a Bacteriophage to the Cell Wall of the Bacterium. Attachment sites on the virus bind to corresponding receptors on the host cell wall.

Exercise: Think-Pair-Share Questions

1. Describe how a lytic bacteriophage might possibly play a role in horizontal gene transfer in bacteria.
2. As will be seen in lab, phage typing is a technique wherein unknown strains of a bacterium are identified by using known strains of bacteriophages. How can we use a bacteriophage to identify a bacterium?
3. We saw in the previous section that a single infected animal cell may produce 10,000-50,000 viruses yet an infected bacterium can only produce 50-200 bacteriophages. Explain this.

Concept Map for the Lytic Life Cycle of Bacteriophages

Summary

1. Bacteriophages that replicate through the lytic life cycle are called lytic bacteriophages,
2. Adsorption is the attachment sites on the phage adsorb to receptor sites on the host bacterium.
3. Specific strains of bacteriophages can only adsorb to specific strain of host bacteria (viral specificity).
4. In the case of bacteriophages that adsorb to the bacterial cell wall, a bacteriophage enzyme "drills" a hole in the bacterial wall and the bacteriophage injects its genome into the bacterial cytoplasm.
5. The bacteriophage replicates its genome and uses the bacterium's metabolic machinery to synthesize bacteriophage enzymes and bacteriophage structural components.
6. During maturation, the bacteriophage parts assemble around the phage genomes.
7. A phage-coded lysozyme breaks down the bacterial peptidoglycan causing osmotic lysis and release of the intact bacteriophages.

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10.7B: The Lysogenic Life Cycle of Bacteriophages

Describe the lysogenic life cycle of temperate phages (including spontaneous induction).

- Define the following:

  a. temperate phage
  b. lysogen
  c. prophage

Bacteriophages capable of a lysogenic life cycle are termed temperate bacteriophages. When a temperate bacteriophage infects a bacterium, it can either replicate by means of the lytic life cycle and cause lysis of the host bacterium, or, it can incorporate its DNA into the bacterium's DNA and become a noninfectious prophage (see Figure 10.7B.1). In the latter case, the cycle begins by the bacteriophage adsorbing to the host bacterium or lysogen and injecting its genome as in the lytic life cycle (see Figure 10.7B.2 and Figure 10.7B.3). However, the bacteriophage does not shut down the host cell. Instead, the bacteriophage DNA inserts or integrates into the host bacterium's DNA (see Figure 10.7B.4). At this stage the virus is called a prophage. Expression of the bacteriophage genes controlling bacteriophage replication is blocked by a repressor protein, and the phage DNA replicates as a part of the bacterium's DNA so that every daughter bacterium now contains the prophage (see Figure 10.7B.5).

Flash animation showing adsorption of a temperate bacteriophage.

html5 version of animation for iPad showing adsorption of a temperate bacteriophage.

Flash animation showing penetration of a temperate bacteriophage.

html5 version of animation for iPad showing penetration of a temperate bacteriophage.

Flash animation showing prophage formation.

html5 version of animation for iPad showing prophage formation.

The number of viruses infecting the bacterium as well as the physiological state of the bacterium appear to determine whether the temperate bacteriophage enters the lytic cycle or becomes a prophage.

In about one out of every million to one out of every billion bacteria containing a prophage, spontaneous induction occurs. The bacteriophage genes are activated and new bacteriophages are produced by the lytic life cycle (see Figure 10.7B.5A, Figure 10.7B.6, Figure 10.7B.7, Figure 10.7B.8, and Figure 10.7B.9).

Flash animation showing spontaneous induction.

html5 version of animation for iPad showing spontaneous induction.

Flash animation showing replication of a temperate bacteriophage.

html5 version of animation for iPad showing replication of a temperate bacteriophage.

Flash animation showing maturation of a temperate bacteriophage.

html5 version of animation for iPad showing maturation of a temperate bacteriophage.

Flash animation showing release of a temperate bacteriophage.

html5 version of animation for iPad showing release of a temperate bacteriophage.

Name a human viral infection that has a life cycle equivalent to the lysogenic life cycle of bacteriophages.

Flash animation summarizing the lysogenic life cycle of a temperate bacteriophage.

GIF Animation summarizing the lysogenic life cycle of a temperate bacteriophage.

Concept Map for the Lysogenic Life Cycle of Bacteriophages

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10.8: Pathogenicity of Animal Viruses

Briefly describe at least 4 ways viruses can damage infected host cells.

- Briefly describe at least 3 different ways viruses can evade host immune defenses.

Animal viruses may cause cytopathic effect or CPE that damages infected host cells in a variety of means, including:

1. Inhibiting normal host cell DNA, RNA, or protein synthesis. This can cause structural or functional defects in the infected host cell leading to cytolysis or altered cell functions.
2. Causing nicks or breaks in the host cell's chromosomes, as seen in congenital rubella syndrome.
3. Viral proteins and glycoproteins changing the antigenic surface of the host cell's cytoplasmic membrane resulting in its being recognized as foreign and destroyed by the body's immune defenses (see Figure 10.8.9, Figure 10.8.10, Figure 10.8.11A and Figure 10.8.11B). This will be discussed further in Unit 6.
4. Depleting the host cell of cellular materials essential for life or normal function.
5. Stimulating body cells to release inflammatory cytokines and chemokines.
6. Stimulating body cells to release inflammatory vasoactive peptides, bradykinins, histamines, etc. resulting in vasodilation and increased mucous secretion.
7. Inducing adjacent host cells to fuse together forming giant multinucleated cells or syncytias (see Figure 10.8.1, Figure 10.8.2 , Figure 10.8.3A, and Figure 10.8.3B) as seen with cytomegalovirus (CMV), varicella-zoster virus (VZV), and HIV.
8. Playing a role in normal cells becoming malignant (cell transformation by oncogenic viruses).
9. Causing cytolysis of the infected host cell (see Figure 10.8.13C).

Evading Host Immune Defenses

As will be seen in Unit 6, one of the major defenses against free viruses is the immune defenses' production of antibody molecules against the virus. The "tips" of the antibody (the Fab portion; see Figure 10.8.4A) have shapes that have a complementary shape to portions of viral attachment proteins and glycoproteins called epitopes found on the viral surface. When antibodies react with these attachment proteins, they block viral adsorption to host cell receptors and, therefore, block viral replication.

Flash animation showing neutralization of viruses by antibodies.

In addition, Antibodies such as IgG function as opsonins and stick viruses to phagocytes.

Flash animation showing opsonization of viruses by antibodies.

html5 version of animation for iPad showing opsonization of viruses by antibodies.

- Antibodies made against the original human influenza virus can no longer bind to the new strain of virus or stick the virus to phagocytes (see Figure 10.8.4A and Figure 10.8.4B).
- Likewise HIV, because of its high rate of mutation and its intracellular recombination with other strains of HIV, as mentioned earlier in this unit, produces altered gp120 to which antibodies made against the earlier strains of HIV can no longer bind.
- The hepatitis C virus (HCV) frequently through mutation produces viral variants ("escape mutants") to resist antibodies.

Another major defense against viruses, as we will see in Unit 6, is the killing of virus-infected host cells by cytotoxic T-lymphocytes (CTLs). Virus-infected host cells naturally bind viral epitopes to a host molecule called MHC-I and place the MHC-1 with bound viral epitope on the surface of the infected cell (see Figure 10.8.5) where they can be recognized by CTLs having a T-cell receptors on its surface with a complementary shape. In this way the CTL can kill the infected cell by apoptosis , a programmed cell suicide (see Figure 10.8.11A and Figure 10.8.11B).

For a preview of CTLs killing virus-infected cells from Unit 6, Cell-Mediated Immunity, see the two animations below.

Flash animation of a CTL triggering apoptosis by way of perforins and granzymes.

html5 version of a CTL triggering apoptosis by way of perforins and granzymes.

Flash animation showing CTL-induced apoptosis of a virus-infected cell.

html5 version of animation for iPad showing CTL-induced apoptosis of a virus-infected cell.

- Epstein-Barr virus (EBV) and cytomegalovirus (CMV) inhibit proteasomal activity so that viral proteins are not degraded into viral peptides. (see Figure 10.8.5A)
- Herpes simplex viruses (HSV) can block the TAP transport of peptides into the endoplasmic reticulum (see Figure 10.8.5 B).
- Numerous viruses, such as the cytomegalovirus (CMV) and adenoviruses can block the formation of MHC-I molecules by the infected cell. As a result, no viral peptide is displayed on the infected cell and the CTLs are no longer able to recognize that the cell is infected and kill it (see Figure 10.8.5C).
- Epstein-Barr virus (EBV) down regulates several host proteins involved in attaching viral epitopes to MHC-I molecules and displaying them on the host cell's surface (see Figure 10.8.5D).
- Adenoviruses and Epstein-Barr Virus (EBV) code for proteins that blocks apoptosis , the programmed cell suicide mechanism triggered by various defense mechanisms in order to destroy virus-infected cells.

3. Another defense cell that is able to kill virus-infected cells is the NK cell. NK cells recognize infected cells displaying stressed-induced proteins and not displaying MHC-I molecules on their surface and kill these cells (see Figure 10.8.7).

MHC-I molecules are the molecules on host cells that display viral epitopes to cytotoxic T-lymphocytes (CTLs). Some viruses suppress the production of MHC molecules by host cells, preventing CTLs from recognizing the infected cell as foreign and killing it. NK cells, however, can recognize cells not displaying MHC-I and kill them anyway.

See the three animations below for a preview of NK cells from Unit 5, Innate Immunity.

Flash animation showing a NK cell interacting with a normal body cell.

html5 version of animation for iPad showing a NK cell interacting with a normal body cell.

Flash animation showing a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

html5 version of animation for iPad showing a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

Flash animation showing apoptosis by NK cells.

html5 version of animation for iPad showing apoptosis by NK cells.

- The cytomegalovirus (CMV) can also trigger its host cell to produce altered MHC-I molecules that are unable to bind viral epitopes, and, therefore, are not recognized by CTLs. However, NK cells are also unable to kill this infected cell because it is still displaying "MHC-I molecules" on its surface.
- CMV also produces microRNAs (miRNAs), small non-coding RNA molecules that down-regulates the production of stress-induced proteins that the killer-activating receptor of NK cells first recognizes. The miRNAs do this by binding to the host cell's mRNA coding for stress-induced proteins (see Figure 10.8.14). Without this binding there is no kill signal by the NK cell.

GIF animation showing antisense RNA.

4. Some viruses cause infected host cells to secrete molecules that bind and tie up cytokines , preventing them from binding to normal cytokine receptors on host cells.

- Poxviruses cause infected host cells to secrete molecules that bind interleukin-1 (IL-1) and interferon-gamma (IFN-gamma).
- Cytomegaloviruses (CMV) cause infected host cells to secrete molecules that bind chemokines.

5. Some viruses suppress immunocompetent cells.

- Epstein-Barr virus (EBV) produces a protein that is homologous to the cytokine interleukin-10 (IL-10). IL-10 inhibits the activation of dendritic cells and macrophages , antigen-presenting cells that are needed to present antigens to T-lymphocytes for their activation. EBV also produces microRNAs (miRNAs), small non-coding RNA molecules that inhibit an interferon response by infected cells. The miRNAs do this by binding to the host cell's mRNA coding for interferon (see Figure 10.8.14).
- The human immunodeficiency virus (HIV) infects immunocompetent dendritic cells and T4-lymphocytes leading to their death or disfunction.

6. Some viruses block apoptosis of infected host cells enabling the infected host cell to survive and produce new viruses.

- Cytomegalovirus (CMV) and herpes simplex type 1 virus (HSV-1) produce microRNAs (miRNAs), small non-coding RNA molecules that block protein involved in apoptosis, a programmed cell suicide. The miRNAs do this by binding to the host cell's mRNA coding for apoptosis-inducing proteins (see Figure 10.8.14).

Describe four different ways viruses may resist immune responses.

Concept Map for Viral Pathogenicity

Summary

1. Alteration of host cell function and/or death of the host cell occurs as a result of viruses using an infected host cell as a factory for manufacturing viruses.
2. The body's immune defenses recognize infected host cells as foreign and destroy infected cells.
3. The body's adaptive immune defenses produce antibodies against viruses that block viral adsorption to host cells or result in opsonization of the virus.
4. The body's adaptive immune defenses produce cytotoxic T-lymphocytes (CTLs) against viruses that bind to infected host cells and induce cell suicide (apoptosis).
5. The body's innate immune defenses produce NK cells that can induce apoptosis of stressed, virus-infected host cells.
6. Viruses can develop resistance to antibodies and cytotoxic T-lymphocytes by altering the order of the amino acids and, therefore, the shape of viral antigens so the antibodies and CTLs no longer fit.
7. Viruses can alter infected host cells in such a way that NK cells no longer kill them.
8. Some viruses block apoptosis of infected host cells enabling the infected host cell to survive and produce new viruses.

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10.9: Bacteriophage-Induced Alterations of Bacteria

Learning Objectives

1. Describe the process of lysogenic conversion and give two examples of exotoxins that result from lysogenic conversion.

1. Lytic bacteriophages usually cause the host bacterium to lyse (see Figure 10.9.1).

2. Lysogenic conversion by prophages

The added genetic information provided by the DNA of a prophage (Figure 10.9.4) may enable a bacterium to possess new genetic traits. For example, some bacteria become virulent only when infected themselves with a specific temperate bacteriophage. The added genetic information of the prophage allows for coding of protein exotoxin or other virulence factors.

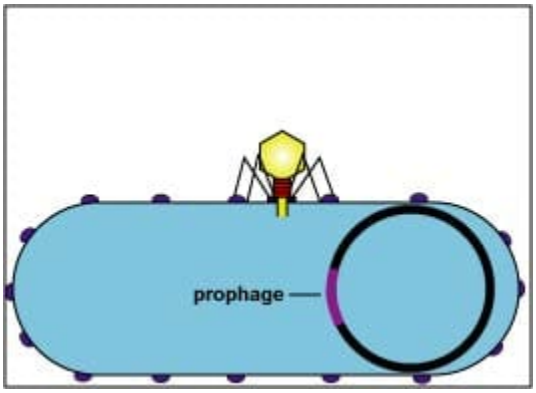
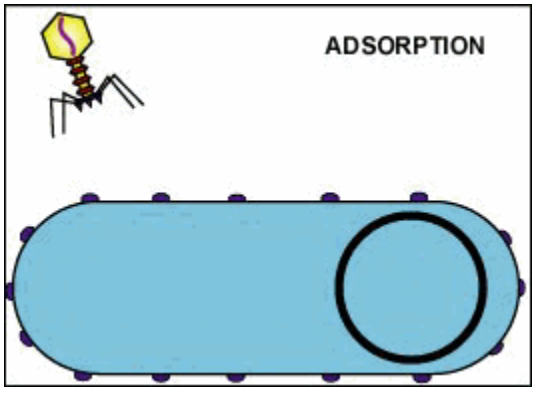


Figure 10.9.4: Prophage Formation during the Lysogenic Life Cycle of a Temperate Bacteriophage. The bacteriophage inserts its genome into the nucleoid of the bacterium to become a prophage.

The following bacterial exotoxins are a result of lysogenic conversion by a prophage:

a. the diphtheria exotoxin of the bacterium *Corynebacterium diphtheriae;*
b. the Streptococcal pyrogenic exotoxin (Spe) produced by rare invasive strains and scarlet fever strains of *Streptococcus pyogenes*;
c. The neurotoxin produced by *Clostridium botulinum*;
d. exfoliatin, an exotoxin that causes scalded skin syndrome, produced by *Staphylococcus aureus*;
e. the cholera exotoxin produced by *Vibrio cholerae;* and
f. the shiga toxins produced by *E. coli* O157:H7.



Animation of the Lysogenic Life Cycle of a Temperate Bacteriophage

Exercise: Think-Pair-Share Questions

State why bacteriophages themselves are harmless to humans but might enable certain bacteria to be more harmful to humans.

Summary

1. Lytic bacteriophages usually cause the host bacterium to lyse.
2. The added genetic information provided by the DNA of a prophage may enable a bacterium to possess new genetic traits.
3. Some bacteria become virulent only when infected themselves with a specific temperate bacteriophage. The added genetic information of the prophage allows for coding of protein exotoxin or other virulence factors.
4. Examples include the diphtheria exotoxin, streptococcal pyrogenic exotoxin (Spe), the botulism exotoxins, the cholera exotoxin, and the shiga toxin.

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10.10: Antiviral Agents

Learning Objectives

1. State why antibiotics are of no use against viruses and what we must rely on to control viruses.
2. State the viruses the following antiviral agents are used against:
   a. amantadine, rimantidine, zanamivar, and oseltamivir
   b. acyclovir, famciclovir, penciclovir, and valacyclovir
   c. foscarnet, gancyclovir, cidofovir, valganciclovir, and fomivirsen
   d. AZT (ZDV), didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, tenofovir, and abacavir
   e. nevirapine, delavirdine, and efavirenz
   f. saquinavir, ritonavir, idinavir, nelfinavir, amprenavir, atazanavir, fosamprenavir, ritonavir
   g. telaprevir, boceprevir, simeprevir, sofosbuvir
3. Compare how the following drugs exhibit their antiviral action against HIV.
   a. nucleoside reverse transcriptase inhibitors
   b. protease inhibitors
   c. entry inhibitors

Since viruses lack the structures and metabolic processes that are altered by common antibiotics, antibiotics are virtually useless in treating viral infections. To date, relatively few antiviral chemotherapeutic agents are available and used to treat just a few limited viruses.

Most of the antiviral agents work by inhibiting viral DNA synthesis. These drugs chemically resemble normal DNA nucleosides, molecules containing deoxyribose and either adenine, guanine, cytosine, or thymine. Viral enzymes then add phosphate groups to these nucleoside analogs to form DNA nucleotide analogs. The DNA nucleotide analogs are then inserted into the growing viral DNA strand in place of a normal nucleotide. Once inserted, however, new nucleotides can't attach and DNA synthesis is stopped. They are selectively toxic because viral polymerases are more prone to incorporate nucleotide analogs into their nucleic acid than are host cell polymerases.

Table 10.10.1*: Antivirals used for viruses other than HIV*

Antiviral	Brand Name	Use
amantadine	*Symmetrel*	used prophylactically against influenza A) in high-risk individuals. It prevents influenza A viruses from the uncoating step necessary for viral replication.
rimantidine	*Flumadine*	used for treatment and prophylaxis of influenza A. It prevents influenza A viruses from the uncoating step necessary for viral replication.
zanamivir:	*Relenza*	used to limit the duration of influenza A and B infections. It is an inhibitor of the influenza virus surface enzyme called neuraminidase that is needed for release of newly formed influenza viruses from the infected cell.
oseltamivir	*Tamiflu*	used limit the duration of influenza infections. It is an inhibitor of the influenza virus surface enzyme called neuraminidase that is needed for release of newly formed influenza viruses from the infected cell.
acyclovir	Zovirax	used against herpes simplex viruses (HSV) to treat genital herpes, mucocutaneous herpes in the immunosuppressed, HSV encephalitis, neonatal herpes, and to reduce the rate of recurrences of genital herpes. It is also used against varicella zoster viruses (VZV)) to treat shingles. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
trifluridine	*Viroptic*	used to treat eye infection (keratitis and conjunctivitis) caused by HSV. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.

Antiviral	Brand Name	Use
famciclovir	Famvir	used to treat HSV and VZV infections. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
valacyclovir	Valtrex	used to treat HSV and VZV infections. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
penciclovir	Denavir	used in treating HSV infections. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
gancyclovir	Cytovene; Vitrasert	used in treating severe cytomegalovirus (CMV) infections such as retinitis. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
valganciclovir	Valcyte	used in treating severe CMV infections such as retinitis). It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
foscarnet	Foscavir	used in treating severe CMV infections such as retinitis. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
cidofovir	Vistide	used in treating CMV retinitis. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
fomivirsen	Vitravene	used in treating CMV retinitis. Fomivirsen inhibits cytomegalovirus (CMV) replication through an antisense RNA (microRNA or miRNA mechanism. The nucleotide sequence of fomivirsen is complementary to a sequence in mRNA transcripts (Figure 10.10.1) that encodes several proteins responsible for regulation of viral gene expression that are essential for production of infectious CMV. Binding of fomivirsen to the target mRNA results in inhibition of protein synthesis, subsequently inhibiting virus replication.
ribavirin	Copegus; Rebetol; Virazole	used in treating severe acute respiratory syndrome (SARS). In combination with other drugs it is used to treat hepatitis C virus (HCV). It chemically resembles a normal RNA nucleoside. Once inserted into the growing RNA chain it inhibits further viral RNA replication.
telaprevir	Incivek	for the treatment of chronic hepatitis C (hepatitis C virus or HCV genotype 1). It is a protease inhibitor that binds to the active site of an HCV-encoded protease and prevent it from cleaving the long polyprotein from polycistronic HCV genes into proteins essential to the structure and function of HCV.
boceprevir	Victrelis	for the treatment of chronic hepatitis C (hepatitis C virus or HCV genotype 1) infection. It is used in combination with peginterferon alfa and ribavirin. Boceprevir is a protease inhibitor that binds to the active site of an HCV-encoded protease and prevent it from cleaving the long polyprotein from polycistronic HCV genes into proteins essential to the structure and function of HCV.
simeprevir	Olysio	use for the treatment of chronic hepatitis C (hepatitis C virus or HCV genotype 1) infection. Used in combination with peginterferon alfa and ribavirin. Simeprevir is a protease inhibitor that binds to the active site of an HCV-encoded protease and prevent it from cleaving the long polyprotein from polycistronic HCV genes into proteins essential to the structure and function of HCV.
sofosbuvir	*Sovaldi*	Use for the treatment of chronic hepatitis C infection. Used in combination with ribavirin for hepatitis C virus or HCV genotypes 2 and 4; used in combination with peginterferon alfa and ribavirin for HCV genotypes 1 and 4. The second indication is the first approval of an interferon-free regimen for the treatment of chronic HCV infection. Sofosbuvir is a nucleotide polymerase inhibitor that binds to the active site of an HCV-encoded RNA polymerase preventing the synthesis of the viral RNA genome.
lamivudine	*Epivir-HBV*	used in treating chronic hepatitis B. It chemically resembles a normal DNA nucleoside. Once inserted into the growing DNA chain it inhibits further viral DNA replication.
adefovir dipivoxil	*Hepsera*	used in treating hepatitis B.

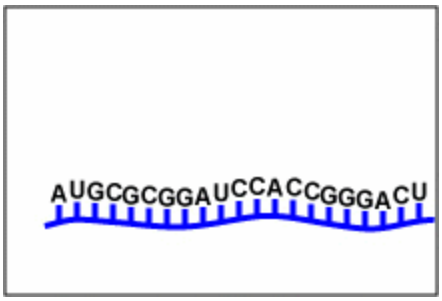


Figure 10.10.1: Antisense RNA. When an antisense RNA (microRNA or miRNA) that is complementary to a mRNA coding for a particular protein or enzyme binds to the mRNA by complementary base pairing, that mRNA cannot be translated and the protein or enzyme is not made.

Current anti-HIV drugs include the following (classified by their action):

HIV nucleoside-analog reverse transcriptase inhibitors

To replicate, HIV uses the enzyme reverse transcriptase to make a DNA copy of its RNA genome. A complementary copy of this DNA is then made to produce a double-stranded DNA intermediate which is able to insert into host cell chromosomes to form a provirus. Most reverse transcriptase inhibitors are nucleoside analogs. A nucleoside is part of the building block of DNA, consisting of a nitrogenous base bound to the sugar deoxyribose but no phosphate group. A nucleoside analog chemically resembles a normal nucleoside (Figure 10.10.2).

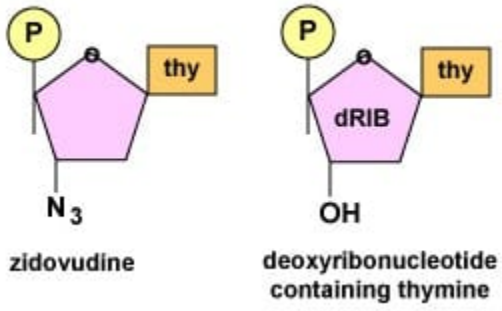


Figure 10.10.2: Zidovudine. A comparison of zidovudine (AZT, ZDV) and the deoxyribonucleotide containing the base thymine.

Once phosphate groups are added by either viral or host cell enzymes, the drugs now chemically resemble normal DNA nucleotides, the building block molecules for DNA synthesis. The nucleotide analog binds to the active site of the reverse transcriptase which, in turn, inserts it into the growing DNA strand in place of a normal nucleotide. Once inserted, however, new DNA nucleotides are unable to attach to the drug and DNA synthesis is stopped. This results in an incomplete provirus. For example, zidovudine (AZT, ZDV, *Retrovir*), as shown in Figure 10.10.1, resembles the deoxyribonucleotide containing the base thymine. Once zidovudine is inserted into the growing DNA strand being transcribed from the viral RNA by reverse transcriptase, no further nucleotides can be attached (Figure 10.10.3).

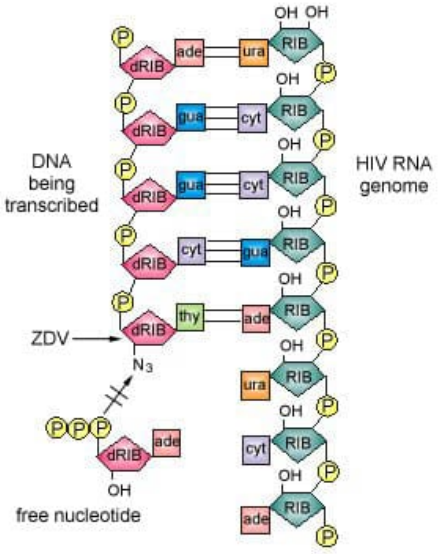


Figure 10.10.3: Zidovudine, (left) Step-1: In order for a DNA strand to elongate, the phosphate group of a free deoxyribonucleotide bonds to the hydroxyl (OH) on the 3' carbon of the deoxyribose of the last deoxyribonucleotide in the strand. (middle) Step-2: To see how zidovudine interferes with this process. (right) Step-3: Zidovudine (ZDV, AZT) has an azide (N3) group instead of a hydroxyl (OH) group on its pentose sugar. Once the phosphate group of the zidovudine bonds to OH of the last deoxyribonucleotide in the strand, no further free deoxyribonucleotides can attach. (The phosphate groups of free deoxyribonucleotides can only bond to OH groups, they are unable to bond to N3groups.) This results in an incomplete provirus.

Examples of nucleoside reverse transcriptase inhibitors include:

a. zidovudine (AZT; ZDV; *Retrovir*)
b. didanosine (ddI; dideoxyinosine; *Videx*)
c. stavudine (d4T; *Zerit*)
d. lamivudine (3TC; *Epivir*)
e. abacavir (ABC; *Ziagen*)
f. emtricitabine (*FTC; Emtriva*, Coviracil)

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

A NtRTI inhibitor is a a nucleotide analog. A nucleotide is the building block of DNA, consisting of a nitrogenous base bound to the sugar deoxyribose, and a phosphate group. A nucleotide analog chemically resembles a normal nucleotide. The nucleotide analog binds to the active site of the reverse transcriptase which, in turn, inserts it into the growing DNA strand in place of a normal nucleotide. Once inserted, however, new DNA nucleotides are unable to attach to the drug and DNA synthesis is stopped. This results in an incomplete provirus. An example of nucleoside reverse transcriptase inhibitor is tenofovir (TDF;*Viread*).

3. HIV Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

These drugs do not resemble regular DNA building blocks. They bind to an allosteric site that regulates reverse transcriptase activity rather than to the enzyme's active site itself as do the above nucleoside analogues (see Figure 10.10.4). This also prevents HIV provirus formation.

a. nevirapine (NVP*; Viramune*)
b. delavirdine (DLV*;Rescriptor*)
c. efavirenz (EFV; *Sustiva*)
d. rilpivirine (*Edurant*)
e. etravirine (ETR, TMC125; *Intelence*)

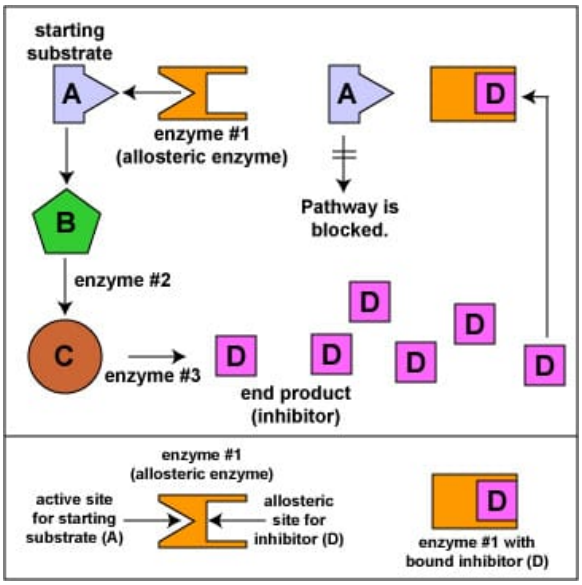


Figure 10.10.4*: Noncompetitive Inhibition with Allosteric Enzymes. When the end product (inhibitor) of a pathway combines with the allosteric site of the enzyme, this alters the active site of the enzyme so it can no longer bind to the starting substrate of the pathway. This blocks production of the end product.*

Flash animation showing the normal function of an allosteric enzyme.

html5 version of animation for iPad showing the normal function of an allosteric enzyme.

Flash animation showing the action of an inhibitor on an allosteric enzyme.

html5 version of animation for iPad showing the action of an inhibitor on an allosteric enzyme.

HIV Protease Inhibitors (PIs)

In order for maturation of HIV to occur, a HIV enzyme termed a protease has to cleave a long HIV-encoded gag-pol polyprotein to produce reverse transcriptase and integrase (coded by the HIV *pol* gene) and gag polyprotein (coded by the HIV *gag* gene). The HIV protease then cleaves the gag polyprotein into capsid protein p17, matrix protein p24, and nucleocapsid protein p7, as well as proteins p6, p2, and p1 whose functions are not yet fully understood (see Figs. 4A, 4B, and 4C). Proteases also cleave the env-polyprotein (coded by the HIV *env* gene) into the envelope glycoproteins gp120 and gp41 (see Figure 10.10.5). Protease inhibitors are drugs that bind to the active site of this HIV-encoded protease and prevent it from cleaving the long gag-pol polyprotein and the gag polyprotein into essential proteins essential to the structure of HIV and to RNA packaging within its nucleocapsid (see 4C). As a result, viral maturation does not occur and noninfectious viral particles are produced.

Flash animation showing the normal function of an HIV protease.

html5 version of animation for iPad showing the normal function of an HIV protease.

Flash animation showing the action of protease inhibitors.

html5 version of animation for iPad showing the action of protease inhibitors.

Protease inhibitors include:

a. saquinavir (SQV; *Inverase*)

b. ritonavir (RTV; *Norvir*)
c. idinavir (IDV; *Crixivan*)
d. nelfinavir (NFV; *Viracept*)
e. amprenavir (APV; *Agenerase*)
f. atazanavir (ATV; *Reyataz*)
g. fosamprenavir (FPV; *Lexiva*)
h. ritonavir (RTV; *Norvir*)
i. darunavir (DRV; TMC114; *Prezista*)
j. tipranavir (TPV; *Aptivus*)

Entry Inhibitors (EIs)

EIs are agents interfering with the entry of HIV-1 into cells. During the adsorption and penetration stages of the life cycle of HIV, a portion or domain of the HIV surface glycoprotein gp120 binds to a CD4 molecule on the host cell. This induces a change in shape that brings the chemokine receptor binding domains of the gp120 into proximity with the host cell chemokine receptor. This brings about another conformational change that exposes a previously buried portion of the transmembrane glycoprotein gp41 that enables the viral envelope to fuse with the host cell membrane. EIs interfere with various stages of this process.

a. Agents that block the binding of gp120 to host chemokine receptor 5 (CCR5).

After the gp120 on the envelope of HIV binds to a CD4 molecule on the host cell, it must then also bind to a co-receptor - a chemokine receptor. CCR5-tropic strains of HIV bind to the chemokine receptor CCR5 (see Figure 10.10.6). (An estimated 50%-60% of people having previously received HIV medication have circulating CCR5-tropic HIV.)

maraviroc (MVC; *Selzentry*; *Celsentri*) is a chemokine receptor binding blocker that binds to CCR5 and blocks gp120 from binding to the co-receptor thus blocking adsorption of HIV to the host cell.

b. Agents that block the fusion of the viral envelope with the cytoplasmic membrane of the host cell.

enfuvirtide (ENF; T-20; *Fuzeon*) binds a gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of the viral envelope with the cellular cytoplasmic membrane.

5. Integrase Inhibitors

Integrase inhibitors disable HIV integrase, the enzyme that inserts the HIV double-stranded DNA intermediate into host cell DNA. It prevents production of a provirus.

raltegravir (*Isentress*)

6. Fixed-dose combinations

Tablets containing two or more anti-HIV medications:

1. abacivir + lamivudine (*Epzicom*)
2. abacivir + lamivudine + zidovudine (*Trizivir*)
3. efavirenz + emtricitabine + tenofovir DF (*Atripla*)
4. emtricitabine + tenofovir DF (*Truvada*)
5. lamivudine + zidovudine (*Combivir*)

Certain antiviral cytokines called type-1 interferons have been produced by recombinant DNA technology and several are used to treat certain severe viral infections. These include:

1. recombinant interferon alfa-2a (*Roferon-A*): a cytokine used to treat Kaposi's sarcoma, chronic myelogenous leukemia, and hairy cell leukemia.
2. peginterferon alfa-2a (*Pegasys*) : used to treat hepatitis C (HCV).
3. recombinant interferon-alpha 2b (*Intron A*): a cytokine produced by recombinant DNA technology and used to treat Hepatitis B; malignant melanoma, Kaposi's sarcoma, follicular lymphoma, hairy cell leukemia, warts, and Hepatitis C.
4. peginterferon alfa-2b (*PEG-Intron; PEG-Intron Redipen*): used to treat hepatitis C (HCV).
5. recombinant Interferon alfa-2b plus the antiviral drug ribavirin (*Rebetron*): used to treat hepatitis C (HCV).

6. recombinant interferon-alpha n3 (*Alferon N*): used to treat warts.
7. recombinant iInterferon alfacon-1 *(Infergen*) : used to treat hepatitis C (HCV).

Most of the current antiviral agents don't kill and eliminate the viruses, but rather inhibit their replication and decrease the severity of the disease. As with other microbes, resistant virus strains can emerge with treatment.

Since there are no antiviral drugs for the vast majority of viral infections and most drugs that are available are only partially effective against limited types of viruses, to control viruses, we must rely on the body's immune responses. As will be seen in detail in Units 5 and 6, the immune responses include innate immunity as well as adaptive immunity (antibody production and cell-mediated immunity). Adaptive immunity can be either naturally acquired or, in some cases, artificially acquired.

For a more detailed description of any specific antimicrobial agent, see the website of RxList - The Internet Drug Index.

Concept Map for Antiviral Agents

Summary

1. Relatively few antiviral chemotherapeutic agents are currently available and they are only somewhat effective against just a few limited viruses.
2. Many antiviral agents resemble normal DNA nucleosides molecules and work by inhibiting viral DNA synthesis.
3. Some antiviral agents are protease inhibitors that bind to a viral protease and prevent it from cleaving the long polyprotein from polycistronic genes into proteins essential to viral structure and function.
4. Some antiviral agents are entry inhibitors that prevent the virus from either binding to or entering the host cell.
5. Antiviral agents are available for only a few viruses, including certain influenza viruses, herpes viruses, cytomegaloviruses, hepatitis C viruses, and HIV.
6. Certain interferon cytokines have been produced by recombinant DNA technology and several are used for certain severe viral infections.

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10.11: General Categories of Viral Infections

Describe and give an example of an acute viral infection, a late complication following an acute infection, a latent viral infection, a chronic viral infection, and a slow viral infection.

Most viruses that infect humans, such as those that cause routine respiratory infections (e.g., cold viruses, influenza viruses) and gastrointestinal infections (e.g., Rotaviruses, Noroviruses), cause acute infections. Acute infections are of relatively short duration with rapid recovery.

In persistent infections, the viruses are continually present in the body. Some persistent infections are late complications following an acute infection and include subacute sclerosing panencephalitis (SSPE) that can follow an acute measles infection and progressive encephalitis that can follow rubella. Other persistent infections are known as latent viral infection. In a latent viral infection the virus remains in equilibrium with the host for long periods of time before symptoms again appear, but the actual viruses cannot be detected until reactivation of the disease occurs. Examples include infections caused by HSV-1 (fever blisters), HSV-2 (genital herpes), and VZV (chickenpox-shingles). In the case of chronic virus infections, the virus can be demonstrated in the body at all times and the disease may be present or absent for an extended period of time. Examples include hepatitis B (caused by HBV) and hepatitis C (caused by HCV). Slow infections are ones in which the infectious agents gradually increase in number over a very long period of time during which no significant symptoms are seen. Examples include AIDS (caused by HIV-1 and HIV-2) and certain lentiviruses that cause tumors in animals. Although not viruses, prions also cause slow infections.

Summary

1. Acute infections are of relatively short duration with rapid recovery.
2. Persistent infections are where the viruses are continually present in the body.
3. In a latent viral infection the virus remains in equilibrium with the host for long periods of time before symptoms again appear, but the actual viruses cannot be detected until reactivation of the disease occurs.
4. In a chronic virus infection, the virus can be demonstrated in the body at all times and the disease may be present or absent for an extended period of time.
5. Slow infections are ones in which the infectious agents gradually increase in number over a very long period of time during which no significant symptoms are seen.

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10.E: Viruses (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

10.1: General Characteristics of Viruses

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State 2 living characteristics of viruses.
   A.
   B.
2. State 2 nonliving characteristics of viruses.
   A.
   B.
3. List 3 criteria used to define a virus.
   A.
   B.
   C.
4. A virus that infects only bacteria is termed a _____.
5. State why viruses can't replicate on environmental surfaces or in synthetic laboratory medium.

10.2: Size and Shapes of Viruses

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Compare the size of most viruses to that of bacteria.
2. List 4 shapes of viruses.
   A.
   B.
   C.
   D.

10.3: Viral Structure

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the structure of most viruses that infect humans.
2. Define the following:
   A. capsid
   B. capsomeres
   C. nucleocapsid
3. Describe how most animal viruses obtain their envelope.
4. State why some bacteriophages are more complex than typical polyhedral or helical viruses.

10.4: Classification of Viruses

10.5: Other Acellular Infectious Agents: Viroids and Prions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Small, circular, single-stranded molecules of infectious that cause of a few plant diseases such as potato spindle-tuber disease,cucumber pale fruit, citrus exocortis disease, and cadang-cadang (coconuts) are called _____.
2. Infectious protein particlesthought to be responsible for a group of transmissible and/or inherited neurodegenerative diseases including Creutzfeldt-Jakob disease, kuru, and Gerstmann-Straussler- syndrome in humans as well as scrapie in sheep and goats are called _____.
3. Name 3 other neurological protein misfolding diseases that apprear to be initiated by prions.

10.6: Animal Virus Life Cycles

10.6A: The Productive Life Cycle of Animal Viruses

10.6B: Productive Life Cycle with Possible Latency

10.6C: The Life Cycle of HIV

10.6D: Natural History of a Typical HIV Infection

10.6E: The Role of Viruses in Tumor Production

10.7: Bacteriophage Life Cycles: An Overview

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Name the 2 types of bacteriophage life cycles and state what the bacteriophage capable of each is called.
   A.
   B.

10.7A: The Lytic Life Cycle of Bacteriophages

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describethe 5 steps involved in the lytic life cycle of bacteriophages.
   A.
   B.
   C.
   D.
   E.

10.7B: The Lysogenic Life Cycle of Bacteriophages

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describehow the lysogenic life cycle of temperate bacteriophages differs from the lytic life cycle of lytic bacteriophages.
2. What is spontaneous induction as it relates to the lysogenic life cycle?
3. When a bacteriophage inserts its DNA into the DNA of the host bacterium, this form of the virus is called a _____.
4. The host bacterium for a bacteriophage is called a _____.
5. A virus capable of the lysogenic life cycle is called a _____.

10.8: Pathogenicity of Animal Viruses

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe 4 ways viruses can damage infected host cells.
   A.
   B.
   C.
   D.
2. Briefly describe 2 different ways viruses can evade host immune defenses and give an example of a virus that uses each mechanism.
   A.
   B.

10.9: Bacteriophage-Induced Alterations of Bacteria

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe how a bacteriophage may in some cases enable a bacterium to become virulent and state 2 examples.

10.10: Antiviral Agents

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Explain why the antibiotics we use to treat bacterial infections are not effective against viral infections.
2. Match the following drugs with the viral infections they are used against:

   _____ amantadine, rimantidine, zanamivar, and oseltamivir

   _____ acyclovir, famciclovir, penciclovir, and valacyclovir

   _____ foscarnet, gancyclovir, cidofovir, valganciclovir, and fomivirsen

   _____ AZT (ZDV), didanosine, zalcitabine, stavudine, nevirapine, delavirdine, saquinavir, and ritonavir

   a. HIV infection and AIDS
   b. influenza A
   c. severe CMV infections such as retinitis
   d. HSV and VZV infections
3. Match the following:

_____ These are drugs that bind to the active site of an HIV-encoded protease and prevent it from cleaving the long gag-pol polyprotein and the gag polyprotein into essential proteins essential to the structure of HIV and to RNA packaging within its nucleocapsid. As a result, viral maturation does not occur and noninfectious viral particles are produced.

_____ These drugs chemically resemble normal DNA nucleotides, the building block molecules for DNA synthesis. They bind to the active site of the reverse transcriptase which, in turn, inserts it into the growing DNA strand in place of a normal nucleotide. Once inserted, however, new DNA nucleotides are unable to attach to the drug and DNA synthesis is stopped. This results in an incomplete provirus.

a. nucleoside reverse transcriptase inhibitors
b. non-nucleoside reverse transcriptase inhibitors
c. protease inhibitors
d. entry inhibitors

10.11: General Categories of Viral Infections

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

   _____ Viral infections in which the infectious agents gradually increase in number over a very long period of time during which no significant symptoms are seen.

   _____ Viral infections of relatively short duration with rapid recovery.

   _____ Viral infections where the virus can be demonstrated in the body at all times and the disease may be present or absent for an extended period of time.

   _____ Viral infections where the virus remains in equilibrium with the host for long periods of time before symptoms again appear, but the actual viruses cannot be detected until reactivation of the disease occurs.

   a. acute viral infection
   b. chronic viral infection
   c. latent viral infection
   d. slow viral infection
2. Give an example of of a virus causing each of the following:
   a. acute viral infection
   b. chronic viral infection
   c. latent viral infection
   d. slow viral infection

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UNIT 5: INNATE IMMUNITY

Innate immunity is an antigen-nonspecific defence mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Innate immunity can be divided into immediate innate immunity and early induced innate immunity. In this section we will learn about immediate innate immunity.

11.1: The Innate Immune System: An Overview

11.2: Defense Cells in the Blood: The Leukocytes

11.3: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells

11.3: Immediate Innate Immunity

11.3A: Antimicrobial Enzymes and Antimicrobial Peptides

11.3B: The Complement System

11.3C: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota

11.4: Early Induced Innate Immunity

11.3A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)

11.3B: Pattern-Recognition Receptors (PRRs)

11.3C: Cytokines Important in Innate Immunity

11.3D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production

11.3E: Phagocytosis

11.3F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)

11.3G: Inflammation

11.3H: Nutritional Immunity

11.3I: Fever

11.3J: The Acute Phase Response

11.3K: Intraepithelial T-lymphocytes and B-1 cells

11.E: Innate Immunity (Exercises)

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11.1: The Innate Immune System: An Overview

Compare adaptive (acquired) immunity with innate immunity.

- Compare immediate innate immunity with early induced innate immunity.
- Define the following:

  a. pathogen-associated molecular patterns (PAMPs)
  b. pattern-recognition receptors (PRRs)
  c. antigen
  d. immunogen
  e. epitope.

In Units 1-4 we looked at microorganisms: how they replicate, why some are potentially more pathogenic than others, and how we can control them with antimicrobial agents. Units 4 and 5 are devoted to the ways in which the body defends itself against microbes and other potentially harmful cells and molecules. The body has two immune systems: the innate immune system and the adaptive immune system. Unit 5 deals with innate immunity while Unit 6 will cover adaptive immunity. Let's first briefly compare acquired and innate immunity.

Innate immunity

Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Innate immunity can be divided into immediate innate immunity and early induced innate immunity.

Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood, our found in extracellular tissue fluids, and are secreted by epithelial cells. These include:

- antimicrobial enzymes and peptides;
- complement system proteins; and
- anatomical barriers to infection, mechanical removal of microbes, and bacterial antagonism by normal body microbiota

These preformed innate defense molecules will be discussed in greater detail later in this unit.

Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs . These recruited defense cells include:

- phagocytic cells: leukocytes such as neutrophils, eosinophils, and monocytes; tissue phagocytic cells in the tissue such as macrophages ;
- cells that release inflammatory mediators: inflammatory cells in the tissue such as macrophages and mast cells ; leukocytes such as basophils and eosinophils; and
- natural killer cells (NK cells).

Unlike adaptive immunity, innate immunity does not recognize every possible antigen. Instead, it is designed to recognize molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells. These unique microbial molecules are called pathogen-associated molecular patterns or PAMPS and include LPS from the gram-negative cell wall, peptidoglycan and lipotechoic acids from the gram-positive cell wall, the sugar mannose (a terminal sugar common in microbial glycolipids and glycoproteins but rare in those of humans), bacterial and viral unmethylated CpG DNA, bacterial flagellin, the amino acid N-formylmethionine found in bacterial proteins, double-stranded and single-stranded RNA from viruses, and glucans from fungal cell walls. In addition, unique molecules displayed on stressed, injured, infected, or transformed human cells also act as PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns

or MAMPs.)

Most body defense cells have pattern-recognition receptors or PRRs for these common PAMPS (see Figure 11.1.1) and so there is an immediate response against the invading microorganism. Pathogen-associated molecular patterns can also be recognized by a series of soluble pattern-recognition receptors in the blood that function as opsonins and initiate the complement pathways. In all, the innate immune system is thought to recognize approximately 10^3 of these microbial molecular patterns.

Flash animation illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

For More Information: Leukocytes from Unit 5

Examples of innate immunity include anatomical barriers, mechanical removal, bacterial antagonism, antigen-nonspecific defense chemicals, the complement pathways, phagocytosis, inflammation, fever, and the acute-phase response. In this current unit we will look at each of these in greater detail.

Concept Map for Innate Versus Adaptive Immunity

Adaptive (acquired) immunity

Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen . This is the immunity one develops throughout life. During adaptive immunity, antigens are transported to lymphoid organs where they are recognized by naive B-lymphocytes and T-lymphocytes. These activated B- and T-lymphocytes subsequently proliferate and differentiate into effector cells.

An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as nonself and stimulates an adaptive immune response. For simplicity we will use the term antigen when referring to both antigens and immunogens. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes .

For More Information: Antigens and Immunogens from Unit 5

For More Information: Antibodies from Unit 6

As we will see later in Unit 5, the body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule . The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

It is estimated that the human body has the ability to recognize 10^7 or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces

10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor. Among this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters. With the adaptive immune responses, the body is able to recognize any conceivable antigen it may eventually encounter.

The downside to the specificity of adaptive immunity is that only a few B-cells and T-cells in the body recognize any one epitope. These few cells then must rapidly proliferate in order to produce enough cells to mount an effective immune response against that particular epitope, and that typically takes several days. During this time the pathogen could be causing considerable harm, and that is why innate immunity is also essential.

For More Information: B-Lymphocytes from Unit 6

For More Information: T4-Lymphocytes from Unit 6

For More Information: T8-Lymphocytes from Unit 6

html5 version of animation for iPad showing epitopes reacting with specific B-cell receptor on a B-lymphocytes.

Flash animation showing epitopes reacting with a specific TCR on a T8-lymphocyte.

html5 version of animation for iPad showing epitopes reacting with a specific TCR on a T8-lymphocyte.

Adaptive immunity usually improves upon repeated exposure to a given infection and involves the following:

- antigen-presenting cells (APCs) such as macrophages and dendritic cells ;
- the activation and proliferation of antigen-specific B-lymphocytes ;
- the activation and proliferation of antigen-specific T-lymphocytes ; and
- the production of antibody molecules , cytotoxic T-lymphocytes (CTLs) , activated macrophages , and cytokines .

Acquired immunity includes both humoral immunity and cell-mediated immunity and will be the topic of Unit 6.

Concept Map for Innate Versus Adaptive Immunity

Compare and contrast how innate immunity and adaptive immunity are typically initiated in response to microbes.

We will now take a closer look at innate immunity.

Summary

1. The body has two immune systems: the innate immune system and the adaptive immune system.
2. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe.

3. Innate immunity is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.
4. Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood and in extracellular tissue fluids.
5. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs.
6. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen.
7. Adaptive immunity is the immunity one develops throughout life.
8. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes.
9. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes.

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11.2: Defense Cells in the Blood: The Leukocytes

State what each of the following determine: CBC and leukocyte differential count.

- State the significance of the following:

  a. an elevated white blood cell count
  b. a shift to the left (elevated bands)

- Describe and state the major functions of the following leukocytes:

  a. neutrophils
  b. basophils
  c. eosinophils
  d. monocytes
  e. B-lymphocytes
  f. T4-lymphocytes
  g. T8-lymphocytes
  h. NK cells

- State what type of cell monocytes differentiate into when they enter tissue.
- State 2 functions of platelets.

All leukocytes are critical to body defense. There are normally between 5,000-10,000 leukocytes per cubic millimeter (mm^3) of blood and these can be divided into five major types: neutrophils, basophils, eosinophils, monocytes, and lymphocytes. The production of colonies of the different types of leukocytes is called leukopoiesis and is induced by various cytokines known as colony stimulating factors or CSFs .

The complete blood count (CBC) is a laboratory test which, among other things, determines the total number of both leukocytes and erythrocytes per ml of blood. In general, an elevated WBC count (leukocytosis) is seen in infection, inflammation, leukemia, and parasitic infestations. A decreased WBC count (leukopenia) is generally seen in bone marrow depression, severe infection, viral infections, autoimmune diseases, malignancies, and malnutrition. For example, infections may increase the total leukocyte count two to three times the normal level by dramatically increasing the number of neutrophils.

The differential white blood cell count (leukocyte differential count) determines the number of each type of leukocyte calculated as a percentage of the total number of leukocytes. This information can be useful diagnostically because different diseases or disorders can cause an increase or a decrease in the various types of WBCs. For example, when doing a differential WBC count, neutrophils are usually divided into segs (a mature neutrophile having a segmented nucleus) and bands (an immature neutrophil with an incompletely segmented or banded nucleus). During an active infection, people are generally producing large numbers of new neutrophils and therefore will have a higher percentage of the immature band forms. (An increase in band forms is sometimes referred to as a "shift to the left" because on laboratory slips used for differential WBC counts, the heading for bands is to the left of the heading for mature neutrophils or segs.)

The five types of leukocytes fall into one of two groups: the polymorphonuclear leukocytes and the mononuclear leukocytes.

Polymorphonuclear Leukocytes

Polymorphonuclear leukocytes (granulocytes) have irregular shaped nuclei with several lobes and their cytoplasm is filled with granules containing enzymes and antimicrobial chemicals. They include the following:

Neutrophils

Neutrophils are the most abundant of the leukocytes, normally accounting for 54-75% of the WBCs. An adult typically has 3,000-7,500 neutrophils/mm^3 of blood but the number may increase two- to three-fold during active infections. They are called neutrophils because their granules stain poorly - they have a neutral color - with the mixture of dyes used in staining leukocytes.

The nucleus of a neutrophil has multiple lobes.

Neutrophils are important phagocytes. Their granules contain various agents for killing microbes. Primary azurophil granules contain acid hydrolase, myeloperoxidase, defensins, cathepsin G, cationic proteins, and bactericidal permeability increasing protein (BPI). Secondary specific granules contain such defense chemicals as lysozyme, lactoferrin, collagenase, and elastase. These agents kill microbes intracellularly during phagocytosis but are also often released extracellularly where they kill not only microbes but also surrounding cells and tissue, as will be discussed later under phagocytosis.

They release the enzyme kallikrein that catalyzes the generation of bradykinins. Bradykinins promote inflammation by causing vasodilation, increasing vascular permeability, and increasing mucous production. They are also chemotactic for leukocytes and stimulate pain. They produce enzymes that catalyze the synthesis of prostaglandins from arachidonic acid in cell membranes. Certain prostaglandins promote inflammation by causing vasodilation and increasing capillary permeability. They also cause constriction of smooth muscles, enhance pain, and induce fever.

They are short-lived, having a life span of a few hours to a few days, and do not multiply. They circulate in the blood for around 6 hours and if the are not recruited, they undergo apoptosis. In tissue, they function for several hours and die. However, the bone marrow makes about 80,000,000 new neutrophils per minute to replace these.

- To view an electron micrograph of a neutrophil, see the Web page for the University of Illinois College of Medicine.
- Scanning electron micrograph of a neutrophil engulfing *Escherichia coli* from sciencephotogallery.com.
- Transmission electron micrograph of a neutrophil engulfing *Neisseria gonorrhoeae* from sciencephotogallery.com.

Eosinophils

Eosinophils normally comprise 1-4% of the WBCs (50-400/mm^3 of blood). They are called eosinophils because their granules stain red with the acidic dye eosin, one of the mixture of dyes used when staining leukocytes. The nucleus of an eosinophil typically appears lobed.

Their granules contain destructive enzymes for killing infectious organisms. These enzymes include acid phosphatase, peroxidases, major basic protein, RNase, DNases, lipase, and plasminogen. They are capable of phagocytosis but primarily they release their contents into the surrounding environment to kill microbes extracellularly. The substances they release defend primarily against fungi, protozoa, and parasitic worms (helminths), pathogens that are too big to be consumed by phagocytosis. They secrete leukotrienes, prostaglandins, chemicals that promotes inflammation by causing vasodilation and increasing capillary permeability. They also secrete various cytokines such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, and TNF alpha. Their life span is 8-12 days.

- To view an electron micrograph of an eosinophil, see the Web page for the University of Illinois College of Medicine.
- Transmission electron micrograph of an eosinophil from sciencephotogallery.com.

Basophils

Basophils normally make up 0-1% of the WBCs (25-100/mm^3 of blood). They are called basophils because their granules stain a dark purplish blue with the basic dye methylene blue, one of the dyes that are used when staining leukocytes. Basophils have a lobed nucleus. Basophils release histamine, leukotrienes, and prostaglandins, chemicals that promotes inflammation by causing vasodilation, increasing capillary permeability, and increasing mucous production. Basophils also produce heparin, platelet-activating factor (PAF) and the cytokine IL-4. Their life span is probably a few hours to a few days.

Mononuclear Leukocytes

Mononuclear leukocytes (agranulocytes) have compact nuclei and have no visible cytoplasmic granules. The following are agranulocytes:

Monocytes

Monocytes normally make up 2-8% of the WBCs (100-500/mm^3 of blood). Monocytes are important phagocytes. Monocytes differentiate into macrophages and dendritic cells when they leave the blood and enter the tissue. Macrophages and dendritic

cells are very important in phagocytosis and serve as antigen-presenting cells in the adaptive immune responses (see below). They produce a variety of cytokines that play numerous roles in body defense. They are long-lived (life span of months) and can multiply.

- To view an electron micrograph of a monocyte, see the Web page for the University of Illinois College of Medicine.
- Transmission electron micrograph of a monocyte from sciencephotogallery.com.

Lymphocytes

Lymphocytes normally represent 25-40% of the WBCs (1,500-4,500/mm^3 of blood). Lymphocytes mediate the adaptive immune responses (Unit 6). Only a small proportion of the body's lymphocytes are found in the blood. The majority are found in lymphoid tissue. In fact the collective mass of all the lymphocytes in the human body is about the same as the mass of the brain! Lymphocytes circulate back and forth between the blood and the lymphoid system of the body. They have a life span of days to years. There are 3 major populations of lymphocytes:

B-lymphocytes (B-cells) mediate humoral immunity, the production of antibody molecules against a specific antigen,and have B-cell receptors (BCR) on their surface for antigen recognition. Generally 10-20% of the lymphocytes are B-lymphocytes. Once activated, most B-lymphocytes differentiate into antibody-secreting plasma cells.

T-lymphocytes (T-cells) are responsible for cell-mediated immunity, the production of cytotoxic T-lymphocytes (CTLs), activated macrophages, activated NK cells, and cytokines against a specific antigen. They also regulate the adaptive immune responses. Generally 60-80% of the lymphocytes are T-lymphocytes. Based on biochemical markers on their surface, there are two major classes of T-lymphocytes:

- T4-lymphocytes ($CD4^+$ T-lymphocytes) have CD4 molecules and T-cell receptors (TCRs) on their surface for protein antigen recognition. They function to regulate the adaptive immune responses through cytokine production. Once activated, they differentiate into effector T4-lymphocytes such as Th1 cells, Th2 cells, and Th17 cells.
- T8-lymphocytes ($CD8^+$ T-lymphocytes) have CD8 molecules and T-cell receptors (TCRs) on their surface for protein antigen recognition. Once activated, they differentiate into cytotoxic T-lymphocytes (CTLs).

Invariant natural killer T (iNKT) cells are a subset of lymphocytes that bridge the gap between innate and adaptive immunity. They have T-cell receptors (TCRs) on their surface for glycolipid antigen recognition. Through the cytokines they produce once activated,i NKT cells are essential in both innate and adaptive immune protection against pathogens and tumors. They also play a regulatory role in the development of autoimmune diseases and transplantation tolerance.

NK cells (natural killer cells) are lymphocytes that lack B-cell receptors and T-cell receptors. They function to kill infected cells and tumor cells. NK cells are able to kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC). They also kill human cells lacking MHC-I molecules on their surface. Lymphocytes will be discussed in greater detail in Unit 6.

Although not white blood cells, platelets (thrombocytes) are another formed element in the blood. They promote clotting by sticking together after becoming activated and forming platelet plugs to close up damaged capillaries. They also secrete cytokines and chemokines to promote inflammation.

Why are there more neutrophils and, specifically, more band form neutrophils found in the blood during an active infection?

- Compare and contrast the functions of B-lymphocytes, T4-lymphocytes, and T8-lymphocytes in immune responses.

Concept Map for Defense Cells in the Blood: Leukocytes

Summary

1. The complete blood count (CBC) is a laboratory test that, among other things, determines the total number of both leukocytes and erythrocytes per ml of blood.

2. In general, an elevated WBC count (leukocytosis) is seen in infection, inflammation, leukemia, and parasitic infestations.
3. Neutrophils are the most abundant of the leukocytes, normally accounting for 54-75% of the WBCs. Neutrophils are important phagocytes and also promote inflammation.
4. Eosinophils normally comprise 1-4% of the WBCs. They are capable of phagocytosis but primarily they release their contents into the surrounding environment to kill microbes, especially parasitic worms, extracellularly. They also promote inflammation.
5. Basophils normally make up 0-1% of the WBCs and release histamine, leukotrienes, and prostaglandins, chemicals that promotes inflammation.
6. Monocytes normally make up 2-8% of the WBCs and differentiate into macrophages and dendritic cells when they leave the blood and enter the tissue.
7. Lymphocytes normally represent 25-40% of the WBCs and mediate the specific immune responses.
8. B-lymphocytes (B-cells) mediate humoral immunity, the production of antibody molecules against a specific antigen, and have B-cell receptors (BCR) on their surface for antigen recognition. Most B-lymphocytes differentiate into antibody-secreting plasma cells.
9. T-lymphocytes (T-cells) are responsible for cell-mediated immunity, the production of cytotoxic T-lymphocytes (CTLs), activated macrophages, activated NK cells, and cytokines against a specific antigen.
10. T4-lymphocytes have CD4 molecules and T-cell receptors on their surface for antigen recognition. They function to regulate the adaptive immune responses through cytokine production. Once activated, they differentiate into effector T4-lymphocytes.
11. T8-lymphocytes have CD8 molecules and T-cell receptors on their surface for antigen recognition. Once activated, they differentiate into T8-suppressor cells and cytotoxic T-lymphocytes (CTLs).
12. NK cells (natural killer cells) are lymphocytes that lack B-cell receptors and T-cell receptors. They function to kill infected cells and tumor cells.

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11.3: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells

Learning Objectives

1. State 3 different functions of macrophages in body defense.
2. State the primary function of dendritic cells in body defense.
3. Name the cells in the tissue whose primary function is to present antigen to naive T-lymphocytes.
4. Name the cells in the tissue whose primary function is to present antigen to effector T-lymphocytes.
5. State the primary function of mast cells in body defense.

Dendritic Cells

Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells. They are located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract, as well as lymphoid tissues and organ parenchyma. In these locations, in their immature form, they are attached by long cytoplasmic processes. Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by inflammatory cytokines, the dendritic cells detach from their initial site, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, they have matured and are now able to present antigen to the ever changing populations of naive T-lymphocytes located in the cortex of the lymph nodes.

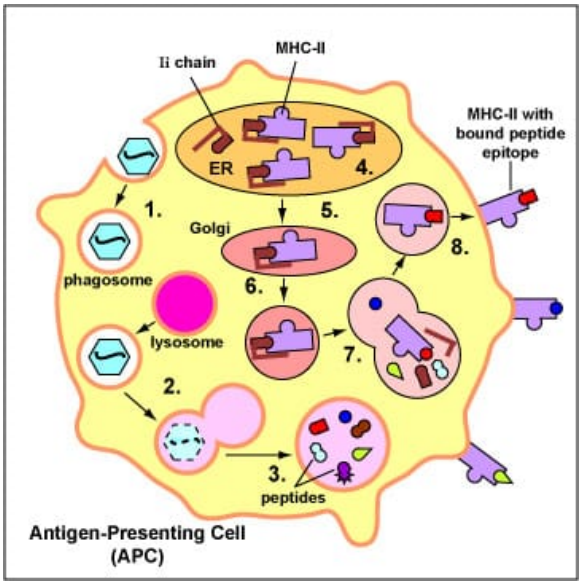


Figure 11.3.1: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules. 1. Exogenous antigens, such as viruses, are engulfed and placed in a phagosome. 2. Lysosomes fuse with the phagosome forming an phagolysosome. 3. Protein antigens are degraded into a series of peptides. 4. MHC-II molecules are synthesized in the endoplasmic reticulum and transported to the Golgi complex. Once assembled, within the endoplasmic reticulum, a protein called the invarient chain (Ii) attaches to the the peptide-binding groove of the MHC-II molecules and in this way prevents peptides designated for binding to MHC-I molecules within the ER from attaching to the MHC-II. 5&6. The MHC-II molecules with bound Ii chain are now transported to the Golgi complex, and placed in vesicles. 7. The vesicles containing the MHC-II molecules fuse with the peptide-containing phaglysosomes. The Ii chain is removed and the peptides are now free to bind to the grooves of the MHC-II molecules. 8. The MHC-II molecules with bound peptides are transported to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-II complexes can be recognized by T4-lymphocytes by way of TCRs and CD4 molecules having a complementary shape.

The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes. (Naive lymphocytes are those that have not yet encountered an antigen.) Dendritic cells engulf microorganisms and other materials and degrade them with their lysosomes. Peptides from microbial proteins are then bound to a groove of unique molecules called MHC-II molecules produced by macrophages, dendritic cells, and B-lymphocytes. The peptide epitopes bound to the MHC-II molecules are then put on the surface of the dendritic cell (Figure 11.3.1) where they can be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on naive T4-lymphocyte (see Figure 11.3.2).

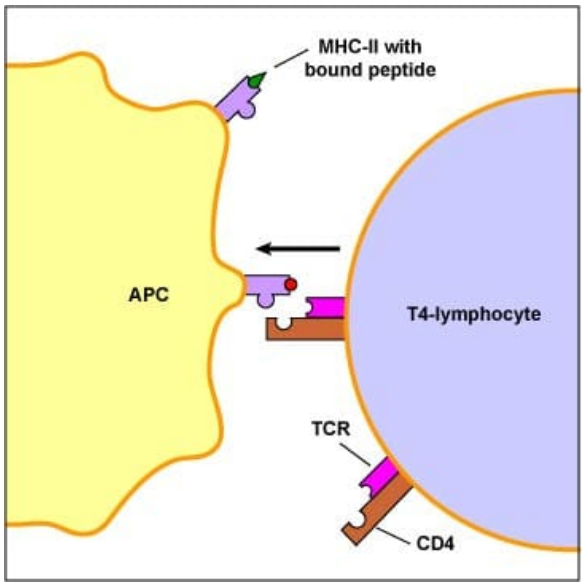


Figure 11.3.2: A T4-Lymphocyte Recognizing Epitope/MHC-II on an Antigen-Presenting Cell (APC). Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

In addition, dendritic cells can bind peptide epitopes to MHC-I molecules and present them to naiveT8-lymphocytes. The MHC-I molecules with bound peptide on the dendritic cell are recognized by complementary shaped T-cell receptors (TCR) and CD8 molecules on naive T8-lymphocyte (Figure 11.3.3).

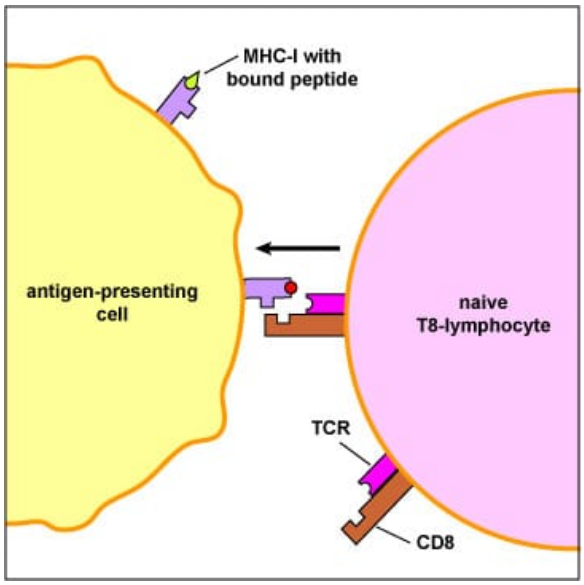
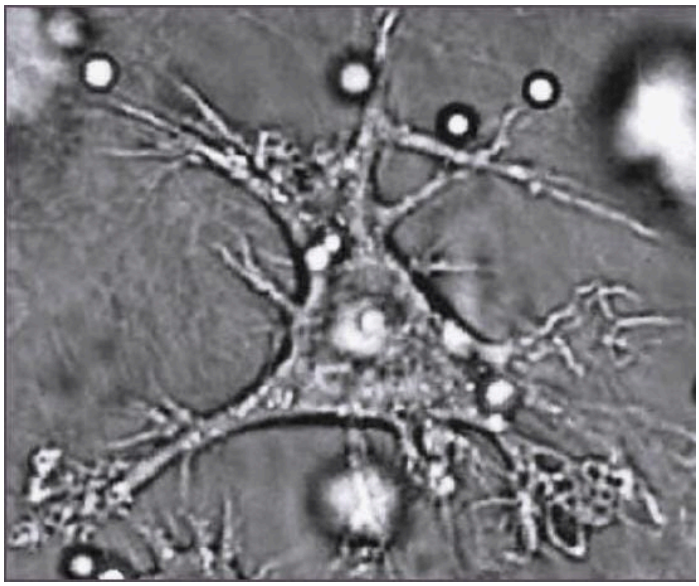


Figure 11.3.3: An Antigen-Presenting Cell Presenting MHC-I with Bound Peptide to a Naive T8-lymphocyte having a Complementary T-Cell Receptor. Antigen-presenting cells (APCs) such as dendritic cells and macrophages produce both MHC-I and MHC-II molecules. These APCs can phagocytose infected cells and tumor cells, place them in phagosomes, and degrade them with lysosomes. During this process, some of the proteins escape from the phagosome into the surrounding cytosol. Here they can be degraded into peptides by proteasomes, bound to MHC-I molecules, and placed on the surface of the APC. Now the peptide/MHC-I complexes can be recognized by a naive T8-lymphocyte having a complementary shaped T-cell receptor (TCR) and CD8 molecule. This activates the naive T8-lymphocyte enabling it to eventually proliferate and differentiate into cytotoxic T-lymphocytes (CTLs).



A dendritic cell. (CC BY-SA 2.5; Judith Behnsen, Priyanka Narang, Mike Hasenberg, Frank Gunzer, Ursula Bilitewski, Nina Klippel, Manfred Rohde, Matthias Brock, Axel A. Brakhage, Matthias Gunzer - Source: PLoS Pathogens).

These interactions enable the T4-lymphocytes or T8-lymphocytes to become activated, proliferate, and differentiate into effector cells. This will be discussed in detail in Unit 6. Myeloid dendritic cells also use pattern-recognition receptors called toll-like receptors (TLRs) to recognize pathogen-associated molecular patterns or PAMPs (Figure 11.3.4). The interaction of the PAMP with its TLR stimulates the production of co-stimulatory molecules that are also required for T-lymphocyte activation. Dendritic cells produce many of the same inflammatory cytokines as macrophages, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8). They also can produce interleukin-12 (IL-12), a cytokine that can activate natural killer T-lymphocytes (NKT cells).

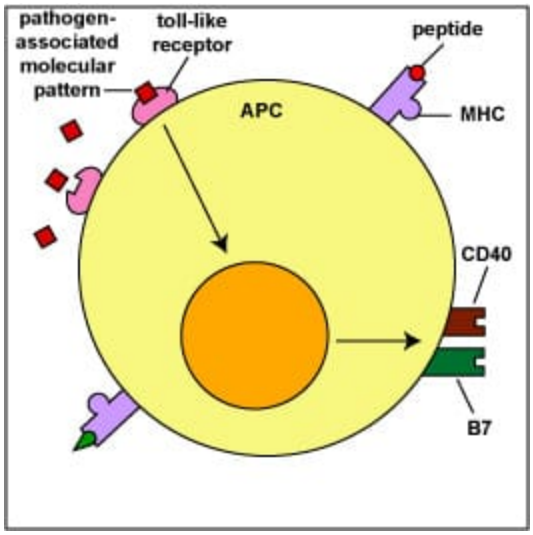


Figure 11.3.4: Production of Co-stimulatory Molecules by Antgen-Presenting Cells (APCs). Antigen-presenting cells such as dendritic cells and macrophages can produce both MHC-I and MHC-II molecules. MHC-I molecules with bound peptides can be recognized by a complementary-shaped TCR/CD8 on the surface of a naive T8-lymphocyte while MHC-II molecules with bound peptides can be recognized by a complementary-shaped TCR/CD4 on the surface of a naive T4-lymphocyte. This represents the first signal necessary for activation of the naive T4- or T8-lymphocyte. Co-stimulatory signals involving the interaction of co-stimulatory molecules such as CD40 and B7 molecules on the APC with their corresponding ligands on the T4- or T8-lymphocyte are also necessary for activation. These co-stimulatory molecules are only synthesized when toll-like receptors on APCs bind to pathogen-associated molecular patterns of microbes. This is another backup system to help assure that the TCR of the lymphocyte is recognizing a nonself peptide and not a self peptide on the MHC molecules of the APC. Without the interaction of the co-stimulatory molecules, the naive T4- or T8-lymphocyte is not activated and undergoes apoptosis.

Another type of dendritic cell, the plasmacytoid dendritic cell, uses its TLRs to recognize viral PAMPs. This interaction results in the production and secretion of type I interferons. Antigen-presenting cells or APCs will be discussed in greater detail in Unit 6.

Macrophages

When monocytes leave the blood and enter the tissue, they become activated and differentiate into macrophages. Those that have recently left the blood during inflammation and move to the site of infection through positive chemotaxis are sometimes referred to as wandering macrophages. In addition, the body has macrophages already stationed throughout all tissues and organs of the body. These are sometimes referred to as fixed macrophages.

Many fixed macrophages are part of the mononuclear phagocytic (reticuloendothelial) system. They, along with B-lymphocytes and T-lymphocytes, are found supported by reticular fibers in lymph nodules, lymph nodes, and the spleen where they filter out and phagocytose foreign matter such as microbes. Similar cells are also found in the liver (Kupffer cells), the kidneys (mesangial cells), the brain (microglia), the bones (osteoclasts), the lungs (alveolar macrophages), and the gastrointestinal tract (peritoneal macrophages). Macrophages actually have a number of very important functions in body defense including:

Function 1

Killing of microbes, infected cells, and tumor cells by phagocytosis. Macrophages that have engulfed microorganisms become activated by a subset of T-helper lymphocytes called T_h1 cells (Figure 11.3.6). Activated macrophages develop a ruffled cytoplasmic membrane and produce increased numbers of lysosomes.

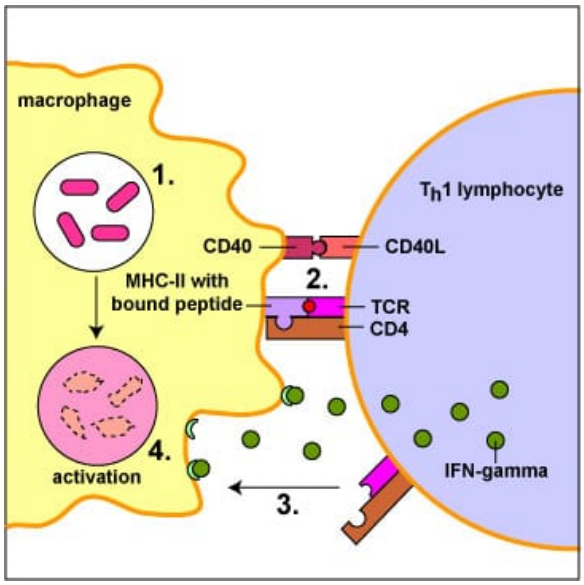


Figure 11.3.6: Activation of a Macrophage by a T_h1 Lymphocyte. 1. Engulfed bacteria inside a phagosome or a phagolysosome. 2. An activated T_h1 lymphocyte binds to a peptide/MHC-II complex on a macrophage by way of its TCR and CD4 molecule. Co-stimulatory molecules such as CD40L on the T_h1 cell then bind to CD40 on a macrophage. 3. This triggers the T_h1 lymphocyte to secrete the cytokine interferon-gamma (IFN-gamma) that binds to IFN-gamma receptors receptors on the macrophage. 4. The IFN-gamma activates the macrophage enabling it to produce more hydrolytic lysosomal enzymes, nitric oxide, and toxic oxygen radicals that destroy the microorganisms within the phagosomes and phagolysosomes.

Function 2

Processing antigens so they can be recognized by effector T-lymphocytes during the adaptive immune responses. Macrophages, as well as the dendritic cells mentioned below, process antigens through phagocytosis and present them to T-lymphocytes. Because of this function, they are often referred to as antigen-presenting cells or APCs.

Macrophages primarily capture and present protein antigens to effector T-lymphocytes. (Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.) Macrophages engulf the microorganism and degrade it with their lysosomes. Peptides from microbial proteins are then bound to a groove of unique molecules called MHC-II molecules produced by macrophages, dendritic cells, and B-lymphocytes. The peptide epitopes bound to the MHC-II molecules are then put on the surface of the macrophage (Figure 11.3.1) where they can be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on an effector T4-lymphocyte (Figure 11.3.2). This interaction leads to the activation of that macrophage.

Like dendritic cells discussed above, macrophages are also capable of capturing and presenting protein antigens to naive T-lymphocytes although they are not as important in this function.

Function 3

Secreting lipid mediators of inflammation such as leukotrienes, prostaglandins, and platelet-activating factor (PAF).

Function 4

Secreting proteins called cytokines that play a variety of roles in non-specific body defense. Macrophage-produced cytokines promote inflammation and induce fever, increase phagocytosis and energy output, promote sleep, activate resting T-lymphocytes , attract and activate neutrophils, and stimulate the replication of endothelial cells to form capillaries and fibroblasts to form connective scar tissue. Four important cytokines that macrophages produce (as mentioned in Unit 1 under endotoxin) are tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8).

There is growing evidence that monocytes and macrophages can be “trained” by an earlier infection to do better in future infections, that is, develop memory. It is thought that microbial pathogen-associated molecular patterns (PAMPs) binding to

pattern-recognition (PRRs) on monocytes and macrophages triggers the cell's epigenome to reprogram or train that cell to react better against new infections.

Macrophages show great functional diversity. In addition to the populations of macrophages involved in body defense and immunity, there are populations of macrophages that play important roles in:

1. The development of a variety of tissues and organs within the body, including the brain, blood cells, mammary gland, pancreas, and kidneys.
2. Modulating normal physiology and maintaining homeostasis in the body, including insulin resistance and sensitivity, long term nutrient storage, thermogenesis, and liver and pancreas function in response to caloric intake.
3. Tissue repair, including the formation of scar tissue and the growth of new capillaries into injured tissues.

Mast Cells

Mast cells are typically the immunological first responders to infection and carry out many of the same inflammatory-mediating functions as basophils. There are two types of mast cells in the body: mast cells found in the connective tissue and mast cells found throughout the mucous membranes. The granules of mast cells contain such mediators as histamine, eosinophil chemotactic factor, neutrophil chemotactic factor, platelet activating factor, and cytokines such as IL-3, IL-4, IL-5, IL-6, and TNF-alpha. They also possess pathways for synthesizing leukotrienes and prostaglandins, chemicals that promote inflammation by causing vasodilation, increasing capillary permeability, and increasing mucous production.

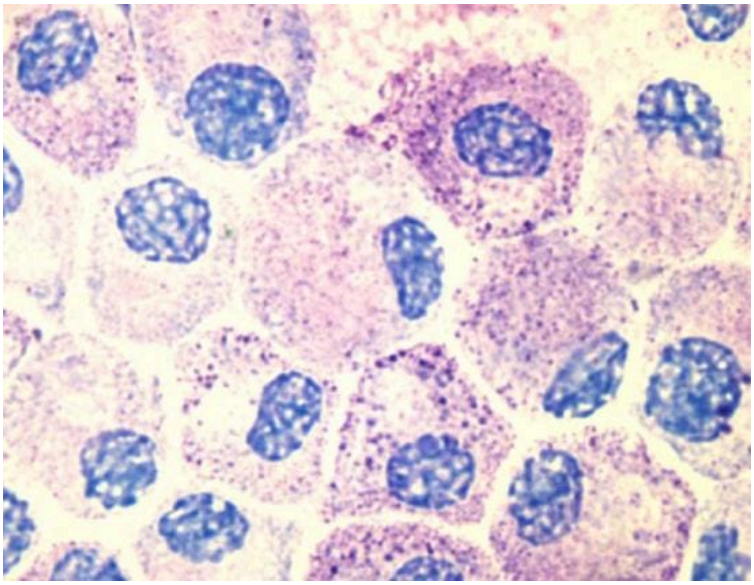


Photo of cultured mast cells at 100X using an oil immersion lens and an olympus digital camera. The cells are stained with Tol Blue, and might appear slightly degranulated as they were activated using an artificial antigen during the course of an experiment. Image use with permission (Kauczuk).

Mast cells have pattern-recognition receptors or PRRs on their surface that interact with pathogen-associated molecular patterns or PAMPs of microbes. After the PAMPs bind to their respective PRRs, they release the contents of their granules. These chemical mediators promote inflammation and attract neutrophils to the infected site.

Summary

1. Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells and are located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract, as well as lymphoid tissues and organ parenchyma.
2. Upon capturing antigens through pinocytosis and, the dendritic cells detach from their initial site, enter lymph vessels, and are carried to regional lymph nodes where they present antigens to the ever changing populations of naive T-lymphocytes.
3. The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes.

4. When monocytes leave the blood and enter the tissue, many become activated and differentiate into macrophages. These macrophages that have recently left the blood during inflammation and move to the site of infection through positive chemotaxis are sometimes referred to as wandering macrophages.
5. The body has macrophages already stationed throughout the tissues and organs of the body and these are sometimes referred to as fixed macrophages.
6. Functions of macrophages include killing of microbes, infected cells, and tumor cells by phagocytosis, processing antigens so they can be recognized by effector T-lymphocytes during the adaptive immune responses, and secreting mediators of inflammation such as leukotrienes, prostaglandins, and platelet-activating factor, and cytokines.
7. Mast cells are typically the immunological first responders to infection and carry out many of the same inflammatory-mediating functions as basophils.

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11.3: IMMEDIATE INNATE IMMUNITY

Immediate innate immunity begins 0-4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood, our found in extracellular tissue fluids, and are secreted by epithelial cells. These include: antimicrobial enzymes and peptides, and complement system proteins. These preformed antimicrobial molecules are designed to immediately begin to remove infectious agents as soon as they enter the body. In addition to preformed antimicrobial molecules, the following also play a role in immediate innate immunity: anatomical barriers to infection, mechanical removal of microbes, and bacterial antagonism by the body's normal microbiota



- Topic hierarchy

11.3A: Antimicrobial Enzymes and Antimicrobial Peptides

11.3B: The Complement System

11.3C: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota

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11.3A: Antimicrobial Enzymes and Antimicrobial Peptides

State how long it takes for immediate innate immunity to become activated and what it involves.

- State the function of the following antimicrobial enzymes and peptides:

  a. lysozyme
  b. phospholipase A_2
  c. defensins
  d. cathelicidins
  e. lactotransferrin and transferrin

Examples include:

a. Lysozyme , found in in tears, mucous, saliva, plasma , tissue fluid, etc., breaks down peptidoglycan in bacteria causing osmotic lysis. Specifically, it breaks the bond between the N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), the two sugars that make up the backbone of peptidoglycan (see Figure 11.3*A*.1).

b. Phospholipase A_2 is an enzyme that penetrates the bacterial cell wall and hydrolyzes the phospholipids in the bacterial cytoplasmic membrane.

c. Human defensins *)* are short cationic peptides 30-40 amino acids long that are directly toxic by disrupting the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs (see Figure 11.3*A*.2). They also activate cells for an inflammatory response. Defensins are produced by leukocytes, epithelial cells, and other cells. They are also found in blood plasma and mucus. Certain defensins also disrupt the envelopes of some viruses.

d. Cathelicidins are proteins produced by skin and mucosal epithelial cells. The two peptides produced upon cleavage of the cathelicidin are directly toxic to a variety of microorganisms. One pepitide also can bind to and neutralize LPS from Gram-negative cell walls to reduce inflammation.

e. Lactic and fatty acids, found in perspiration and sebaceous secretions , inhibit microbes on the skin.

f. Lactoferrin and transferrin , found in body secretions, plasma, and tissue fluid, trap iron for use by human cells while preventing its use by microorganisms.

g. Hydrochloric acid and enzymes found in gastric secretions destroy microbes that are swallowed.

Keep in mind that in Unit 3 under "Virulence Factors that Promote Bacterial Colonization of the Host" we learned several mechanisms that various bacteria use to resist the body's antibacterial peptides. By resisting these immediate innate immune defenses, some bacteria have a better chance of colonizing their host.

Concept Map for Antibacterial Enzymes and Peptides

Summary

1. Immediate innate immunity begins 0-4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood and are found in extracellular tissue fluids.
2. Lysozyme, found in in tears, mucous, saliva, plasma, tissue fluid, etc., breaks down peptidoglycan in bacteria causing osmotic lysis.
3. Phospholipase A2 is an enzyme that penetrates the bacterial cell wall and hydrolyzes the phospholipids in the bacterial cytoplasmic membrane.
4. Human defensins are short cationic peptides 30-40 amino acids long that are directly toxic by disrupting the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs.

5. Cathelicidins are proteins produced by skin and mucosal epithelial cells that are directly toxic to a variety of microorganisms.
6. Lactoferrin and transferrin, found in body secretions, plasma, and tissue fluid, trap iron for use by human cells while preventing its use by microorganisms.

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11.3B: The Complement System

Briefly describe how the classical complement pathway is activated.

- Briefly describe the beneficial effects of the following complement pathway products:

  a. C5a
  b. C3a
  c. C3b
  d. C4b
  e. C3d
  f. $C5b6789_n$ (MAC)

- Briefly describe how the lectin pathway is activated.
- Briefly describe how the alternative complement pathway is activated.

In this section we will look at how the body's complement system functions to remove infectious agents. The complement system refers to a series of more than 30 soluble, preformed proteins circulating in the blood and bathing the fluids surrounding tissues. The proteins circulate in an inactive form, but in response to the recognition of molecular components of microorganism, they become sequentially activated, working in a cascade where in the binding of one protein promotes the binding of the next protein in the cascade. There are 3 complement pathways that make up the complement system: the classical complement pathway, the lectin pathway, and the alternative complement pathway. The pathways differ in the manner in which they are initiated and ultimately produce a key enzyme called C3 convertase:

- The **classical complement pathway** is initiated by activation of C1. C1 is primarily activated by interacting with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen. C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity.
- The **lectin pathway** is activated by the interaction of microbial carbohydrates (lectins) with mannose-binding lectin (MBL) or ficolins found in the plasma and tissue fluids.
- The **alternative complement pathway** is activated by C3b binding to microbial surfaces and to antibody molecules.

The end results and defense benefits of each pathway, however, are the same. All complement pathways carry out 6 beneficial innate defense functions. Proteins produced by the complement pathways:

1. Trigger inflammation,
2. Chemotactically attract phagocytes to the infection site,
3. Promote the attachment of antigens to phagocytes (enhanced attachment or opsonization),
4. Cause lysis of Gram-negative bacteria, human cells displaying foreign epitopes,and viral envelopes,
5. Play a role in the activation of naive B-lymphocytes during adaptive immunity, and
6. Remove harmful immune complexes from the body.

We will now look at each of these complement pathways and see how they function to protect the body.

The Classical Complement Pathway

The classical complement pathway is primarily activated when a complement protein complex called C1 interacts with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen via their Fab portion. C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity. The C1 complex is composed of three complement proteins called C1q, C1r, and C1s.

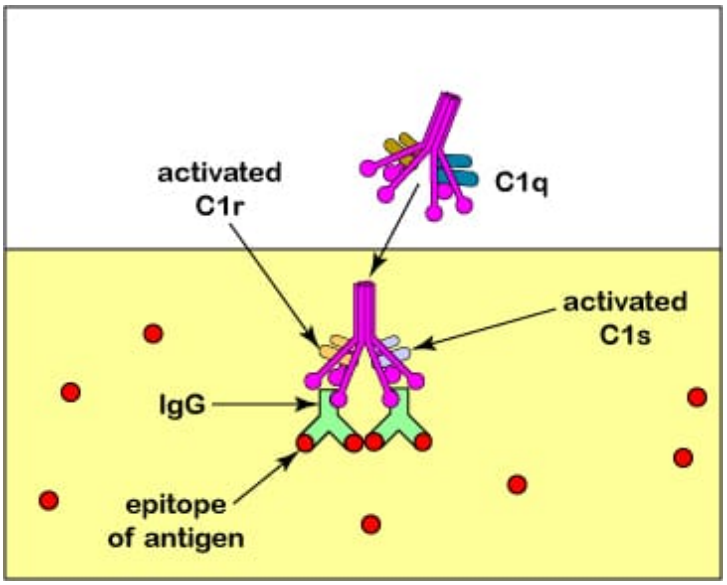


Figure 11.3B.1: Activation of C1 during the Classical Complement Pathway. The Fab of 2 molecules of IgG or 1 molecule of IgM bind to epitopes on an antigen. C1, consisting of C1q, C1r, and C1s then binds to the Fc portion of the antibodies. The binding of C1q to the antibody molecules activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b and complement protein C2 into C2a and C2b.

C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity.

Flash animation showing assembly of C1 during the classical complement pathway.

html5 version of animation for iPad showing assembly of C1 during the classical complement pathway.

2. The binding of C1q activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b (see Figure 11.3B.2A and Figure 11.3B.2B).

3. C2 then binds to C4b and is cleaved by C1 into C2a and C2b (see Figure 11.3B.3A and Figure 11.3B.3B).

4. C4b and C2a combine to form C4b2a, the C3 convertase. C3 convertase can now cleave hundreds of molecules of C3 into C3a and C3b (see Figure 11.3B.4).

5. Some molecules of C3b bind to C4b2a, the C3 convertase, to form C4b2a3b, a C5 convertase that cleaves C5 into C5a and C5b (see Figure 11.3B.5).

Flash animation showing formation of C3 convertase and C5 convertase during the classical complement pathway.

html5 version of animation for iPad showing formation of C3 convertase and C5 convertase during the classical complement pathway.

6. C5b binds to the surface of the target cell and subsequently binds C6, C7, C8, and a number of monomers of C9 to form $C5b6789_n$, the Membrane Attack Complex (MAC) (see Figure 11.3B.6 and Figure 11.3B.7).

Flash animation showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

For More Information: Antigens and Immunogens from Unit 5

For More Information: Antibodies from Unit 6

As mentioned above, proteins of the complement pathways carry out 6 beneficial innate defense functions. These include:

1. Triggering inflammation: C5a is the most potent complement protein triggering inflammation. It reacts with blood vessels causing vasodilation. It also causes mast cells to release vasodilators such as histamine,increasing blood vessel permeability as well as increasing the expression of adhesion molecules on leukocytes and the vascular endothelium so that leukocytes can squeeze out of the blood vessels and enter the tissue (diapedesis). C5a also causes neutrophils to release toxic oxygen radicals for extracellular killing and induces fever. To a lesser extent C3a and C4a also promote inflammation. As we will see later in this unit, inflammation is a process in which blood vessels dilate and become more permeable, thus enabling body defense cells and defense chemicals to leave the blood and enter the tissues.

2. Chemotactically attracting phagocytes to the infection site: C5a also functions as a chemoattractant for phagocytes. Phagocytes will move towards increasing concentrations of C5a and subsequently attach, via their CR1 receptors to the C3b molecules attached to the antigen. This will be discussed in greater detail later in this unit under phagocytosis.

3. Promoting the attachment of antigens to phagocytes (enhanced attachment or opsonization): C3b and to a lesser extent, C4b can function as opsonins, that is, they can attach antigens to phagocytes. One portion of the C3b binds to proteins and polysaccharides on microbial surfaces; another portion attaches to CR1 receptors on phagocytes, B-lymphocytes, and dendritic cells for enhanced phagocytosis. (see Figure $11.3B.8$). In actuality, C3b molecule can bind to pretty much any protein or polysaccharide. Human cells, however, produce Factor H that binds to C3b and allows Factor I to inactivate the C3b. On the other hand, substances such as LPS on bacterial cells facilitate the binding of Factor B to C3b and this protects the C3b from inactivation by Factor I. In this way, C3b does not interact with our own cells but is able to interact with microbial cells. C3a and C5a increase the expression of C3b receptors on phagocytes and increase their metabolic activity.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

4. Causing lysis of Gram-negative bacteria, human cells displaying foreign epitopes,and viral envelopes: $C5b6789_n$, functions as a Membrane Attack Complex (MAC). This helps to destroy gram-negative bacteria as well as human cells displaying foreign antigens (virus-infected cells, tumor cells, etc.) by causing their lysis; see Figure $11.3B.6$ and Figure $11.3B.7$. It can also damage the envelope of enveloped viruses.

Flash animation showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

5. Serving as a second signal for activating naive B-lymphocytes during adaptive immunity: Some C3b is converted to

C3d. C3d binds to CR2 receptors on B-lymphocytes. This serves as a second signal for the activation of B-lymphocytes whose B-cell receptors have just interacted with their corresponding antigen.

6. Removing harmful immune complexes from the body: C3b and to a lesser extent, C4b help to remove harmful immune complexes from the body. The C3b and C4b attach the immune complexes to CR1 receptors on erythrocytes. The erythrocytes then deliver the complexes to fixed macrophages within the spleen and liver for destruction. Immune complexes can lead to a harmful Type III hypersensitivity, as will be discussed later in Unit 5 under Hypersensitivities.

YouTube animation illustrating benefits of the complement pathways.

Concept Map for the Complement Pathways

Some bacterial capsules are rich in sialic acid, a common component of host cell glycoprotein, that has an affinity for serum protein H, a complement regulatory protein that leads to the degradation of C3b.

Describe what significance this has in the bacterium resisting phagocytosis and why.

2. *S. pyogenes* produces a protease that cleaves the complement protein C5a.

Describe what significance this has in the bacterium resisting phagocytosis and why.

The Lectin Pathway

The lectin pathway is activated by the interaction of microbial carbohydrates with mannose-binding lectin (MBL) or ficolins found in the plasma and tissue fluids. (Lectins are carbohydrate-binding proteins.) The lectin pathway is mediated by two groups of proteins found in the plasma of the blood and in tissue fluids:

1. Mannose-binding lectin (MBL) - also known as mannose-binding protein or MBP. MBL is a soluble pattern-recognition receptor that binds to various microbial carbohydrates such as those rich in mannose or fucose, and to N-acetylglucosamine (NAG). These glycans are common in microbial glycoproteins and glycolipids but rare in those of humans. MBL is synthesized by the liver and released into the bloodstream as part of the acute phase response that will be discussed later in this unit. The MBL is equivalent to C1q in the classical complement pathway.

Ficolins are similar in their structure to MBL and bind to microbial carbohydrates such as N-acetylglucosamine (NAG), lipoteichoic acids, and lipopolysaccharide (LPS). Ficolin is also equivalent to C1q in the classical complement pathway.

2. Both mannose-binding lectin (MBL) and ficolin form complexes with MBL-associated serine proteases called MASP1 and MASP2, which are equivalent to C1r and C1s of the classical pathway.

a. The binding of the MBL (or the ficolin) to the microbial carbohydrate activates the associated MASP2 giving it the enzymatic activity to split C4 into C4a and C4b (see Figure 11.3B.9A and Figure 11.3B.9B).

b. C2 then binds to C4b and is cleaved by MASP2 into C2a and C2b (see Figure 11.3B.10A and Figure 11.3B.10B).

c. C4b and C2a combine to form C4b2a, the C3 convertase. C3 convertase can now cleave hundreds of molecules of C3 into C3a and C3b (see Figure 11.3B.11).

d. Some molecules of C3b bind to C4b2a, the C3 convertase, to form C4b2a3b, a C5 convertase that cleaves C5 into C5a and C5b (see Figure 11.3B.12).

e. C5b binds to the surface of the target cell and subsequently binds C6, C7, C8, and a number of monomers of C9 to form C5b6789$_n$, the Membrane Attack Complex (MAC) (see Figure 11.3B.6 and Figure 11.3B.7).

Flash animation showing activation of the lectin pathway

html5 version of animation for iPad showing activation of the lectin pathway

Flash animation showing formation of C3 convertase and C5 convertase during the lectin pathway.

html5 version of animation for iPad showing formation of C3 convertase and C5 convertase during the lectin pathway.

Flash animation showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

The beneficial results of the activated complement proteins are the same as in the classical complement pathway above. The complement proteins:

1. Trigger inflammation : C5a>C3a>c4a;
2. Chemotactically attract phagocytes to the infection site: C5a;
3. Promote the attachment of antigens to phagocytes via enhanced attachment or opsonization : C3b>C4b;
4. Cause lysis of Gram-negative bacteria and human cells displaying foreign epitopes : MAC;
5. Serve as a second signal for the activation of naive B-lymphocytes *)*: C3d; and

6 Remove harmful immune complexes from the body: C3b>C4b.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

Flash animation showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

Concept Map for the Complement Pathways

YouTube animation illustrating benefits of the complement pathways.

The Alternative Complement Pathway

The alternative complement pathway is mediated by C3b, produced either by the classical or lectin pathways or from C3 hydrolysis by water. (Water can hydrolyze C3 and form C3i, a molecule that functions in a manner similar to C3b.)

Activation of the alternative complement pathway begins when C3b (or C3i) binds to the cell wall and other surface components of microbes. C3b can also bind to IgG antibodies. Alternative pathway protein Factor B then combines with the cell-bound C3b to form C3bB. Factor D then splits the bound Factor B into Bb and Ba, forming C3bBb. A serum protein called properdin then binds to the Bb to form C3bBbP that functions as a C3 convertase (see Figure $11.3B.13$) capable of enzymatically splitting hundreds of molecules of C3 into C3a and C3b. The alternative complement pathway is now activated.

Some of the C3b subsequently binds to some of the C3bBb to form C3bBb3b, a C5 convertase capable of splitting molecules of C5 into C5a and C5b (see Figure $11.3B.14$). From here, the alternative complement pathway is identical to the other complement pathways.

Flash animation showing the activation of the alternative complement pathway, the formation of C3 convertase, and the formation of C5 convertase.

html5 version of animation for iPad showing the activation of the alternative complement pathway, the formation of C3 convertase, and the formation of C5 convertase.

The beneficial results are the same as in the classical complement pathway above. The complement proteins:

1. Trigger inflammation : C5a>C3a>c4a;
2. Chemotactically attract phagocytes to the infection site: C5a;
3. Promote the attachment of antigens to phagocytes via enhanced attachment or opsonization : C3b>C4b;
4. Cause lysis of Gram-negative bacteria, human cells displaying foreign epitopes,and viral envelopes: MAC; and
5. Serve as a second signal for the activation of naive B-lymphocytes *)*: C3d;
6. Remove harmful immune complexes from the body: C3b>C4b.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

Flash animation showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

Concept Map for the Complement Pathways

YouTube animation illustrating benefits of the complement pathways.

Keep in mind that in Unit 3, we learned several mechanisms that various bacteria use to resist the body's complement pathways. By resisting these immediate innate immune defenses, some bacteria have a better chance of colonizing their host.

Summary

1. The proteins of the complement system circulate in an inactive form, but in response to the recognition of molecular components of microorganism, they become sequentially activated, working in a cascade where in the binding of one protein promotes the binding of the next protein in the cascade.
2. There are 3 complement pathways that make up the complement system: the classical complement pathway, the lectin pathway, and the alternative complement pathway.
3. The classical complement pathway is initiated by activation of C1. C1 is primarily activated by interacting with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen. C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity.
4. The lectin pathway is activated by the interaction of microbial carbohydrates (lectins) with mannose-binding lectin (MBL) or ficolins found in the plasma and tissue fluids.
5. The alternative complement pathway is activated by C3b binding to microbial surfaces and to antibody molecules.
6. All complement pathways carry out the same 6 beneficial innate defense functions.
7. The complement proteins C5a and, to a lesser extent, C3a, and C4a trigger vasodilation and inflammation in order to deliver defense cells and defense chemicals to the infection site.
8. The complement protein C5a also functions as a chemoattractant for phagocytes.
9. The complement proteins C3b and to a lesser extent, C4b can function as opsonins, that is, they can attach antigens to phagocytes.
10. The complement proteins C5b6789n, functions as a Membrane Attack Complex (MAC) causing lysis of Gram-negative bacteria, human cells displaying foreign epitopes, and viral envelopes.
11. The complement protein C3d serves as a second signal for activating naive B-lymphocytes during adaptive immunity.
12. The complement proteins C3b and to a lesser extent, C4b help to remove harmful immune complexes from the body.

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11.3C: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota

Describe what is meant by anatomical barriers to infection.

- List 4 ways in which the body can physically remove microorganisms or their products.
- Briefly describe how intraepithelial T-lymphocytes and B-1 cells play a role in innate immunity.
- Describe how bacterial antagonism by normal microbiota acts as a non-specific body defense mechanism and name 2 opportunistic microbes that may cause superinfection upon destruction of the normal microbiota.
- Briefly describe the process involved in the development of antibiotic-associated colitis.

Anatomical barriers are tough, intact barriers that prevent the entry and colonization of many microbes. Examples include the skin, the mucous membranes, and bony encasements.

The skin

The skin, consisting of the epidermis and the dermis, is dry, acidic, and has a temperature lower than 37 degrees Celsius (body temperature). These conditions are not favorable to bacterial growth. Resident normal microbiota of the skin also inhibits potentially harmful microbes. In addition, the dead, keratinized cells that make up the surface of the skin are continuously being sloughed off so that microbes that do colonize these cells are constantly being removed. Hair follicles and sweat glands produce lysozyme and toxic lipids that can kill bacteria. Epithelial cells also produce defensins and cathelicidins to kill microbes. Beneath the epidermis of the skin are Langerhans' cells - immature dendritic cells - that phagocytose and kill microbes, carry them to nearby lymph nodes, and present antigens of these microbes to T-lymphocytes to begin adaptive immune responses against them. Finally, intraepithelial T-lymphocytes and B-1 lymphocytes are associated with the epidermis and the mucosal epithelium. These cells recognize microbes common to the epidermis and mucous membranes and start immediate adaptive immune responses against these commonly encountered microbes.

The mucous membranes

Mucous membranes line body cavities that open to the exterior, such as the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Mucous membranes are composed of an epithelial layer that secretes mucus, and a connective tissue layer. The mucus is a physical barrier that traps microbes. Mucus also contains lysozyme to degrade bacterial peptidoglycan, an antibody called secretory IgA that prevents microbes from attaching to mucosal cells and traps them in the mucous, lactoferrin to bind iron and keep it from from being used by microbes, and lactoperoxidase to generate toxic superoxide radicals that kill microbes. Resident normal microbiota of the mucosa also inhibits potentially harmful microbes. In addition, the mucous membrane, like the skin, is constantly sloughing cells to remove microbes that have attached to the mucous membranes. Beneath the mucosal membrane is mucosa-associated lymphoid tissue (MALT) that contains Langerhans' cells - immature dendritic cells - that phagocytose and kill microbes, carry them to nearby lymph nodes, and present antigens of these microbes to T-lymphocytes to begin adaptive immune responses against them. Intraepithelial T-lymphocytes and B-1 lymphocytes are associated with the epidermis and the mucosal epithelium. These cells recognize microbes common to the epidermis and mucous membranes and start immediate adaptive immune responses against these commonly encountered microbes.

Bony encasements

Bony encasements, such as the skull and the thoracic cage, protect vital organs from injury and entry of microbes.

Mechanical removal is the process of physically flushing microbes from the body. Methods include:

1. **Mucus and cilia:** Mucus traps microorganisms and prevents them from reaching and colonizing the mucosal epithelium. Mucus also contains lysozyme to degrade bacterial peptidoglycan, an antibody called secretory IgA that prevents microbes from attaching to mucosal cells and traps them in the mucus, lactoferrin to bind iron and keep it from from being used by microbes, and lactoperoxidase to generate toxic superoxide radicals that kill microbes. Cilia on the surface of the epithelial cells propel mucus and trapped microbes upwards towards the throat where it is swallowed and the microbes are killed in the stomach. This is sometimes called the tracheal toilet.
2. **The cough and sneeze reflex:** Coughing and sneezing removes mucus and trapped microbes.
3. **Vomiting and diarrhea:** These processes remove pathogens and toxins in the gastrointestinal tract.
4. **he physical flushing action of body fluids:** Fluids such as urine, tears, saliva, perspiration, and blood from injured blood vessels also flush microbes from the body.

Bacterial Antagonism by Normal Microbiota

Approximately 100 trillion bacteria and other microorganisms reside in or on the human body. The normal body microbiota keeps potentially harmful opportunistic pathogens in check and also inhibits the colonization of pathogens by:

1. Producing metabolic products (fatty acids, bacteriocins, etc.) that inhibit the growth of many pathogens;
2. Adhering to target host cells so as to cover them and preventing pathogens from colonizing;
3. Depleting nutrients essential for the growth of pathogens; and
4. Non-specifically stimulating the immune system.

Destruction of normal bacterial microbiota by the use of broad spectrum antibiotics may result in superinfections or overgrowth by antibiotic-resistant opportunistic microbiota. For example, the yeast *Candida*, that causes infections such as vaginitis and thrush, and the bacterium *Clostridium difficile*, that causes potentially severe antibiotic-associated colitis, are opportunistic microorganisms normally held in check by the normal microbiota.

In the case of *Candida* infections, the *Candida* resists the antibacterial antibiotics because being a yeast, it is eukaryotic, not prokaryotic like the bacteria. Once the bacteria are eliminated by the antibiotics, the *Candida* has no competition and can overgrow the area.

Clostridium difficile is an opportunistic Gram-positive, endospore-producing bacillus transmitted by the fecal-oral route that causes severe antibiotic-associated colitis. *C. difficile* is a common healthcare-associated infection (HAIs) and is the most frequent cause of health-care-associated diarrhea. *C. difficile* infection often recurs and can progress to sepsis and death. CDC has estimated that there are about 500,000 *C. difficile* infections (CDI) in health-care associated patients each year and is linked to 15,000 American deaths each year.

Antibiotic-associated colitis is especially common in older adults. It is thought that *C. difficile* survives the exposure to the antibiotic by sporulation. After the antibiotic is no longer in the body, the endospores germinate and *C. difficile* overgrows the intestinal tract and secretes toxin A and toxin B that have a cytotoxic effect on the epithelial cells of the colon. *C. difficile* has become increasingly resistant to antibiotics in recent years making treatment often difficult. There has been a great deal of success in treating the infection with fecal transplants, still primarily an experimental procedure. Polymerase chain reaction (PCRs) assays, which test for the bacterial gene encoding toxin B, are highly sensitive and specific for the presence of a toxin-producing *Clostridium difficile* organism. The most successful technique in restricting *C. difficile* infections has been the restriction of the use of antimicrobial agents.

A patient is given large doses of broad spectrum antibiotics and subsequently develops a *Candida albicans* infection of the vagina. Discuss why this might happen in terms of immediate innate immunity. Why didn't the antibiotic kill the *Candida albicans* too?

- Often during intestinal infections drugs are given to suppress diarrhea. Discuss why this may not always be a good idea, especially with microbial infections that cause ulceration of the intestines.

Summary

Anatomical barriers such as the skin, the mucous membranes, and bony encasements are tough, intact barriers that prevent the entry and colonization of many microbes. Mechanical removal is the process of physically flushing microbes from the body. Examples include mucus and cilia, coughing and sneezing, vomiting and diarrhea, and the flushing action of bodily fluids. The normal microbiota keeps potentially harmful opportunistic pathogens in check and also inhibits the colonization of pathogens by producing metabolic products that inhibit the growth of many pathogens, adhering to target host cells so as to cover them and prevent pathogens from colonizing, depleting nutrients essential for the growth of pathogens, and non-specifically stimulating the immune system.

Destruction of normal bacterial microbiota by the use of broad spectrum antibiotics may result in superinfections or overgrowth by antibiotic-resistant opportunistic microbiota such as *Candida* and *Clostridium difficile*.

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11.4: EARLY INDUCED INNATE IMMUNITY

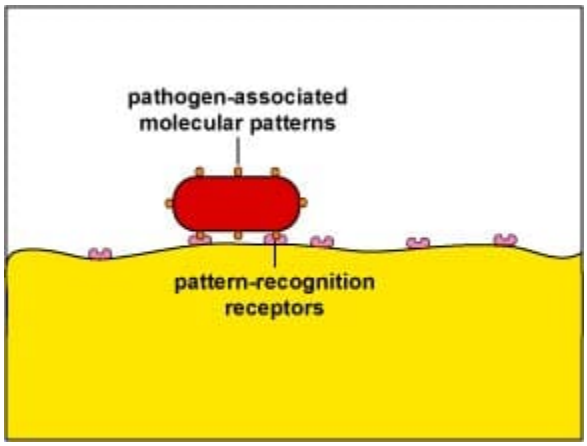


Figure 11.4.1: Pathogen-Associated Molecular Patterns Binding to Pattern-Recognition Receptors on Defense Cells. Glycoprotein molecules known as pattern-recognition receptors are found on the surface of a variety of body defense cells. They are so named because they recognize and bind to pathogen-associated molecular patterns - molecular components associated with microorganisms but not found as a part of eukaryotic cells. These include bacterial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, flagellin, pilin, and bacterial DNA. There are also pattern-recognition molecules for viral double-stranded RNA (dsRNA) and fungal cell walls components such as lipoteichoic acids, glycolipids, mannans, and zymosan. Many of these pattern recognition receptors are known as toll-like receptors.

Most body defense cells have pattern-recognition receptors or PRRs for these common PAMPs enabling an immediate response against the invading microorganism. Pathogen-associated molecular patterns can also be recognized by a series of soluble pattern-recognition receptors in the blood that function as opsonins and initiate the complement pathways. In all, the innate immune system is thought to recognize approximately 10^3 of these microbial molecular patterns.

- Topic hierarchy

11.3A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)

11.3B: Pattern-Recognition Receptors (PRRs)

11.3C: Cytokines Important in Innate Immunity

11.3D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production

11.3E: Phagocytosis

11.3F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)

11.3G: Inflammation

11.3H: Nutritional Immunity

11.3I: Fever

11.3J: The Acute Phase Response

11.3K: Intraepithelial T-lymphocytes and B-1 cells

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11.3A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)

State how long it takes for early induced innate immunity to become activated and what it involves.

- State what is meant by pathogen-associated molecular patterns (PAMPs), and the role PAMPs play in inducing innate immunity.
- Name at least 5 PAMPS associated with bacteria.
- Name at least 2 PAMPS associated with viruses.
- Define DAMPs and give two examples.

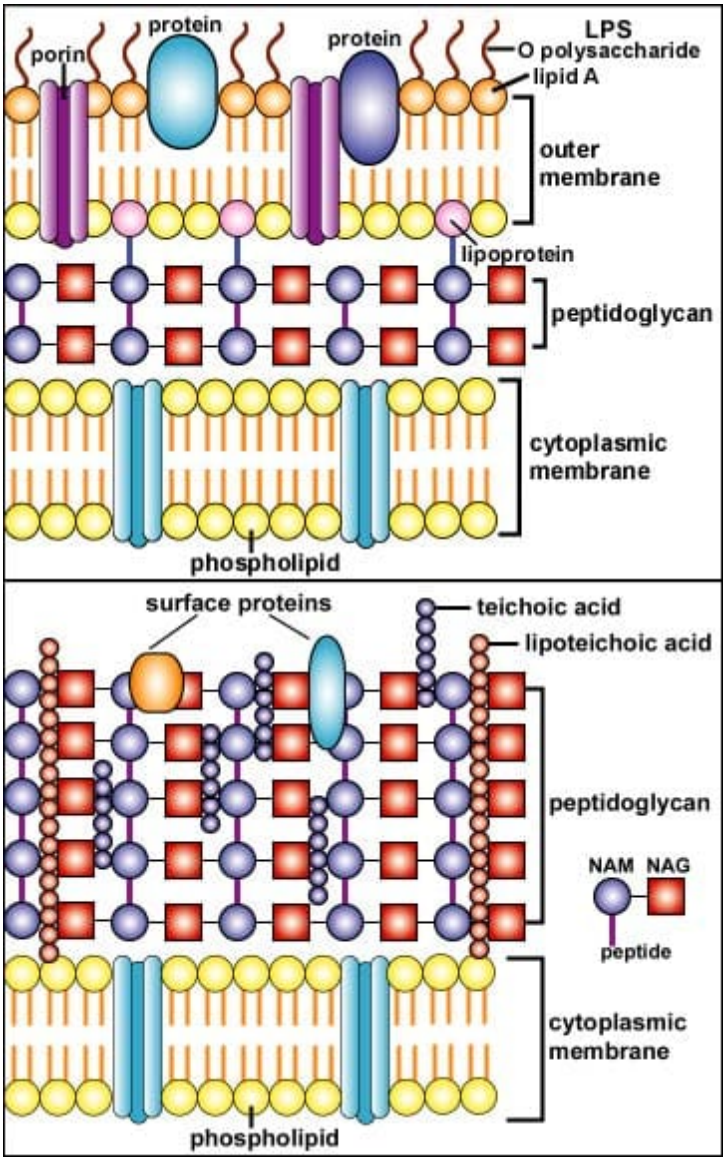


Figure 11.3A.1: (left) Structure of a Gram-Negative Cell Wall. The Gram-negative cell wall is composed of a thin, inner layer of peptidoglycan and an outer membrane consisting of molecules of phospholipids, lipopolysaccharides (LPS), lipoproteins and surface proteins. The lipopolysaccharide consists of lipid A and O polysaccharide. (right) The Gram-positive cell wall appears as dense layer typically composed of numerous rows of peptidoglycan, and molecules of lipoteichoic acid, wall teichoic acid and surface proteins.

Examples of microbial-associated PAMPs include:

a. lipopolysaccharide (LPS) from the outer membrane of the Gram-negative cell wall (see Figure 11.3A.1A);
b. bacterial lipoproteins and lipopeptides (see Figure 11.3A.1A);
c. porins in the outer membrane of the Gram-negative cell wall (see Figure 11.3A.1A);
d. peptidoglycan found abundantly in the Gram-positive cell wall and to a lesser degree in the gram-negative cell wall (see Figure 11.3A.1B);
e. lipoteichoic acids found in the Gram-positive cell wall (Figure 11.3A.1B);
f. lipoarabinomannan and mycolic acids found in acid-fast cell walls (Figure 11.3A.2B)
g. mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar). These are common in microbial glycoproteins and glycolipids but rare in those of humans (see Figure 11.3A.6).
h. flagellin found in bacterial flagella;
i. bacterial and viral nucleic acid. Bacterial and viral genomes contain a high frequency of unmethylated cytosine-guanine dinucleotide or CpG sequences (a cytosine lacking a methyl or CH_3 group and located adjacent to a guanine). Mammalian DNA has a low frequency of CpG sequences and most are methylated which may mask recognition by pattern-recognition receptors . Also, human DNA and RNA does not normally enter cellular endosomes where the pattern-recognition receptors for microbial DNA and RNA are located;
j. *N*-formylmethionine , an amino acid common to bacterial proteins;
k. double-stranded viral RNA unique to many viruses in some stage of their replication;
l. single-stranded viral RNA from many` viruses having an RNA genome;
m. lipoteichoic acids, glycolipids, and zymosan from yeast cell walls; and
n. phosphorylcholine and other lipids common to microbial membranes.

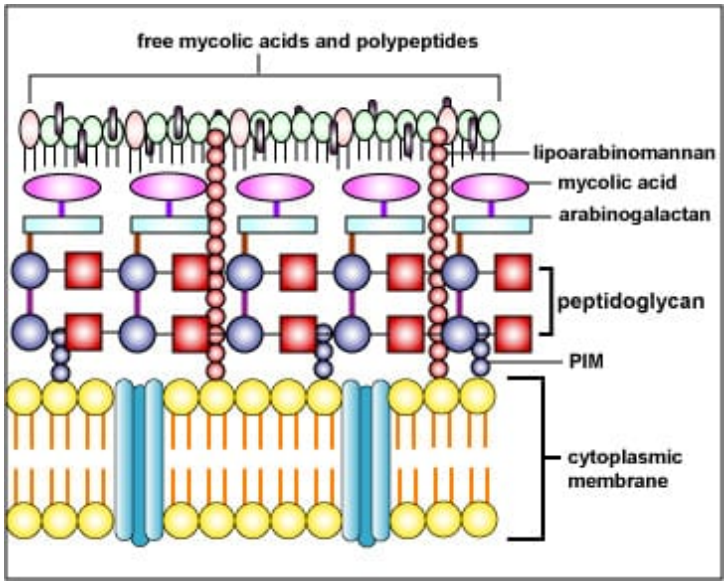


Figure 11.3A.2: Structure of an Acid-Fast Cell Wall. In addition to peptidoglycan, the acid-fast cell wall of Mycobacterium contains a large amount of glycolipids, especially mycolic acids. The peptidoglycan layer is linked to arabinogalactan (D-arabinose and D-galactose) which is then linked to high-molecular weight mycolic acids. The arabinogalactan/mycolic acid layer is overlaid with a layer of polypeptides and mycolic acids consisting of free lipids, glycolipids, and peptidoglycolipids. Other glycolipids include lipoarabinomannan and phosphatidyinositol mannosides (PIM). Because of its unique cell wall, when it is stained by the acid-fast procedure, it will resist decolorization with acid-alcohol and stain red, the color of the initial stain, carbol fuchsin. With the exception of a very few other acid-fast bacteria such as Nocardia, all other bacteria will be decolorized and stain blue, the color of the methylene blue counterstain.

Examples of DAMPs associated with stressed, injured, infected, or transformed host cells and not found on normal cells include:

a. heat-shock proteins;
b. altered membrane phospholipids; and
c. molecules normally located inside phagosomes and lysosomes that enter the cytosol only when these membrane-bound compartments are damaged as a result of infection, including antibodies bound to microbes from opsonization.
d. molecules normally found within cells, such as ATP, DNA, and RNA, that spill out of damaged cells.

To recognize PAMPs such as those listed above, various body cells have a variety of corresponding receptors called pattern-recognition receptors or PRRs capable of binding specifically to conserved portions of these molecules. Cells that typically have pattern recognition receptors include macrophages , dendritic cells , endothelial cells , mucosal epithelial cells, and lymphocytes

.

What are DAMPs and why would it be an advantage for them to initiate an inflammatory response similar to PAMPs?

Summary

1. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs.
2. Pathogen-associated molecular patterns or PAMPs are molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells. Examples include LPS, porins, peptidoglycan, lipoteichoic acids, mannose-rich glycans, flagellin, bacterial and viral genomes, mycolic acid, and lipoarabinomannan.
3. Danger-associated molecular patterns or DAMPs are unique molecules displayed on stressed, injured, infected, or transformed human cells also be recognized as a part of innate immunity. Examples include heat-shock proteins and altered membrane phospholipids.
4. PAMPs and DAMPs bind to pattern-recognition receptors or PRRs associated with body cells to induce innate immunity.

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11.3B: Pattern-Recognition Receptors (PRRs)

State the function of the following as they relate to innate immunity.

a. pattern recognition receptors (PRRs)
b. endocytic pattern recognition receptors
c. signaling pattern recognition receptors
d. danger-associated molecular patterns
e. danger recognition receptors
f. inflammasome
g. pyroptosis

- Name 2 endocytic PRRs.
- Name 2 signaling PRRs found on host cell surfaces.
- Name 2 signaling PRRs found in the endosomes of phagocytic cells.
- Name 2 signaling PRRs found on the host cell cytoplasm.
- Briefly describe the major difference between the effect of the cytokines produced in response to PAMPs that bind to cell surface signaling PRRs and endosomal PRRs.

In order to recognize PAMPs, various body cells have a variety of corresponding receptors called pattern-recognition receptors or PRRs (see Figure 11.3B.5) capable of binding specifically to conserved portions of these molecules. Cells that typically have pattern recognition receptors include macrophages, dendritic cells, endothelial cells, mucosal epithelial cells, and lymphocytes.

Many pattern-recognition receptors are located on the surface of these cells where they can interact with PAMPs on the surface of microbes. Others PRRs are found within the phagolysosomes of phagocytes where they can interact with PAMPs located within microbes that have been phagocytosed. Some PRRs are found in the cytosol of the cell.

There are two functionally different major classes of pattern-recognition receptors: endocytic pattern-recognition receptors and signaling pattern-recognition receptors.

Endocytic (Phagocytic) Pattern-Recognition Receptors

Endocytic pattern-recognition receptors, also called phagocytic pattern-recognition receptors, are found on the surface of phagocytes and promote the attachment of microorganisms to phagocytes leading to their subsequent engulfment and destruction. They include:

1. Mannose receptors

Mannose receptors on the surface of phagocytes bind to various microbial carbohydrates such as those rich in mannose or fucose, and to N-acetylglucosamine (NAG). Human glycoproteins and glycolipids typically have terminal N-acetylglucosamine and sialic acid groups. C-type lectins found on the surface of phagocytes are mannose receptors (see Figure 11.3B.6).

It is now thought that mannose receptors may be quite important in removing potentially harmful mannose-containing glycoproteins such as lysosomal hydrolases that are produced in increased amounts during inflammation.

2. Dectin-1

Dectin-1 recognizes beta-glucans (polymers of glucose) commonly found in fungal cell walls.

3. Scavenger receptors

Scavenger receptors found on the surface of phagocytic cells bind to bacterial cell wall components such as LPS, peptidoglycan and teichoic acids (see Figure 11.3B.7). There are also scavenger receptors for certain components of other types of

microorganisms, as well as for stressed, infected, or injured cells. Scavenger receptors include CD-36, CD-68, and SRB-1.

4. Opsonin receptors

Opsonins are soluble molecules produced as a part of the body's immune defenses that bind microbes to phagocytes. One portion of the opsonin binds to a PAMP on the microbial surface and another portion binds to a specific receptor on the phagocytic cell.

- Acute phase proteins circulating in the plasma, such as:
  - mannose-binding lectin (also called mannose-binding protein) that binds to various microbial carbohydrates such as those rich in mannose or fucose, and to N-acetylglucosamine (NAG); and
  - C-reactive protein (CRP) that binds to phosphorylcholine portion of teichoic acids and lipopolysaccharides of bacterial and fungal cell walls. It also binds to the phosphocholine found on the surface of damaged or dead human cells.
- Complement pathway proteins, such as C3b (see Figure 11.3B.8) and C4b recognize a variety of PAMPS.
- Surfactant proteins in the alveoli of the lungs, such as SP-A and SP-D are opsonins.
- During adaptive immunity, the antibody molecule IgG can function as an opsonin (see Figure 11.3B.16).

Flash animation illustrating the function of endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating the function of endocytic pattern-recognition receptors on phagocytes.

5. *N*-formyl Met receptors

N-formyl methionine is the first amino acid produced in bacterial proteins since the f-met-tRNA in bacteria has an anticodon complementary to the AUG start codon (see Figure 11.3B.17). This form of the amino acid is not typically seen in mammalian proteins. FPR and FPRL1 are *N*-formyl receptors on neutrophils and macrophages. Binding of *N*-formyl Met to its receptor promotes the motility and the chemotaxis of these phagocytes. It also promotes phagocytosis.

Signaling Pattern-Recognition Receptors

Signaling pattern-recognition receptors bind a number of microbial molecules: LPS, peptidoglycan, teichoic acids, flagellin, pilin, unmethylated cytosine-guanine dinucleotide or CpG sequences from bacterial and viral genomes; lipoteichoic acid, glycolipids, and zymosan from fungi; double-stranded viral RNA, and certain single-stranded viral RNAs. Binding of microbial PAMPs to signaling PRRs promotes the production of:

- inflammatory cytokines, such as such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interleukin-12 (IL-12);
- antiviral cytokines called type-1 interferons (IFN), such as IFN-alpha and IFN-beta;
- chemotactic factors, such as the chemokines interleukin-8 (IL-8), MCP-1, and RANTES; and
- antimicrobial peptides, such as human defensins *)* and cathelicidins.

These molecules are crucial to initiating innate immunity and adaptive immunity.

1. Signaling PRRs found on cell surfaces (see Figure 11.3B.5):

A series of signaling pattern-recognition receptors known as toll-like receptors (TLRs) are found on the surface of a variety of defense cells and other cells. These TLRs play a major role in the induction of innate immunity and contribute to the induction of adaptive immunity.

Different combinations of TLRs appear in different cell types and may occur in pairs. Different TLRs directly or indirectly bind different microbial molecules. For example:

a. TLR-2 - recognizes peptidoglycan, bacterial lipoproteins, lipoteichoic acid (Gram-positive bacteria), and porins (gram-

negative bacteria).
b. TLR-4 - recognizes lipopolysaccharide (Gram-negative bacteria), fungal mannans, viral envelope proteins, parasitic phospholipids, heat-shock proteins.
c. TLR-5 - recognizes bacterial flagellin;
d. TLR-1/TLR-2 pairs - binds to bacterial lipopeptides, lipomannans (mycobacteria) lipoteichoic acids (Gram-positive bacteria), cell wall beta gucans (bacteria and fungi), zymosan (fungi) and glycosylphosphatidylinositol (GPI)-anchored proteins (protozoa).
e. TLR-2/TL6 pairs - also binds to bacterial lipopeptides, lipomannans (mycobacteria) lipoteichoic acids (Gram-positive bacteria), cell wall beta gucans (bacteria and fungi), zymosan (fungi) and glycosylphosphatidylinositol (GPI)-anchored proteins (protozoa).

Many of the TLRs, especially those that bind to bacterial and fungal cell wall components, stimulate the transcription and translation of inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interleukin-12 (IL-12), as well as chemokines such as interleukin-8 (IL-8), MCP-1, and RANTES. These cytokines trigger innate immune defenses such as inflammation, fever, and phagocytosis in order to provide an immediate response against the invading microorganism (see Figure 11.3B.9). Because cytokines such as IL-I, TNF-alpha, and IL-12 that trigger an inflammatory response, they are often referred to as inflammatory cytokines. Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation. To counter inflammation, anti-inflammatory cytokines such as IL-1 receptor antagonist, IL-4, and IL-10 are produced.

Another cell surface PRR is CD14. CD14 is found on monocytes, macrophages, and neutrophils and promotes the ability of TLR-4 to respond to LPS. LPS typically binds to LPS-binding protein in the plasma and tissue fluid. The LPS-binding protein promotes the binding of LPS to the CD14 receptors. At that point the LPS-binding protein comes off and the LPS-CD14 bind to TLR-4. Interaction of LPS and CD14 with TLR-4 leads to an elevated synthesis and secretion of inflammatory cytokines such as IL-1, IL-6, IL-8, TNF-alpha, and platelet-activating factor (PAF). These cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway (see Figure 11.3B.9).

The signaling process for the CD14 and TLR-4 response to LPS is shown in Figure 11.3B.15.

Flash animation illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

Flash animation illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

For More Information: Inflammation from Unit 5

TLRs also participate in adaptive immunity by triggering various secondary signals needed for humoral immunity (the production of antibodies) and cell-mediated immunity (the production of cytotoxic T-lymphocytes, activated macrophages, and additional cytokines). Without innate immune responses there could be no adaptive immunity.

a. T-independent (TI) antigens allow B-lymphocytes to mount an antibody response without the requirement of interaction with effector T4-lymphocytes. The resulting antibody molecules are generally of the IgM isotype and do not give rise to a memory response. There are two basic types of T-independent antigens: TI-1 and TI-2. TI-1 antigens are pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) from the outer membrane of the gram-negative cell wall and lipoteichoic acids from the gram-positive cell wall. These antigens activate B-lymphocytes by binding to their specific toll-like receptors rather than to B-cell receptors (see Figure 11.3B.11). Antibody molecules generated against TI-1 antigens are often called "natural antibodies" because they are always being made against bacteria present in the body.

b. The activation of naive T-lymphocytes requires co-stimulatory signals involving the interaction of accessory molecules on

antigen-presenting cells or APCs with their corresponding ligands on T-lymphocytes. These co-stimulatory molecules are only synthesized when toll-like receptors on APCs bind to pathogen-associated molecular patterns of microbes (see Figure 11.3B.12).

2. Signaling PRRs found in the membranes of the endosomes (phagolysosomes) used to degrade pathogens (see Figure 11.3B.5):

a. TLR-3 - binds double-stranded viral RNA;
b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs;
c. TLR-8 - binds single-stranded viral RNA;
d. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes but uncommon or masked in human DNA and RNA.

Most of the TLRs that bind to viral components trigger the synthesis of cytokines called interferons that block viral replication within infected host cells as well as inflammatory cytokines.

Flash animation showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

html5 version of animation for iPad showing showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

GIF animation showing the antiviral nature of interferon.

3. Signaling PRRs and DRRs found in the cytoplasm (see Figure 11.3B.5)

Pattern-recognition receptors or PRRs found in the cytoplasm include:

a. NODs (nucleotide-binding oligomerization domain)

NOD proteins, including NOD-1 and NOD-2, are cytostolic proteins that allow intracellular recognition of peptidoglycan components.

1. NOD-1 recognizes peptidoglycan containing the muramyl dipeptide NAG-NAM-gamma-D-glutamyl-meso diaminopimelic acid, part of the peptidoglycan monomer in common gram-negative bacteria and just a few gram-positive bacteria.

2. NOD-2 recognizes peptidoglycan containing the muramyl dipeptide NAG-NAM-L-alanyl-isoglutamine found in practically all bacteria (see Figure 11.3B.5).

As macrophages phagocytose either whole bacteria or peptidoglycan fragments released during bacterial growth, the peptidoglycan is broken down into muramyl dipeptides. Binding of the muramyl dipetides to NOD-1 or NOD-2 leads to the activation of genes coding for inflammatory cytokines such as IL-1, TNF-alpha, IL-8, and IL-12 in a manner similar to the cell surface TLRs. Activation of NOD-2 also induces the production of antimicrobial peptides such as defensins as well as microbicidal reactive oxygen species (ROS).

b. CARD-containing proteins

CARD (caspase activating and recruitment domain)-containing proteins, such as RIG-1 (retinoic acid-inducible gene-1) and MDA-5 (melanoma differentiation-associated gene-5), are cytoplasmic sensors of viral RNA molecules that trigger the synthesis of type-1 interferons, antiviral cytokines that block viral replication within infected host cells in a manner similar to the endosomal TLRs. RIG-1 recognizes 5'-PPPs on viral RNAs. The 5'-PPPs on host cell RNAs are either capped or removed and are not recognized by RIG-1. Rig-1 and MDA-5 can also, through another regulatory pathway, stimulate the production of inflammatory cytokines.

Detection of PAMPs by PRRs in the cytosol trigger the formation of multi-protein complexes called inflammasomes which, in turn, leads to the activation of caspase-1. Caspase-1 triggers the formation of inflammatory cytokines and can also result in an inflammatory response-induced cell suicide called pyroptosis. Pyroptosis, unlike apoptosis, leads to the release of PAMPS as well as inflammatory cytokines from the lysed cell.

Pyroptosis is initiated by PAMPs binding to pattern-recognition receptors (PRRs) on various defense cells which then triggers the production of inflammatory cytokines and type-1 interferons. Other PRRs, called nod-like receptors (NLRs) located in the cytosol of these defense cells recognize PAMPs and DAMPs that have entered the host cell's cytosol. Some NLRs trigger the production of inflammatory cytokines while others activate caspase 1-dependent pyroptosis of the cell causing the release of its intracellular inflammatory cytokines (see Figure $11.3B.1$). The binding of PAMPs or DAMPs to their respective NLRs triggers the assembly of multiprotein complexes called inflammasomes in the cytosol of the host cell. It is these inflammasomes that activate caspase 1 and induce inflammation and pyroptosis. Pyroptosis results in production of proinflammatory cytokines, rupture of the cell's plasma membrane, and subsequent release of proinflammatory intracellular contents. It plays an essential role in innate immunity by promoting inflammation to control microbial infections. At highly elevated levels, however, it can cause considerable harm to the body and even death.

c. Danger recognition receptors or DRRs

Danger recognition receptors or DRRs found in the cytoplasm recognize danger-associated molecular patterns (DAMPS) in the cytosol such as altered membrane phospholipids, and materials released from damaged phagosomes and damaged lysosomes, including antibodies bound to microbes from opsonization. DAMPs are also produced as a result of tissue injury during cancer, heart attack, and stroke. Detection of DAMPs by DRRs in the cytosol also triggers the activation of inflammasomes, release of inflammatory cytokines, and pyroptosis.

4. Secreted signaling PRRs found in plasma and tissue fluid

In addition to the PRRs found on or within cells, there are also secreted pattern-recognition receptors. These PRRs bind to microbial cell walls and enable them to activate the complement pathways, as well as by phagocytes. For example, mannan-binding lectin -also known as mannan-binding protein - is synthesized by the liver and released into the bloodstream as part of the acute phase response discussed later in Unit 4. Here it can bind to the carbohydrates on bacteria, yeast, some viruses, and some parasites (see Figure $11.3B.6$). This, in turn, activates the lectin complement pathway (discussed later in Unit 4) and results in the production of a variety of activated complement proteins that are able to trigger inflammation, chemotactically attract phagocytes to the infection site, promote the attachment of antigens to phagocytes via enhanced attachment or opsonization, and cause lysis of gram-negative bacteria and infected or transformed human cells.

Other secreted PRRs include C-reactive protein (CRP), surfactant protein A (SP-A), surfactant protein D (SP-D), collectin liver 1 (CL-L1), and ficolins.

Flash animation showing activation of the lectin pathway, formation of C3 convertase, and formation of C5 convertase.

html5 version of animation for iPad showing activation of the lectin pathway, formation of C3 convertase, and formation of C5 convertase.

Compare and contrast the functions of endocytic pattern-recognition receptors and signaling pattern-recognition receptors.

- Compare and contrast signaling pattern-recognition receptors found on cell surfaces with those found in the membranes of endosomes (phagolysosomes).

Concept Map for PRRs and DRRs

Summary

1. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs and danger-associated molecular patterns or DAMPs binding to danger-recognition receptors or DRRs.
2. Endocytic pattern-recognition receptors are found on the surface of phagocytes and promote the attachment of microorganisms to phagocytes leading to their subsequent engulfment and destruction. They include mannose receptors, scavenger receptors, and opsonin receptors.
3. Binding of microbial PAMPs to signaling PRRs promotes the production of inflammatory cytokines, antiviral cytokines called type-1 interferons (IFN), chemotactic factors, and antimicrobial peptides. They include toll-like receptors (TLRs) and NODs.
4. PRRs found on the surface of the body's cells typically bind to surface PAMPs on microbes and stimulate the production of inflammatory cytokines.
5. PRRs found within cellular phagolysosomes (endosomes) typically detect nucleic acid PAMPs released during the phagocytic destruction of viruses and stimulate the production of antiviral cytokines called type-1 interferons.
6. PRRs and DRRs found within the cytoplasm of host cells typically trigger the formation of multi-protein complexes called inflammasomes which, in turn, triggers the formation of inflammatory cytokines and can also leads to an inflammatory response-induced cell suicide called pyroptosis.
7. PRRs circulating in the blood and tissue fluid activate the complement pathways and may function as opsonins.

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11.3C: Cytokines Important in Innate Immunity

Learning Objectives

1. Describe the following:
   a. cytokines
   b. chemokines
   c. interferons
2. State what is meant by the phrase "Cytokines are pleiotropic, redundant, and multifunctional."
3. Name the two cytokines that are most important in stimulating acute inflammation.
4. Describe specifically how type I interferons are able to block viral replication within an infected host cell.

Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems. They are produced by virtually all cells involved in innate and adaptive immunity, but especially by T- helper (Th) lymphocytes. The activation of cytokine-producing cells triggers them to synthesize and secrete their cytokines. The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity in some manner.

Cytokines are pleiotropic, redundant, and multifunctional.

- Pleiotropic means that a particular cytokine can act on a number of different types of cells rather than a single cell type.
- Redundant refers to to the ability of a number of different cytokines to carry out the same function.
- Multifunctional means the same cytokine is able to regulate a number of different functions.

Some cytokines are antagonistic in that one cytokine stimulates a particular defense function while another cytokine inhibits that function. Other cytokines are synergistic wherein two different cytokines have a greater effect in combination than either of the two would by themselves. There are three functional categories of cytokines:

1. cytokines that regulate innate immune responses,
2. cytokines that regulate adaptive Immune responses, and
3. cytokines that stimulate hematopoiesis.

Cytokines that regulate innate immunity are produced primarily by mononuclear phagocytes such as macrophages and dendritic cells, although they can also be produced by T-lymphocytes, NK cells, endothelial cells, and mucosal epithelial cells. They are produced primarily in response to pathogen-associated molecular patterns (PAMPs) such as LPS, peptidoglycan monomers, teichoic acids, unmethylated cytosine-guanine dinucleotide or CpG sequences in bacterial and viral genomes, and double-stranded viral RNA. Cytokines produced in response to PRRs on cell surfaces, such as the inflammatory cytokines IL-1, IL-6, IL-8, and TNF-alpha, mainly act on leukocytes and the endothelial cells that form blood vessels in order to promote and control early inflammatory responses (Figure $11.3C.1$). Cytokines produced in response to PRRs that recognize viral nucleic acids, such as type I interferons, primarily block viral replication within infected host cells (see Figure $11.3C.2$A and Figure $11.3C.2$B).

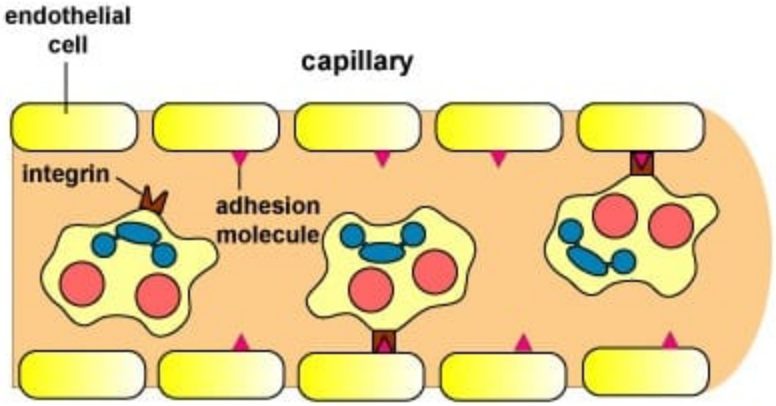


Figure $11.3C.1$***:*** *Integrins on the surface of the leukocyte bind to adhesion molecules on the inner surface of the vascular endothelial cells. The leukocytes flatten out and squeeze between the endothelial cells to leave the blood vessels and enter the tissue. The increased capillary permeability also allows plasma to enter the tissue.*

Examples include:

a. Tumor necrosis factor-alpha (TNF-a)

TNF-a is the principle cytokine that mediates acute inflammation. In excessive amounts it also is the principal cause of systemic complications such as the shock cascade. Functions include acting on endothelial cells to stimulate inflammation and the coagulation pathway; stimulating endothelial cells to produce selectins and ligands for leukocyte integrins during diapedesis ; stimulating endothelial cells and macrophages to produce chemokines that contribute to diapedesis, chemotaxis, and the recruitment of leukocytes; stimulating macrophages to secrete interleukin-1 (IL-1) for redundancy; activating neutrophils and promoting extracellular killing by neutrophils; stimulating the liver to produce acute phase proteins, and acting on muscles and fat to stimulate catabolism for energy conversion. TNF-a stimulates the endothelial cells that form capillaries to express proteins that activate blood clot formation within the capillaries. This occludes local blood flow to help prevent microbes from entering the bloodstream. In addition, TNF is cytotoxic for some tumor cells; interacts with the hypothalamus to induce fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; and activates macrophages. TNF is produced by monocytes,macrophages, dendritic cells, T_H1 cells, and other cells.

b. Interleukin-1 (IL-1)

IL-1 function similarly to TNF in that it mediates acute inflammatory responses. It also works synergistically with TNF to enhance inflammation. Functions of IL-1 include promoting inflammation ; activating the coagulation pathway, stimulating the liver to produce acute phase proteins, catabolism of fat for energy conversion, inducing fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; stimulates the synthesis of adhesion factors on endothelial cells and leukocytes (see Figure $11.3C.1$) for diapedesis ; and activates macrophages. IL-1 is produced primarily by monocytes, macrophages, dendritic cells, endothelial cells, and some epithelial cell.

c. Chemokines

Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation. They increase the affinity of integrins on leukocytes for ligands on the vascular wall (see Figure $11.3C.1$ during diapedesis, regulate the polymerization and depolymerization of actin in leukocytes for movement and migration, and function as chemoattractants for leukocytes. In addition, they trigger some WBCs to release their killing agents for extracellular killing and induce some WBCs to ingest the remains of damaged tissue. Certain chemokines promote angiogenesis. Chemokines also regulate the movement of B-lymphocytes, T-lymphocytes, and dendritic cells through the lymph nodes and the spleen. When produced in excess amounts, chemokines can lead to damage of healthy tissue as seen in such disorders as rheumatoid arthritis, pneumonia, asthma, adult respiratory distress syndrome (ARDS), and septic shock. Examples of chemokines include IL-8, MIP-1a, MIP-1b, MCP-1, MCP-2, MCP-3, GRO-a, GRO-b, GRO-g, RANTES, and eotaxin. Chemokines are produced by

many cells including leukocytes, endothelial cells, epithelial cells, and fibroblasts.

d. Interleukin-12 (IL-12)

IL-12 is a primary mediator of early innate immune responses to intracellular microbes. It is also an inducer of cell-mediated immunity. It functions to stimulate the synthesis of interferon-gamma by T-lymphocytes and NK cells ; increases the killing activity of cytotoxic T-lymphocytes and NK cells; and stimulates the differentiation of naive T4-lymphocytes into interferon-gamma producing T_H1 cells. It is produced mainly by macrophages and dendritic cells.

e. Type I Interferons

Interferons modulate the activity of virtually every component of the immune system. Type I interferons include 13 subtypes of interferon-alpha, interferon-beta, interferon omega, interferon-kappa, and interferon tau. (There is only one type II interferon, interferon-gamma, which is involved in the inflammatory response.)

The most powerful stimulus for type I interferons is the binding of viral DNA or RNA to toll-like receptors TLR-3, TLR-7, and TLR-9 in endosomal membranes.

a. TLR-3 - binds double-stranded viral RNA;
b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs;
c. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes but uncommon or masked in human DNA and RNA.

Flash animation showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

html5 version of animation for iPad showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

Signaling pattern recognition receptors located in the cytoplasm of cells such as RIG-1 and MDA-5 also signal synthesis and secretion of type-I interferons.

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

Type I interferons, produced abundantly by plasmacytoid dendritic cells, by virtually any virus-infected cell, and by other defense cells provide an early innate immune response against viruses. Interferons induce uninfected cells to produce an enzyme capable of degrading viral mRNA, as well as one that blocks translation in eukaryotic cells. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade viral mRNA and block translation in the host cell. This not only blocks viral protein synthesis, it also eventually kills the infected cell (see Figure 11.3C.2A and Figure 11.3C.2B). In addition, type I interferons also cause infected cells to produce enzymes that interfere with transcription of viral RNA or DNA. They also promote body defenses by enhancing the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-producing cells, as well as induce chemokine production to attract leukocytes to the area.

GIF animation showing the antiviral nature of interferon.

Type I interferons also induce MHC-I antigen expression needed for recognition of antigens by cytotoxic T-lymphocytes ; augment macrophages, NK cells, cytotoxic T-lymphocytes, and B-lymphocytes activity; and induce fever. Interferon-alpha is produced by T-lymphocytes, B-lymphocytes, NK cells, monocytes/macrophages; interferon-beta by virus-infected cells, fibroblasts, macrophages, epithelial cells, and endothelial cells.

f. Interleukin-6 (IL-6)

IL-6 functions to stimulate the liver to produce acute phase proteins ; stimulates the proliferation of B-lymphocytes ; and increases neutrophil production. IL-6 is produced by many cells including T-lymphocytes, macrophages, monocytes, endothelial cells, and fibroblasts.

g. Interleukin-10 (IL-10)

IL-10 is an inhibitor of activated macrophages and dendritic cells and as such, regulates innate immunity and cell-mediated immunity. IL-10 inhibits their production of IL-12, co-stimulator molecules, and MHC-II molecules, all of which are needed for cell-mediated immunity. IL-10 is produced mainly by macrophages, and T_H2 cells.

h. Interleukin 15 (IL-15)

IL-15 stimulates NK cell proliferation and proliferation of memory T8-lymphocytes. IL-15 is produced by various cells including macrophages.

i. Interleukin-18 (IL-18)

IL-18 stimulates the production of interferon-gamma by NK cells and T-lymphocytes and thus induces cell-mediated immunity. It is produced mainly by macrophages.

A number of human cytokines produced by recombinant DNA technologies are now being used to treat various infections or immune disorders. These include:

1. recombinant interferon alfa-2a (*Roferon-A*): a cytokine used to treat Kaposi's sarcoma, chronic myelogenous leukemia, and hairy cell leukemia.
2. peginterferon alfa-2a (*Pegasys*) : used to treat hepatitis C (HCV).
3. recombinant interferon-alpha 2b (*Intron A*): a cytokine produced by recombinant DNA technology and used to treat Hepatitis B; malignant melanoma, Kaposi's sarcoma, follicular lymphoma, hairy cell leukemia, warts, and Hepatitis C.
4. peginterferon alfa-2b (*PEG-Intron; PEG-Intron Redipen*): used to treat hepatitis C (HCV).
5. recombinant Interferon alfa-2b plus the antiviral drug ribavirin (*Rebetron*): used to treat hepatitis C (HCV).
6. recombinant interferon-alpha n3 (*Alferon N*): used to treat warts.
7. recombinant iInterferon alfacon-1 *(Infergen*) : used to treat hepatitis C (HCV).
8. G-CSF (granulocyte colony stimulating factor): for reduction of infection in people after myelotoxic anticancer therapy for solid tumors.
9. GM-CSF (granulocyte-macrophage colony stimulating factor): for hematopoietic reconstruction after bone marrow transplant in people with lymphoid cancers.

Concept Map for Cytokines Important in Innate Immunity

Summary

1. Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
2. Cytokines are pleiotropic, meaning meaning that a particular cytokine can act on a number of different types of cells rather than a single cell type.
3. Cytokines are redundant, meaning that a number of different cytokines are able to carry out the same function.
4. Cytokines are multifunctional, meaning that the same cytokine is able to regulate a number of different functions.
5. Tumor necrosis factor-alpha (TNF-a) and interleukin-1 (IL-1) are the principle cytokines that mediates acute inflammation.
6. Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation.
7. Type I interferons, produced abundantly by plasmacytoid dendritic cells, by virtually any virus-infected cell, and by other defense cells provide an early innate immune response against viruses by inducing uninfected cells to produce enzymes capable of degrading viral mRNA and blocking translation in eukaryotic cells. They also enhancing the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-producing cells and induce chemokine production to attract leukocytes to the area.
8. Type II interferon is involved in stimulating an inflammatory response.

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11.3D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production

Describe how an overactive TLR-4 receptor can increase the risk of SIRS in a person if Gram-negative bacteria enter the bloodstream.

- Briefly describe two specific examples of how an improper functioning PRR can lead to an increased risk of a specific infection or disease.

The Ability of Pathogen-Associated Molecular Patterns or PAMPs to Trigger the Synthesis and Secretion of Excessive Levels of Inflammatory Cytokines and Chemokines

As learned in Unit 3 under sepsis and systemic inflammatory response syndrome (SIRS), during severe systemic infections with large numbers of bacteria present, high levels of cell wall PAMPs are released resulting in excessive cytokine production by the defense cells and this can harm the body (see Figure 11.3*D*.10). In addition, neutrophils start releasing their proteases and toxic oxygen radicals that kill not only the bacteria, but the surrounding tissue as well. Harmful effects include high fever, hypotension, tissue destruction, wasting, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and damage to the vascular endothelium. This can result in shock, multiple system organ failure (MOSF), and death.

For More Information: Review of The Ability of PAMPs to Trigger the Production of Inflammatory Cytokines that Result in an Excessive Inflammatory Response from Unit 3

Harmful Effects Associated with either an Overactive or an Underactive Innate Immune Response

There are a number of harmful effects that are known to occur as a result of either an overactive or an underactive innate immune response. This occurs as a result of people possessing different polymorphisms in the various genes participating in PRR signaling.

- People born with underactive PRRs or deficient PRR immune signaling pathways are at increased risk of infection by specific pathogens due to a decrease innate immune response.
- People born with overactive PRRs or deficient PRR immune signaling pathways are at increased risk of inflammatory damage by lower numbers of specific pathogens.

Examples include:

1. People with an underactive form of TLR-4, the toll-like receptor for bacterial LPS, have been found to be five times as likely to contract a severe bacterial infection over a five year period than those with normal TLR-4. People with overactive TLR-4 receptors may be more prone to developing SIRS from gram-negative bacteria.

2. Most people that die as a result of Legionnaire's disease have been found to have a mutation in the gene coding for TLR-5 that enables the body to recognize the flagella of *Legionella pneumophila*.

3. B-lymphocytes, the cells responsible for recognizing foreign antigens and producing antibodies against those antigens, normally don't make antibodies against the body's own DNA and RNA. The reason is that any B-lymphocytes that bind the

body's own antigens normally undergo apoptosis, a programmed cell suicide. People with the autoimmune disease systemic lupus erythematosus have a mutation in a gene that signals the cell to undergo apoptosis. As a result, these B-cells are able to bind and engulf the body's own DNA and RNA and place them in an endosome or phagolysosome where the the DNA can be recognized by TLR-9 and the RNA by TLR-7. This, in turn, triggers those B-lymphocytes to make antibody molecules against the body's own DNA and RNA. Another gene error enables these B- cells to increase the expression of TLR-7.

4. TLR-4, MyD88, TLR-1 and TLR-2 have been implicated in the production of atherosclerosis in mice and some humans.

5. Mutations resulting in loss-of-function in the gene coding for NOD-2 that prevents the NOD-2 from recognizing muramyl dipeptide make a person more susceptible to Crohn's disease, an inflammatory disease of the large intestines. Mutations resulting in over-activation in the gene coding for NOD-2 can lead to an inflammatory disorder called Blau syndrome.

6. People with chronic sinusitis that does not respond well to treatment have decreased activity of TLR-9 and produce reduced levels of human beta-defensin 2, as well as mannan-binding lectin needed to initiate the lectin complement pathway.

7. Pathogenic strains of *Staphylococcus aureus* producing leukocidin and protein A, including MRSA, cause an increased inflammatory response. Protein A, a protein that blocks opsonization and functions as an adhesin, binds to cytokine receptors for TNF-alpha. It mimics the cytokine and induces a strong inflammatory response. As the inflammatory response attracts neutrophils to the infected area, the leukocidin causes lysis of the neutrophils. As a result, tissue is damaged and the bacteria are not phagocytosed.

8. People with chronic mucocutaneous candidiasis disease have a mutation either in the gene coding for IL-17F or the gene encoding IL-17F receptor. T_H17 cells secrete cytokines such as IL-17 that are important for innate immunity against organisms that infect mucous membranes.

9. A polymorphism in the gene for TLR-2 makes individuals less responsive to *Treponema pallidum* and *Borrelia burgdorferi* and possibly more susceptible to tuberculosis and staphylococcal infections.

10. Polymorphisms in a gene locus called *A20*, a gene that helps to control inflammation, are considered as risk alleles for rheumatoid arthritis, systemic lupus erythematosus, psoriasis, type I diabetes, and Chron's disease.

11. The innate immune response to *Mycobacterium tuberculosis* and the severity of tuberculosis depends on the response of TLRs 1/2, TLR 6, and TLR 9 to the bacterium. Polymorphisms in Toll-interacting protein (TOLLIP), a negative regulator of TLR signaling, influence the response of the patient to *M. tuberculosis*.

What is the significance of underactive and overactive PRRs in innate immunity?

Therapeutic Possibilities

Researchers are now looking at various ways to either artificially activate TLRs in order to enhance immune responses or inactivate TLRs to lessen inflammatory disorders. Examples of agents being evaluated in clinical studies or animal studies include:

1. TLR activators to activate immune responses

    a. Both TLR-4 and TLR-9 activators are being tried in early clinical trials as vaccine adjuvants to improve the immune response to vaccines. TLR-9 activators are being tried as an adjuvant for the hepatitis B and anthrax vaccines and a TLR-4 activator is being tried as an adjuvant for the vaccine against the human papillomaviruses that cause most cervical cancer.
    b. Both TLR-7 and TLR-9 activators are being tried in early clinical trials as an antiviral against hepatitis C. Activation of these TLRs triggers the synthesis and secretion of type I interferons that block viral replication within infected host cells.
    c. TLR-9 activators are being tried in early clinical trials as an adjuvant for chemotherapy in the treatment of lung cancer.
    d. TLR-9 activators are being tried in early clinical trials to help in the treatment and prevention of allergies and asthma. Activation of TLR-9 in macrophages and other cells stimulates these cells to kill T_H2 cells, the subclass of T-helper lymphocytes responsible for most allergies and asthma.

2. TLR inhibitors to suppress immune responses

a. General TLR inhibitors might one day be used to treat autoimmune disorders.
b. A TLR-4 inhibitor, a mimic of the endotoxin from the gram-negative cell wall, is being tried in early clinical trials to block or reduce the death rate from Gram-negative sepsis and SIRS.
c. TLR-4, TLR-2, and MyD88 inhibitors might possibly one day lessen atherosclerotic plaques and the risk of heart disease.

Of course using TLR activators or TLR inhibitors to turn up or turn down immune responses also carries risks. Trying to suppress harmful inflammatory responses may also result in increased susceptibility to infections; trying to activate immune responses could lead to SIRS or autoimmune disease.

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

Summary

1. In severe bacterial infections, pathogen-associated molecular patterns or PAMPs can trigger the synthesis and secretion of excessive levels of inflammatory cytokines and chemokines leading to systemic inflammatory response syndrome or SIRS.
2. People born with underactive PRRs or deficient PRR immune signaling pathways are at increased risk of infection by specific pathogens due to a decrease innate immune response.
3. People born with overactive PRRs or deficient PRR immune signaling pathways are at increased risk of inflammatory damage by lower numbers of specific pathogens.
4. Researchers are now looking at various ways to either artificially activate underactive PRRs in order to enhance immune responses, or inactivate overactive PRRs to lessen inflammatory disorders.

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11.3E: Phagocytosis

Briefly describe the role of the following as they relate to phagocytosis:

a. inflammation
b. lymph nodules
c. lymph nodes
d. spleen

- Describe the following steps in phagocytosis:

a. activation
b. chemotaxis
c. attachment (both unenhanced and enhanced)
d. ingestion
e. destruction

- State what happens when either phagocytes are overwhelmed with microbes or they adhere to cells to large to be phagocytosed.
- Describe what causes most of the tissue destruction seen during microbial infections.
- Compare the oxygen-dependent and oxygen-independent killing systems of neutrophils and macrophages.
- Briefly describe the role of autophagy in removing intracellular microbes.

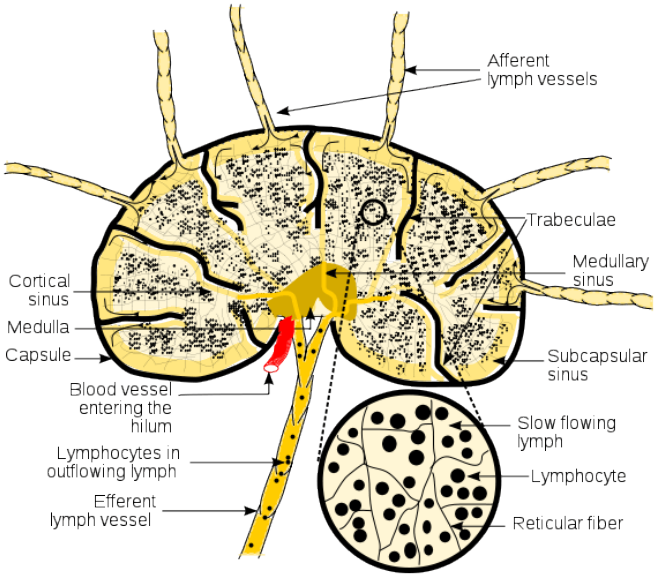


Figure $11.3E.1$: Diagram of a Lymph Node. Schematic diagram of a lymph node showing flow of lymph through lymph sinuses. Image used wtih permission (Public Domain; KC Panchal).

In addition, Langerhans' cells (immature dendritic cells) are located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract where in their immature form they are attached by long cytoplasmic processes. Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by proinflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, they have matured and are now able to present antigen to the ever changing populations of naive T-lymphocytes located in the cortex of the lymph nodes.

The spleen contains many reticular fibers that support fixed macrophages and dendritic cells, as well as ever changing populations of circulating B-lymphocytes and T-lymphocytes. Blood carries microorganisms to the spleen where they are filtered out and phagocytosed by the fixed macrophages and dendritic cells and presented to the circulating B-lymphocytes and T-lymphocytes to initiate adaptive immune responses. There are also specialized macrophages and dendritic cells located in

the brain (microglia), lungs (alveolar macrophages), liver (Kupffer cells), kidneys (mesangial cells), bones (osteoclasts), and the gastrointestinal tract (peritoneal macrophages).

The Steps Involved in Phagocytosis

There are a number of distinct steps involved in phagocytosis:

Step 1: Activation of the Phagocyte

Resting phagocytes are activated by inflammatory mediators such as bacterial products (bacterial proteins, capsules, LPS, peptidoglycan, teichoic acids, etc.), complement proteins, inflammatory cytokines, and prostaglandins. As a result, the circulating phagocytes produce surface glycoprotein receptors that increase their ability to adhere to the inner surface of capillary walls, enabling them to squeeze out of the capillary and be attracted to the site of infection.

In addition, they produce endocytic pattern-recognition receptors that recognize and bind to pathogen-associated molecular patterns or PAMPs - components of common microbial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, and mannose-rich glycans that are not found in human cells - to attach the microbe to the phagocyte for what is called unenhanced attachment (discussed below). They also exhibit increased metabolic and microbicidal activity by increasing their production of ATPs, lysosomal enzymes, lethal oxidants, etc.

Step 2: Chemotaxis of Phagocytes (for wandering macrophages, neutrophils, and eosinophils)

Chemotaxis is the movement of phagocytes toward an increasing concentration of some attractant such as bacterial factors (bacterial proteins, capsules, LPS, peptidoglycan, teichoic acids, etc.), complement proteins (C5a), chemokines (chemotactic cytokines such as interleukin-8 secreted by various cells), fibrin split products, kinins, and phospholipids released by injured host cells.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

Movie showing chemotaxis by neutrophil. Chemotaxis of Neutrophils. © From Intimate Strangers: Unseen Life on Earth. Created by Mondo Media. Peter Baker, Executive Producer. Licensed for use, ASM MicrobeLibrary.

You Tube animation summarizing phagocytosis by a macrophage.

You Tube movie illustrating chemotaxis.

Some microbes, such as the influenza A viruses, *Mycobacterium tuberculosis*, blood invasive strains of *Neisseria gonorrhoeae*, and *Bordetella pertussis* have been shown to block chemotaxis.

Step 3: Attachment of the Phagocyte to the Microbe or Cell

Attachment of microorganisms is necessary for ingestion. Attachment may be unenhanced or enhanced.

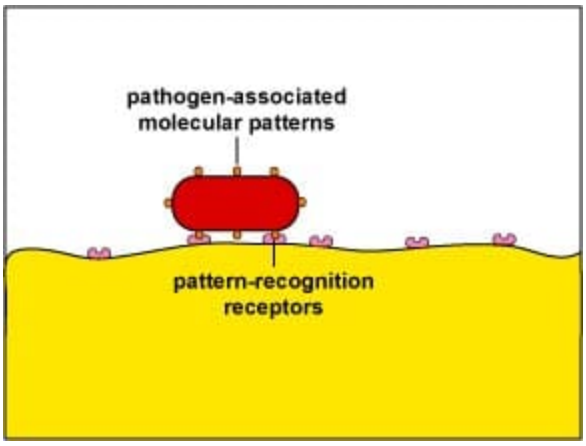


Figure $11.3E.2$: Unenhanced Attachment of Bacteria to Phagocytes. Glycoprotein molecules known as pattern-recognition receptors are found on the surface of phagocytes. They are so named because they recognize and bind to pathogen-associated molecular patterns - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, and glucans - found in many microorganisms.

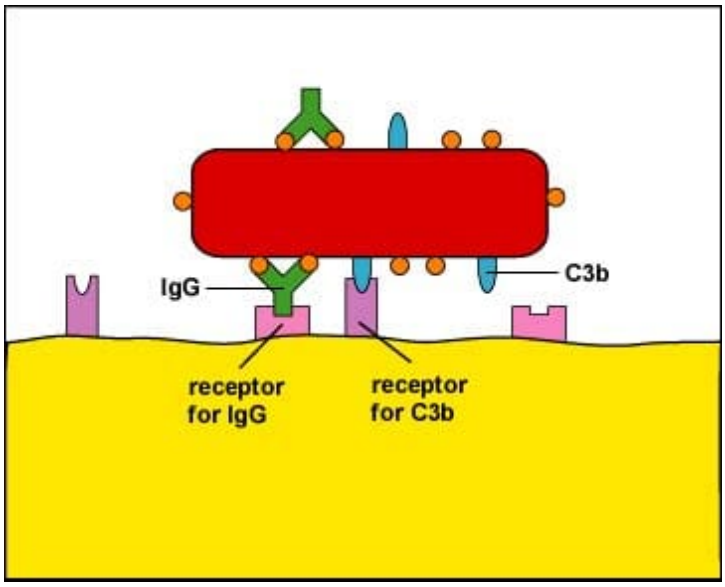


Figure $11.3E.3$: Enhanced Attachment of Bacteria to Phagocytes. One of the functions of certain antibody molecules known as IgG is to stick antigens such as bacterial proteins and polysaccharides to phagocytes. The "tips" of the antibody, the Fab portion, have a shape that fits epitopes, portions of an antigen with a complementary shape. The "stalk" of the antibody is called the Fc portion and is able to bind to Fc receptors on phagocytes. Also, when body defense pathways known as the complement pathways are activated, one of the beneficial defense proteins made is called C3b. C3b binds by one end to bacterial surface proteins and by the other end to C3b receptors on phagocytes. The IgG and C3b are also known as opsonins and the process of enhanced attachment is also called opsonization.

Flash animation illustrating the function of enhanced attachment by way of IgG.

html5 version of animation for iPad illustrating the function of enhanced attachment by way of IgG.

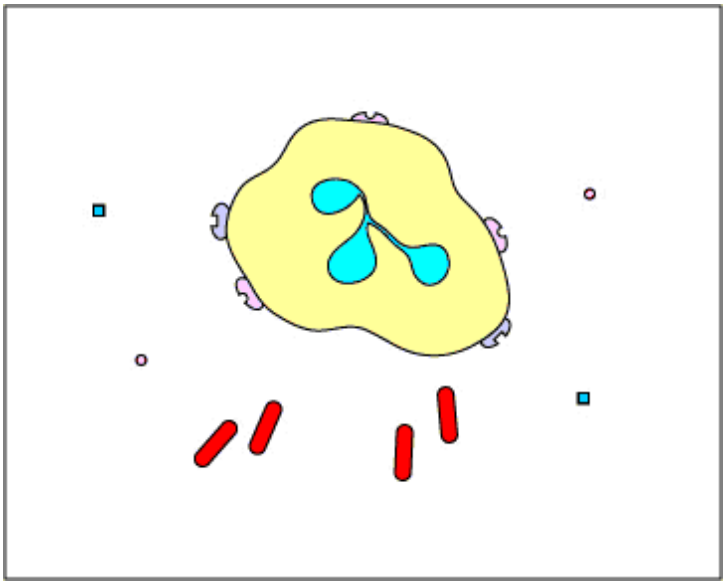
Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

For More Information: Antibodies from Unit 6

For More Information: The Complement Pathways from Unit 5

c. Extracellular trapping with NETs: In response to certain pathogen associated molecular patterns such as LPS, and certain cytokines such as IL-8, neutrophils release DNA and antimicrobial granular proteins. These neutrophil extracellular traps (NETs) bind to bacteria, prevent them from spreading, and kill them with antimicrobial proteins (see Figure $11.3E.15$ and Figure $11.3E.16$).



Neutrophil NETS Trapping and Killing Bacteria. In response to certain pathogen associated molecular patterns such as LPS, and certain cytokines such as IL-8, neutrophils release DNA and antimicrobial granular proteins. These neutrophil extracellular traps (NETs) bind to bacteria, prevent them from spreading, and kill them with antimicrobial proteins such as histones and elastins. One hypothesis, shown in this animation, proposes that the NETs are produced by living neutrophils in response to bacteria. Alternately, NETs may be released as a result of necrotic cell death of neutrophils.

Some microorganisms are more resistant to phagocytic attachment.

a. Capsules can resist unenhanced attachment by preventing the endocytic pattern recognition receptors on phagocytes from recognizing the bacterial cell wall components and mannose-containing carbohydrates (see Figure $11.3E.14$). *Streptococcus. pneumonia* activates the classical complement pathway, but resists C3b opsonization, and complement causes further inflammation in the lungs.

Flash animation illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

Movie of an encapsulated bacterium resisting engulfment by a neutrophil. Phagocytosis. © James Sullivan, author. Licensed for use, ASM MicrobeLibrary.

b. Some capsules prevent the formation of C3 convertase, an early enzyme in the complement pathways. Without this enzyme, the opsonins C3b and C4b, as well as the other beneficial proteins are not produced.

Flash animation showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

html5 version of animation for iPad showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

c. Other capsules, rich in sialic acid, a common component of host cell glycoprotein, have an affinity for serum protein H, a complement regulatory protein that leads to the degradation of the opsonin C3b by factor I and the formation of C3 convertase. (Serum protein H is what normally leads to the degradation of any C3b that binds to host glycoproteins so that we don't stick our own phagocytes to our own cells with C3b.)

d. Some capsules simply cover the C3b that does bind to the bacterial surface and prevent the C3b receptor on phagocytes from making contact with the C3b (see Figure 11.3*E*.3). This is seen with the capsule of *Streptococcus pneumoniae*.

Flash animation showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

html5 version of animation for iPad showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

e. *Neisseria meningitidis* has a capsule composed of sialic acid *while Streptococcus pyogenes* (group A beta streptococci) has a capsule made of hyaluronic acid. Both of these polysaccharides closely resemble carbohydrates found in human tissue polysaccharides and because they are not recognized as foreign by the lymphocytes that carry out the immune responses, antibodies are not made against these capsules. Likewise, some bacteria are able to coat themselves with host proteins such as fibronectin, lactoferrin, or transferrin and in this way avoid antibodies.

f. An outer membrane molecule of *Neisseria gonorrhoeae* called Protein II and the M-protein of *Streptococcus pyogenes* allow these bacteria to be more resistant to phagocytic engulfment. The M-protein of *S. pyogenes*, for example, binds factor H of the complement pathway and this results in the degradation of the opsonin C3b by factor I and the formation of C3 convertase. *S. pyogenes* also produces a protease that cleaves the complement protein C5a.

g. *Staphylococcus aureus* produces protein A while *Streptococcus pyogenes* produces protein G. Both of these proteins bind to the Fc portion of antibodies (see Figure 11.3*E*.4) and in this way the bacteria become coated with antibodies in a way that does not result in opsonization (see Figure 11.3*E*.5).

Step 4: Ingestion of the Microbe or Cell by the Phagocyte

Following attachment, polymerization and then depolymerization of actin filaments send pseudopods out to engulf the microbe (see Figure 11.3*E*.6) and place it in an endocytic vesicle called a phagosome (see Figure 11.3*E*.7).

Flash animation showing ingestion and phagosome formation.

html5 version of animation for iPad showing ingestion and phagosome formation.

During this process, an electron pump brings protons (H^+) into the phagosome. This lowers the pH within the phagosome to 3.5 - 4.0 so that when a lysosome fuses with the phagosome, the pH is correct for the acid hydrolases to effectively break down cellular proteins. The acidification also releases defensins, cathelicidin, and bacterial permeability inducing protein (BPI), peptides and enzymes that can kill microbes, from a matrix and enabling their activation.

Flash animation showing acidification of the phagosome following ingestion.

html5 version of animation for iPad showing acidification of the phagosome following ingestion.

Scanning electron micrographs of a macrophage with pseudopods and a macrophage phagocytozing *E. coli* on a blood vessel; courtesy of Dennis Kunkel's Microscopy.

You Tube Movie illustrating bacterial phagocytosis by a neutrophil.

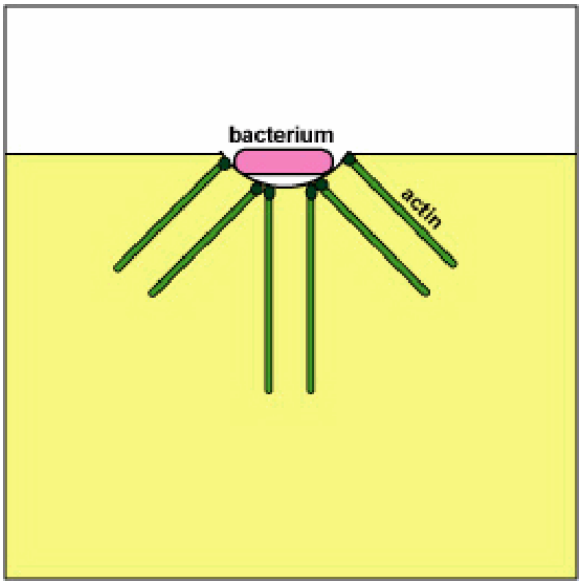
You Tube Movie illustrating a neutrophil phagocytosing MRSA

Intracellular microbes, such as viruses and bacteria that invade host cells, can also be engulfed once they enter the cytosol of the cell by a process called autophagy. A membrane-bound compartment called an autophagosome grows around the microbe and the surrounding cytosol and subsequently delivers it to lysosomes for destruction (see Figure 11.3E.17). (This process is also used by eukaryotic cells to engulf and degrade unnecessary or dysfunctional cellular components such as damaged organelles.)

Some microorganisms are more resistant to phagocytic ingestion

a. Pathogenic *Yersinia*, such as the one that causes plague, contact phagocytes and, by means of a type III secretion system, deliver proteins which depolymerize the actin microfilaments needed for phagocytic engulfment into the phagocytes (see Figure 11.3E.8). Another *Yersinia* protein degrades C3b and C5a.

b. Some bacteria, like *Mycobacterium tuberculosis, Salmonella*, and *Listeria monocytogenes* can block autophagy.



Blocking Phagosome Formation by Depolymerizing Actin. Molecules of some bacteria, through a type III secretion system, deliver proteins which depolymerize the phagocyte's actin microfilaments used for phagocytic engulfment.

Step 5: Destruction of the Microbe or Cell

Phagocytes contain membranous sacs called lysosomes produced by the Golgi apparatus that contain various digestive enzymes, microbicidal chemicals, and toxic oxygen radicals. The lysosomes travel along microtubules within the phagocyte and fuse with the phagosomes containing the ingested microbes and the microbes are destroyed (see Figure 11.3E.9).

To view an electron micrograph of a phagolysosome, see the Web page for the University of Illinois College of Medicine.

Flash animation showing intracellular destruction.

html5 version of animation for iPad showing intracellular destruction.

Flash animation summarizing phagocytosis by unenhanced attachment.

html5 version of animation for iPad summarizing phagocytosis by unenhanced attachment.

Flash animation summarizing phagocytosis by enhanced attachment (opsonization).

html5 version of animation for iPad summarizing phagocytosis by enhanced attachment (opsonization).

You Tube animation summarizing phagocytosis by a macrophage.

Some bacteria are more resistant to phagocytic destruction once engulfed.

a. Some bacteria, such as *Legionella pneumophilia* and *Mycobacterium* species, cause the phagocytic cell to place them into an endocytic vacuole via a pathway that decreases their exposure to toxic oxygen compounds.

b. Some bacteria, such as *Salmonella*, are more resistant to toxic forms of oxygen and to defensins (toxic peptides that kill bacteria).

c. Some bacteria, such as *Shigella flexneri* and the spotted fever *Rickettsia*, escape from the phagosome into the cytoplasm prior to the phagosome fusing with a lysosome (see Figure 11.3E.10).

Flash animation showing a bacterium resisting phagocytosis by escaping from a phagosome prior to the phagosome fusing with the lysosome.

html5 version of animation for iPad showing a bacterium resisting phagocytosis by escaping from a phagosome prior to the phagosome fusing with the lysosome.

d. *Neisseria gonorrhoeae* produces Por protein (protein I) that prevents phagosomes from fusing with lysosomes enabling the bacteria to survive inside phagocytes.

Flash animation showing a bacterium resisting phagocytosis by blocking the fusion of the phagosome with the lysosome.

html5 version of animation for iPad showing a bacterium resisting phagocytosis by blocking the fusion of the phagosome with the lysosome.

e. Some bacteria, such as species of *Salmonella*, *Mycobacterium*, *Legionella*, and *Chlamydia*, block the vesicular transport machinery that enables the phagosome to fuse with the lysosome.

Flash animation showing a bacterium resisting phagocytosis by blocking the lysosome from moving to the phagosome.

html5 version of animation for iPad showing a bacterium resisting phagocytosis by blocking the lysosome from moving to the phagosome.

f. Some bacteria, such as pathogenic *Mycobacterium* and *Legionella pneumophilia*, prevent the acidification of the phagosome which is needed for effective killing of microbes by lysosomal enzymes. (Normally after the phagosome forms, the contents become acidified because the lysosomal enzymes used for killing function much more effectively at an acidic pH.)

Flash animation showing a bacterium preventing acidification of the phagosome following ingestion.

html5 version of animation for iPad showing a bacterium preventing acidification of the phagosome following ingestion.

g. The carotenoid pigments that give *Staphylococcus aureus* its golden color and group B streptococci (GBS) its orange tint shield the bacteria from the toxic oxidants that neutrophils use to kill bacteria.

h. Cell wall lipids of *Mycobacterium tuberculosis*, such as lipoarabinomannan, arrest the maturation of phagosomes preventing delivery of the bacteria to lysosomes.

i. Some bacteria are able to kill phagocytes. Bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes* produce the exotoxin leukocidin which damages the cytoplasmic membrane of the phagocyte. On the other hand, bacteria, such as *Shigella* and *Salmonella*, induce macrophage apoptosis, a programmed cell death.

Flash animation showing a bacterium using leukocidin to kill a phagocyte.

html5 version of animation for iPad showing a bacterium using leukocidin to kill a phagocyte.

If the the infection site contains very large numbers of microorganisms and high levels of inflammatory cytokines and chemokines are being produced in response to PAMPs, the phagocyte will empty the contents of its lysosomes by a process called degranulation in order to kill the microorganisms or cell extracellularly.

These released lysosomal contents, however, also kill surrounding host cells and tissue. Most tissue destruction associated with infections is a result of this process (see Figure $11.3E.11$).

The phagocyte will also empty the contents of its lysosomes for extracellular killing if the cell to which the phagocyte adheres is too large to be engulfed (see Figure $11.3E.12$ and Figure $11.3E.13$).

Flash animation summarizing extracellular killing by phagocytosis.

html5 version of animation for iPad summarizing extracellular killing by phagocytosis.

There are 2 killing systems in neutrophils and macrophages: the oxygen-dependent system and the oxygen-independent system.

1. The oxygen-dependent system: production of reactive oxygen species (ROS)

The cytoplasmic membrane of phagocytes contains the enzyme oxidase which converts oxygen into superoxide anion (O^{2-}). This can combine with water by way of the enzyme dismutase to form hydrogen peroxide (H_2O_2) and hydroxyl (OH) radicals.

In the case of neutrophils, but not macrophages, the hydrogen peroxide can then combine with chloride (Cl^{2-}) ions by the action of the enzyme myeloperoxidase (MPO) to form hypochlorous acid (HOCL), and singlet oxygen.

In macrophages, nitric oxide (NO) can combine with hydrogen peroxide to form peroxynitrite radicals. (In addition to ROS and NO, macrophages secrete inflammatory cytokines such as TNF-alpha, IL-1, IL-8, and IL-12 to promote an inflammatory response.)

These compounds are very microbicidal because they are powerful oxidizing agents which oxidize most of the chemical groups found in proteins, enzymes, carbohydrates, DNA, and lipids. Lipid oxidation can break down cytoplasmic membranes. Collectively, these oxidizing free radicals are called reactive oxygen species (ROS).

Oxidase also acts as an electron pump that brings protons (H^{+}) into the phagosome. This lowers the pH within the phagosome so that when lysosomes fuse with the phagosome, the pH is correct for the acid hydrolases, like elastase, to effectively break down cellular proteins.

In addition to phagocytes using this oxygen-dependant system to kill microbes intracellularly, neutrophils also routinely release these oxidizing agents, as well as acid hydrolases, for the purpose of killing microbes extracellularly. These agents, however, also wind up killing the neutrophils themselves as well as some surrounding body cells and tissues as mentioned above.

2. The oxygen-independent system

Some lysosomes contain defensins *)*, cationic peptides that alter cytoplasmic membranes; lysozyme, an enzyme that breaks down peptidoglycan, lactoferrin, a protein that deprives bacteria of needed iron; cathepsin G, a protease that causes damage to microbial membranes; elastase, a protease that kills many types of bacteria; cathelicidins, proteins that upon cleavage are directly toxic to a variety of microorganisms; bactericidal permeability inducing protein (BPI), proteins used by neutrophils to kill certain bacteria by damaging their membranes; collagenase ; and various other digestive enzymes that exhibit antimicrobial activity by breaking down proteins, RNA, phosphate compounds, lipids, and carbohydrates.

Concept Map for Phagocytosis

Streptococcus pyogenes has a capsule made of hyaluronic acid, a polysaccharide also found on human cells.

Describe what significance this has in the bacterium resisting phagocytosis and why.

2. *Streptococcus pyogenes* produces a protein called protein G that binds to the Fc portion of human IgG.

   Describe what significance this has in the bacterium resisting phagocytosis and why.

3. Many bacteria produces capsules that cover their cell wall.

   Describe what significance this has in the bacterium resisting phagocytosis and why.

4. People born with chronic granulomatious disease have neutrophils that lack the enzyme oxidase in their cytoplasmic membrane.

   Describe what significance this has in the bacterium resisting phagocytosis and why.

Summary

Phagocytosis is the primary method used by the body to remove free microorganisms in the blood and tissue fluids. An inflammatory response to injury and/or infection allows phagocytes to leave the bloodstream, enter the tissue, and go to the site of infection or injury. Microorganisms entering lymph nodules found in the respiratory, gastrointestinal, and genitourinary tract can be phagocytosed by fixed macrophages and dendritic cells and presented to B-lymphocytes and T-lymphocytes to initiate

adaptive immune responses.Tissue fluid picks up microbes in the tissue, enters the lymph vessels as lymph, and carries the microbes to regional lymph nodes where they are filtered out and phagocytosed by fixed macrophages and dendritic cells and presented to the circulating B-lymphocytes and T-lymphocytes to initiate adaptive immune responses.

Dendritic cells located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract phagocytize microbes, enter lymph vessels, and carry the microbes to regional lymph nodes where the dendritic cells present antigens associated with the microbes to the ever changing populations of naive T-lymphocytes.Blood carries microorganisms to the spleen where they are filtered out and phagocytosed by fixed macrophages and dendritic cells and presented to the circulating B-lymphocytes and T-lymphocytes to initiate adaptive immune responses. There are also specialized macrophages and dendritic cells located in the brain (microglia), lungs (alveolar macrophages), liver (Kupffer cells), kidneys (mesangial cells), bones (osteoclasts), and the gastrointestinal tract (peritoneal macrophages.

1. Resting phagocytes are activated by inflammatory mediators and produce surface receptors that increase their ability to adhere to the inner surface of capillary walls enabling them to squeeze out of the capillary and enter the tissue, a process called diapedesis.
2. Activation also enables phagocytes to produce endocytic pattern-recognition receptors that recognize and bind to microbial PAMPs in order to attach the microbe to the phagocyte, as well as to exhibit increased metabolic and microbicidal activity.
3. Phagocytes then use chemotaxis to move towards an increasing concentration of some attractant such as bacterial factors or defense molecules.
4. Attachment of phagocytes to the microbes or cells can be through unenhanced attachment or enhanced attachment.
5. Unenhanced attachment is the recognition of pathogen-associated molecular patterns or PAMPs by endocytic pattern-recognition receptors on the surface of the phagocytes.
6. Enhanced attachment, or opsonization, is the attachment of microbes to phagocytes by way of an antibody molecule called IgG, the complement proteins C3b and C4b, and acute phase proteins such as mannose-binding lectin (MBL) and C-reactive protein (CRP).
7. Following attachment, polymerization and then depolymerization of actin filaments send pseudopods out to engulf the microbe and place it in an endocytic vesicle called a phagosome.
8. During this process, an electron pump brings protons (H+) into the phagosome to lowers the pH within the phagosome to a pH that is correct for the acid hydrolases to effectively break down cellular proteins.
9. Phagocytes contain membranous sacs called lysosomes that contain various digestive enzymes, microbicidal chemicals, and toxic oxygen radicals. The lysosomes fuse with the phagosomes containing the ingested microbes and the microbes are destroyed.
10. If the infection site contains very large numbers of microorganisms and high levels of inflammatory cytokines and chemokines are being produced in response to PAMPs, the phagocyte will empty the contents of its lysosomes in order to kill the microorganisms or cell extracellularly.
11. Lysosomal contents released during extracellular killing also kill surrounding host cells and tissue. Most tissue destruction associated with infections is a result of extracellular killing by phagocytes.

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11.3F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)

Describe how NK cells are able to recognize and kill infected cells and cancer cells lacking MHC-I molecules.

- State two factors that can result in a nucleated human cell not producing MHC-I molecules.
- State how iNKT cells recognize glycolipids in order to become activated.
- Describe the overall function of iNKT cells in terms how they promote both innate and adaptive immunity and may also help to regulate the immune responses.

We will now take a closer look at natural killer (NK) cells and invariant natural killer T-lymphocytes (iNKT cells).

Natural Killer Cells (NK Cells)

NK cells are important in innate immunity because they are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses. For example, through cytokine production NK cells also suppress and/or activate macrophages , suppress and/or activate the antigen-presenting capabilities of dendritic cells, and suppress and/or activate T-lymphocyte responses.

NK cells use a dual receptor system in determining whether to kill or not kill human cells. When cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules such as MHC class I polypeptide-related sequence A (MICA) and MHC class I polypeptide-related sequence B (MICB) are produced and are put on the surface of that cell.

The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.

This second receptor, called the killer-ihibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. MHC-I molecules, produced by all nucleated cells in the body, possess a deep groove that can bind peptides from proteins found within the cytosol of human cells, transport them to the surface of that cell, and display the MHC-!/peptide complex to receptors on cytotoxic T-lymphocytes or CTLs. If the MHC-I molecules have peptides from the body's own proteins bound to them, CTLs do not recognize those cells as foreign and the cell is not killed. If, on the other hand, the MHC-I molecules have peptides from viral, bacterial, or mutant proteins bound to them, CTLs recognize that cell as foreign and kill that cell. (CTLs will be discussed in greater detail in Unit 6.)

For More Information: CTLs from Unit 6

If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound (see Figure $11.3F.3$).

Viruses, stress, and malignant transformation, however, can often interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound (see Figure $11.3F.4$).

The NK cell then releases pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes (see Figure $11.3F.5$). Perforins can also sometimes result in cell lysis.

Flash animation of a NK cell interacting with a normal body cell.
Flash animation of a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

html5 version of animation for iPad of a NK cell interacting with a normal body cell.
html5 version of animation for iPad of a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

Flash animation of apoptosis by NK cells

html5 version of animation for iPad of apoptosis by NK cells

Cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) produced by T_H1 lymphocytes activate NK cells.

NK cells also play a role in adaptive immune responses. As will be seen in Unit 6, NK cells are also capable of antibody-dependent cellular cytotoxicity or ADCC where they kill cells to which antibody molecules have bound.

For More Information: ADCC from Unit 6

Invariant Natural Killer T-Lymphocytes (iNKT Cells)

iNKT cells are a subset of lymphocytes that bridge the gap between innate and adaptive immunity. They have T-cell receptors (TCRs) on their surface for glycolipid antigen recognition. They also have natural killer (NK) cell receptors.

Through the cytokines they produce once activated, iNKT cells are essential in both innate and adaptive immune protection against pathogens and tumors. They also play a regulatory role in the development of autoimmune diseases, asthma, and transplantation tolerance. It has been shown that iNKT cell deficiency or disfunction can lead to the development of autoimmune diseases, human asthma, and cancers.

Pathogens may not directly activate iNKT cells. The TCR of iNKT cells recognize exogenous glycolipid antigens , as well as endogenous self glycolipid antigens presented by MHC-I-like CD1d molecules on antigen presenting dendritic cells. iNKT cells can also be activated by the cytokine interleukin-12 (IL-12) produced by dendritic cells that have themselves become activated by pathogen-associated molecular patterns (PAMPs) of microbes binding to the pattern-recognition receptors (PRRs) of the dendritic cell.

Once activated, the iNKT cells rapidly produce large quantities of cytokines, including interferon-gamma (IFN-?), interleukin-4 (IL-4), interleukin-2 (IL-2), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-a), interleukin-13 (IL-13), and chemokines. Through the rapid productions of such cytokines, iNKT cells are able to promote and suppress different innate and adaptive immune responses. For example, large amounts of IFN-? are produced by activated iNKT cells. IFN-? activates NK cells and macrophages as a part of innate immunity.

It has been proposed that if the iNKT cell is repeatedly stimulated by the body's own glycolipids in the absence of microbes that this might stimulate the iNKT cell /dendritic cell interaction to produce tolerizing signals that inhibit the T_H1 cell response and possibly stimulate the production of regulatory T-lymphocytes (T_{reg} cells). In this way it might suppress autoimmune responses and prevent tissue damage.

There is also growing evidence that early childhood exposure to microbes is associated with protection against allergic diseases, asthma, and inflammatory diseases such as ulcerative colitis. It has been found that germ-free mice have large accumulations of mucosal iNKT cells in the lungs and intestines and increased morbidity from allergic asthma and inflammatory bowel disease.

However, colonization of neonatal germ-free mice with normal microbiota resulted in mucosal iNKT cell tolerance to these diseases. It has been proposed that microbes the human body has been traditionally exposed to from early childhood throughout most of human history might play a role in developing normal iNKT cell numbers and iNKT cell responses.

iNKT cells will be discussed in further detail in Unit 6.

Concept Map for NK Cells and iNKT Cells

Summary

1. Natural Killer (NK) cells are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses.
2. When body cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell.
3. NK cells use a dual receptor system in determining whether to kill or not kill human cells.
4. The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.
5. The second receptor, called the killer-ihibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound.
6. Viruses, stress, and malignant transformation can often interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound.
7. NK cells kill their target cells by inducing apoptosis, a programmed cell suicide.
8. NK cells also play a role in adaptive immune responses by way of antibody-dependent cellular cytotoxicity or ADCC where they bind to and kill cells to which antibody molecules have bound.
9. Invariant natural killer T-lymphocytes (iNKT cells) are a subset of lymphocytes that have T-cell receptors on their surface for glycolipid antigen recognition. They also have natural killer (NK) cell receptors.
10. Through the cytokines they produce, iNKT cells are able to promote and suppress different innate and adaptive immune responses. They also play a regulatory role in the development of autoimmune diseases, asthma, and transplantation tolerance. iNKT cell deficiency or disfunction can lead to the development of autoimmune diseases, human asthma, and cancers.

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11.3G: Inflammation

Describe the 4 processes that make up the inflammatory mechanism.

- Briefly describe the various beneficial effects of inflammation that are associated with plasma leakage and with diapedesis.
- Briefly describe the process of diapedesis, indicating the role of P-selectins, integrins, and adhesion molecules.
- Briefly describe the healing stage of inflammation.
- Briefly describe the problems that arise from chronic inflammation.

The inflammatory response is an attempt by the body to restore and maintain homeostasis after injury and is an integral part of body defense. Most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site. Inflammation is essentially beneficial, however, excess or prolonged inflammation can cause harm.

The Mechanism of Inflammation

Essentially, four processes make up the inflammatory mechanism:

a. Smooth muscles around larger blood vessels contract to slow the flow of blood through the capillary beds at the infected or injured site. This gives more opportunity for leukocytes to adhere to the walls of the capillary and squeeze out into the surrounding tissue.

b. The endothelial cells that make up the wall of the smaller blood vessels contract. This increases the space between the endothelial cells resulting in increased capillary permeability. Since these blood vessels get larger in diameter as a result of this, the process is called vasodilation (see Figure 11.3*G*.1).

Scanning electron micrographs of a cross section of a capillary showing an endothelial cell and a capillary with a red blood cell; courtesy of Dennis Kunkel's Microscopy).

Animation showing a capillary prior to vasodilation.

Animation showing vasodilation.

html5 version of animation for iPad showing a capillary prior to vasodilation.

html5 version of animation for iPad showing vasodilation.

c. Molecules called selectins are produced on the membrane of the leukocyte and are able to reversibly bind to corresponding selectin glycoprotein receptors on the inner wall of the venule. This reversible binding enables the leukocyte to roll along the inner wall of the venule. This reversible binding enables the leukocyte to roll along the inner wall of the venule. Adhesion molecules are activated on the surface of the endothelial cells on the inner wall of the capillaries. Corresponding molecules on the surface of leukocytes called integrins attach to these adhesion molecules allowing the leukocytes to flatten and squeeze through the space between the endothelial cells. This process is called diapedesis or extravasation.

d. Activation of the coagulation pathway causes fibrin clots to physically trap the infectious microbes and prevent their entry into the bloodstream. This also triggers blood clotting within the surrounding small blood vessels to both stop bleeding and further prevent the microorganisms from entering the bloodstream.

You Tube animation illustrating leukocyte rolling along the inner wall of a blood vessel.

You Tube movie and animation of leukocyte extravasation (diapedesis)
from ImmuneDocumentary

These four events are triggered and enhanced by a variety of chemical inflammatory mediators. We will now divide the inflammatory response into two stages: early inflammation and late inflammation.

Early Inflammation and Diapedesis

Most leukocyte diapedesis (extravasation) occurs in post-capillary venules because hemodynamic shear forces are lower in these venules. This makes it easier for leukocytes to attach to the inner wall of the vessel and squeeze out between the endothelial cells. We will look at this process in more detail below.

1. During the very early stages of inflammation, stimuli such as injury or infection trigger the release of a variety of mediators of inflammation such as leukotrienes, prostaglandins, and histamine. The binding of these mediators to their receptors on endothelial cells leads to vasodilation, contraction of endothelial cells, and increased blood vessel permeability. In addition, the basement membrane surrounding the capillaries becoming rearranged so as to promote the migration of leukocytes and the movement of plasma macromolecules from the capillaries into the surrounding tissue. Mast cells in the connective tissue as well as basophils, neutrophils and platelets leaving the blood from injured capillaries, release or stimulate the synthesis of vasodilators such as histamine, leukotrienes, kinins, and prostaglandins. Certain products of the complement pathways (C5a and C3a) can bind to mast cells and trigger their release their vasoactive agents. In addition, tissue damage activates the coagulation cascade and production of inflammatory mediators like bradykinins.
2. The binding of histamine to histamine receptors on endothelial cells triggers an upregulation of P-selectin molecules and platelet-activating factor or PAF on the endothelial cells that line the venules.
3. The P-selectins then are able to reversibly bind to corresponding P-selectin glycoprotein ligands (PSGL-1) on leukocytes. This reversible binding enables the leukocyte to now roll along the inner wall of the venule.
4. The binding of PAF to its corresponding receptor PAF-R on the leukocyte upregulates the surface expression of an integrin called leukocyte function-associated molecule-1 (LFA-1) on the surface of the leukocyte.
5. The LFA-1 molecules on the rolling leukocytes can now bind firmly to an an adhesion molecule called intercellular adhesion molecule-1 (ICAM-1) found on the surface of the endothelial cells forming the inner wall of the blood vessel (see Figure 11.3G.4).
6. The leukocytes flatten out, squeeze between the constricted endothelial cells, and use enzymes to breakdown the matrix that forms the basement membrane surrounding the blood vessel. The leukocytes then migrate towards chemotactic agents such as the complement protein C5a and leukotriene B_4 generated by cells at the site of infection or injury (see Figure 11.3G.5).

Late Inflammation and Diapedesis

1) Usually within two to four hours of the early stages of inflammation, activated macrophages and vascular endothelial cells release inflammatory cytokines such as TNF and IL-1 when their toll-like receptors bind pathogen-associated molecular patterns - molecular components associated with microorganisms but not found as a part of eukaryotic cells. This enables vascular endothelial cells of nearby venules to increase their expression of adhesion molecules such as P-selectins, E-selectins, intercellular adhesion molecules (ICAMs), and chemokines.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

For More Information: Cytokines from Unit 5

2) The binding of TNF and IL-1 to receptors on endothelial cells triggers an maintains the inflammatory response by upregulation the production of the adhesion molecule E-selectin and maintaining P-selectin expression on the endothelial cells that line the venules.

3). The E-selectins on the inner surface of the endothelial cells can now bind firmly to its corresponding integrin E-selectin ligand-1 (ESL-1) on leukocytes (see Figure $11.3G.4$).

4) The leukocytes flatten out, squeeze between the constricted endothelial cells, and move across the basement membrane as they are are attracted towards chemokines such as interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1) generated by cells at the site of infection or injury (see Figure $11.3G.5$). Leakage of fibrinogen and plasma fibronectin then forms a molecular scaffold that enhances the migration and retention of leukocytes at the infected site.

Animation summarizing late inflammation and diapedesis.

html5 version of animation for iPad summarizing late inflammation and diapedesis.

Benefits of Inflammation

As a result of this increased permeability:

a. Plasma flows out of the blood into the tissue.

Beneficial molecules in the plasma (see Figure $11.3G.2$) include:

1. Clotting factors. Tissue damage activates the coagulation cascade causing fibrin clots to form to localize the infection, stop the bleeding, and chemotactically attract phagocytes.

2. Antibodies. These help remove or block the action of microbes through a variety of methods that will be explained in Unit 6.

For More Information: Antibodies from Unit 6

3. Proteins of the complement pathways. These, in turn: 1) stimulate more inflammation (C5a, C3a, and C4a), 2) stick microorganisms to phagocytes (C3b and C4b), 3) chemotactically attract phagocytes (C5a), and 4) lyse membrane-bound cells displaying foreign antigens (membrane attack complex or MAC).

For More Information: The Benefits of the Complement Pathways from Unit 5

4. Nutrients. These feed the cells of the inflamed tissue.

5. Lysozyme, cathelicidins, phospholipase A_2,and human defensins. Lysozyme degrades peptidoglycan. Cathelicidins are cleaved into two peptides that are directly toxic to microbes and can neutralize LPS from the gram-negative bacterial cell wall. Phospholipase A_2 hydrolyzes the phospholipids in the bacterial cytoplasmic membrane. Human defensins put pores in the cytoplasmic membranes of many bacteria. Defensins also activate cells involved in the inflammatory response.

6. Transferrin.Transferrin deprives microbes of needed iron.

b. Leukocytes enter the tissue through a process called diapedesis or extravasation, discussed above under early inflammation and late inflammation.

Benefits of diapedesis include (see Figure 11.3G.2):

1. Increased phagocytosis. Neutrophils, monocytes that differentiate into macrophages when they enter the tissue, and eosinophils are phagocytic leukocytes.

2. More vasodilation. Basophils, eosinophils, neutrophils, and platelets enter the tissue and release or stimulate the production of vasoactive agents that promote inflammation.

3. Cytotoxic T-lymphocytes (CTLs), effector T4-cells, and NK cells enter the tissue to kill cells such as infected cells and cancer cells that are displaying foreign antigens on their surface (discussed in Unit 6).

For More Information: Leukocytes from Unit 5

Concept Map for Inflammation

Cytokines called chemokines are especially important in this part of the inflammatory response. They play key roles in diapedesis -enabling white blood cells to adhere to the inner surface of blood vessels, migrate out of the blood vessels into the tissue, and be chemotactically attracted to the injured or infected site. They also trigger extracellular killing by neutrophils.

Finally, within 1 to 3 days, macrophages release the cytokines interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-a). These cytokines stimulate NK cells and T-lymphocytes to produce the cytokine interferon-gamma. (IF-?). The IF-? then binds to receptors on macrophages causing them to produce fibroblast growth factor and angiogenic factors for tissue remodeling. With the proliferation of endothelial cells and fibroblasts, endothelial cells form a fine network of new capillaries into the injured area to supply blood, oxygen, and nutrients to the inflamed tissue. The fibroblasts deposit the protein collagen in the injured area and form a bridge of connective scar tissue to close the open, exposed area. This is called fibrosis or scarring, and represents the final healing stage.

Inflammation is normally carefully regulated by cytokines. Inflammatory cytokines such as interferon-gamma and interleukin-12 enhance the inflammatory response whereas the cytokine interleukin-10 inhibits inflammation by decreasing the expression of inflammatory cytokines.

So as can be seen, acute inflammation is essential to body defense. Chronic inflammation, however, can result in considerable tissue damage and scarring. With prolonged increased capillary permeability, neutrophils continually leave the blood and accumulate in the tissue at the infected or injured site. As they discharge their lysosomal contents and reactive oxygen species or ROS, surrounding tissue is destroyed and eventually replaced with scar tissue. Anti-inflammatory agents such as antihistamines or corticosteroids may have to be given to relieve symptoms or reduce tissue damage.

For example, as learned in Unit 3, during severe systemic infections with large numbers of microorganisms present, high levels of pathogen-associated molecular patterns (PAMPs) are released resulting in excessive cytokine production by macrophages and this can harm the body. In addition, neutrophils start releasing their proteases and reactive oxygen species that kill not only the bacteria, but the surrounding tissue as well. Harmful effects include high fever, hypotension, tissue destruction, wasting, acute respiratory distress syndrome or ARDS, disseminated intravascular coagulation or DIC, damage to the vascular endothelium, hypovolemia, and reduced perfusion of blood through tissues and organs resulting to shock, multiple system organ failure (MOSF), and often death. This excessive inflammatory response is referred to as Systemic Inflammatory Response Syndrome or SIRS or the Shock Cascade.

For More Information: The Shock Cascade from Unit 3

Briefly describe the mechanisms that enable to slow the flow of blood at an infection site and get phagocytes, complement proteins and antibodies to the infection site.

- Why is it important to deliver plasma to an infection site?
- Why is it important for diapedesis to occur during inflammation?

Chronic inflammation also contributes to heart disease, Alzheimer's disease, diabetes, and cancer.

- In the case of cancer,it is proposed that when macrophages produce inflammatory cytokines, such as TNF-alpha, these cytokines activate a gene switch in the cancer cell that turns on the synthesis of proteins that promote cell replication and inflammation while blocking apoptosis of the cancer cell.
- In heart disease, it is thought that macrophages digest low density lipoprotein or LDL, the bad cholesterol, and are then encased in a fibrous cap that forms arterial plaque.
- With diabetes, it is thought that the metabolic stress of obesity triggers innate immune cells and fat cells to produce cytokines such as TNF-alpha that can interfere with the normal function of insulin.
- In the case of Alzheimer's disease, microglial cells, macrophage-like cells in the brain, interact with the beta-amyloid proteins that build up in neurons of those with Alzheimer's and subsequently produce inflammatory cytokines and free radicals that destroy the neurons.

Concept Map for Inflammation

Summary

1. Most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site.
2. As part of the mechanism for inflammation, smooth muscles around larger blood vessels contract to slow the flow of blood through the capillary beds at the infected or injured site. This gives more opportunity for leukocytes to adhere to the walls of the capillary and squeeze out into the surrounding tissue.
3. As part of the mechanism for inflammation, the endothelial cells that make up the wall of the smaller blood vessels contract. This increases the space between the endothelial cells resulting in increased capillary permeability.
4. As part of the mechanism for inflammation, adhesion molecules are activated on the surface of the endothelial cells on the inner wall of the capillaries and corresponding molecules on the surface of leukocytes called integrins attach to these adhesion molecules allowing the leukocytes to flatten and squeeze through the space between the endothelial cells. This process is called diapedesis or extravasation.
5. As part of the mechanism for inflammation, activation of the coagulation pathway causes fibrin clots to physically trap the infectious microbes and prevent their entry into the bloodstream.
6. Acute inflammation is essential to body defense.
7. As a result of this increased permeability, plasma flows out of the blood into the tissue delivering clotting factors, antibody molecules, complement pathway proteins, nutrients, antibacterial enzymes and peptides, and transferrin for innate body defense.
8. As a result of this increased permeability, leukocytes enter the tissue delivering phagocytic cells, inflammation-inducing cells, cytotoxic T-lymphocytes, effector T4-lymphocytes, and NK cells.
9. Inflammatory cytokines also, enable endothelial cells form a fine network of new capillaries into the injured area to supply blood, oxygen, and nutrients to the inflamed tissue, and enable fibroblasts to deposit the protein collagen in the injured area and form a bridge of connective scar tissue to close the open, exposed area.
10. Chronic inflammation can result in considerable tissue damage and scarring, primarily to extracellular killing by phagocytes and hypoperfusion.
11. Chronic inflammation is thought to also contribute to heart disease, Alzheimer's disease, diabetes, and cancer.

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11.3H: Nutritional Immunity

Learning Objectives

- Describe at least four ways the body deprives microorganisms of iron.

We will now take a closer look at nutritional immunity. Iron is needed as a cofactor for certain enzymes in both bacteria and humans. Both bacteria and human cells produce iron chelators that trap free iron from their environment and transport it into the cell. During infection, the body makes considerable metabolic adjustment in order to make iron unavailable to microorganisms. Much of this is due to production of a defense chemical called leukocyte-endogenous mediator (LEM). As a result of infection, there is:

1. decreased intestinal absorption of iron from the diet;
2. a decrease of iron in the plasma and an increase in iron in storage as ferritin;
3. increased synthesis of the human iron-binding proteins (iron chelators) such as lactoferrin, transferrin, ferritin, and hemin that trap iron for use by human cells while making it unavailable to most microbes;
4. coupled with the febrile response, decreased ability of bacteria to synthesize their own iron chelators called siderophores;
5. prior stationing of lactoferrin at common sites of microbial invasion such as in the mucous of mucous membranes, and the entry of transferrin into the tissue during inflammation.

This lack of iron, which is needed as a cofactor for certain enzyme reactions, can inhibit the growth of many bacteria.

As seen in Unit 3, some bacteria produce in addition to their own siderophore, receptors for siderophores of other bacteria in this way take iron from other bacteria. Furthermore, a number of pathogenic bacteria are able to bind human transferrin, lactoferrin, ferritin, and hemin and use that as their iron source. For example, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Haemophilus influenzae*are able to use iron bound to human transferrin and lactoferrin for their iron needs, while pathogenic *Yersinia* species are able to use transferrin and hemin as iron sources. *Borrelia burgdorferi* doesn't even use iron as a cofactor, but instead uses manganese. Furthermore, a number of bacteria are able to produce exotoxins that kill host cells only when iron concentrations are low. Perhaps in this way the bacteria can gain access to the iron that was in those cells.

Summary

1. Iron is needed as a cofactor for certain enzymes in both bacteria and humans.
2. Both bacteria and human cells produce iron chelators that trap free iron from their environment and transport it into the cell.
3. During infection, the body makes considerable metabolic adjustment in order to make iron unavailable to microorganisms.
4. The lack of iron can inhibit the growth of many bacteria.
5. Some bacteria in addition to their own siderophores, produce receptors for iron chelators of other bacteria and/or human cells and in this way take iron being trapped for use by other organisms.
6. A number of bacteria are able to produce toxins that kill host cells only when iron concentrations are low and in this way gain access to the iron that was in those cells.

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11.3I: Fever

Describe the mechanism behind fever induction and indicate its possible benefits.

- Define hyperpyrexia.

Activated macrophages and other leukocytes release inflammatory cytokines such as TNF-alpha, IL-1, and IL-6 when their pattern-recognition receptors (PRRs) bind pathogen associated molecular patterns or PAMPs - molecular components associated with microorganisms but not found as a part of eukaryotic cells. These include bacterial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, flagellin, and bacterial DNA. There are also pattern-recognition molecules for viral double-stranded RNA (dsRNA) and fungal cell walls components such as lipoteichoic acids, glycolipids, mannans, and zymosan.

These cytokines stimulate the anterior hypothalamus of the brain, the part of the brain that regulates body temperature, to produce prostaglandin E2, which leads to an increase bodily heat production and increased vasoconstriction. This, in turn, decreases the loss of heat from the skin and increases body temperature. Up to a certain point, fever is beneficial:

1. Fever increases the environmental temperature above the optimum growth temperature for many microorganisms. If the microorganisms are growing more slowly, the body's defenses have a better chance of removing them all.
2. Fever leads to the production of heat shock proteins that are recognized by some intraepithelial T-lymphocytes called delta gamma T-cells, resulting in the production of inflammation-promoting cytokines.
3. Fever elevates the temperature of the body increasing the rate of enzyme reactions, and speeding up metabolism within the body. An elevation in the rate of metabolism can increase the production and activity of phagocytes, speed up the multiplication of lymphocytes, increase the rate of antibody and cytokine production, increase the rate at which leukocytes are released from the bone marrow into the bloodstream, and speed up tissue repair.

Too high of a body temperature, however, may cause damage by denaturing the body's enzymes. Hyperpyrexia is a fever with an extreme elevation of body temperature greater than or equal to 41.5 °C (106.7 °F). Body temperature this elevated often indicates a serious underlying condition and may lead to potentially hazardous side effects. As a result, hyperpyrexia is considered as a medical emergency.

Summary

1. Activated macrophages and other leukocytes release inflammatory cytokines such as TNF-alpha, IL-1, and IL-6 when their pattern-recognition receptors (PRRs) bind pathogen associated molecular patterns or PAMPs.
2. These cytokines stimulate the anterior hypothalamus of the brain, the part of the brain that regulates body temperature, to produce prostaglandin E2, which leads to an increase bodily heat production and increased vasoconstriction.
3. Vasoconstriction decreases the loss of heat from the skin and increases body temperature.
4. Fever increases the environmental temperature above the optimum growth temperature for many microorganisms.
5. Fever leads to the production of heat shock proteins that are recognized by some intraepithelial T-lymphocytes resulting in the production of inflammation-promoting cytokines.
6. Fever elevates the temperature of the body increasing the rate of enzyme reactions, and speeding up metabolism within the body including that involved in innate and adaptive immunity as well as tissue repair.

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11.3J: The Acute Phase Response

Briefly describe the mechanism behind the acute phase response.

- State the functions of the following acute phase proteins:

  a. C-reactive protein
  b. mannose-binding lectin

We will now take a closer look at the acute phase response. The acute phase response is an innate body defense seen during acute illnesses and involves the increased production of certain blood proteins termed acute phase proteins.

Activated macrophages and other leukocytes release inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-6 (IL-6) when their pattern-recognition receptors (PRRs) bind pathogen associated molecular patterns or PAMPs - molecular components associated with microorganisms but not found as a part of eukaryotic cells. These include bacterial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, flagellin, pilin, and bacterial DNA. There are also pattern-recognition molecules for viral double-stranded RNA (dsRNA) and fungal cell walls components such as lipoteichoic acids, glycolipids, mannans, and zymosan.

These cytokines travel through the blood and stimulate hepatocytes in the liver to synthesize and secrete acute phase proteins. This response provides an early defense and enables the body to recognize foreign substances early on in the infection process prior to the full activation and implementation of the immune responses. Two important acute phase proteins are C-reactive protein and mannose-binding protein. They function as soluble pattern-recognition receptors.

1. C-reactive protein (CRP) binds to the phosphorylcholine portion of teichoic acids and lipopolysaccharides of bacterial and fungal cell walls. It also binds to the phosphocholine found on the surface of damaged or dead human cells. It functions as an opsonin, sticking the microorganism to phagocytes, and activates the classical complement pathway by binding C1q, the first component in the pathway.
2. Mannan-bindinglectin (MBL) - also known as mannan-binding protein or MBP -binds to mannose-richglycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar). These are common in microbial glycoproteins and glycolipids but rare in those of humans. It functions as an opsonin, sticking the microorganism to phagocytes, and activates the lectin pathway.

Products of the complement pathways, in turn, promote inflammation, attach microbes to phagocytes, cause to MAC cytolysis, and chemotactically attract phagocytes to the infected area.

Summary

1. The acute phase response is an innate body defense seen during acute illnesses and involves the increased production of certain blood proteins termed acute phase proteins.
2. Inflammatory cytokines produced during innate immunity travel through the blood and stimulate hepatocytes in the liver to synthesize and secrete acute phase proteins.
3. Two important acute phase proteins are C-reactive protein and mannose-binding protein, both functioning as soluble pattern-recognition receptors.
4. C-reactive protein (CRP) binds to certain PAMPs bacterial and fungal cell walls as well as to phosphocholine found on the surface of damaged or dead human cells.
5. CRP functions as an opsonin, sticking the microorganism to phagocytes, and activates the classical complement pathway by binding C1q, the first component in the pathway.
6. Mannan-binding lectin (MBL) - also known as mannan-binding protein or MBP - binds to mannose-rich glycans on microbial cell walls.
7. MBL functions as an opsonin, sticking the microorganism to phagocytes, and activates the lectin pathway.

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11.3K: Intraepithelial T-lymphocytes and B-1 cells

Briefly describe how intraepithelial T-lymphocytes (gamma:delta T-lymphocytes) play a role in innate immunity.

- Briefly describe how B-1 cells play a role in innate immunity.

We will now take a closer look at Intraepithelial T-lymphocytes (e.g., T4 and T8) and B-1 cells. Most of the T-lymphocytes and B-lymphocytes in the body are involved in the adaptive immune responses that will be discussed in Unit 6. In adaptive immunity, specific receptors on T-lymphocytes (T-cell receptors or TCRs) and B-lymphocytes (B-cell receptors or BCRs) recognize specific antigens of specific microbes.

Intraepithelial T-lymphocytes and B-1 cells, on the other hand, are subpopulations of T-lymphocytes and B-lymphocytes that possess a more limited diversity of receptors and are designed to directly recognize the more common microbes that enter the epidermis or the mucosal epithelia. As such, they function more as effector cells for innate immunity rather than adaptive immunity.

a. Intraepithelial T-lymphocytes (IELs) are found in the epidermis of the skin and the mucosal epithelia. These T-lymphocytes, known as gamma:delta T-lymphocytes, differ from the T-lymphocytes (alpha:beta T-lymphocytes) associated with adaptive immunity. The alpha:beta T-lymphocytes are designed to recognize peptide antigens bound to MHC-I molecules of infected cells and tumor cells.

   Although their exact function is unknown, it has been proposed that they recognize molecules associated with epithelial cells but expressed only when those cells are infected, such as MHC-I molecules and heat shock proteins. They then trigger apoptosis of these stressed or infected cells using perforins and granzymes similar to cytotoxic T-lymphocytes (CTLs) of adaptive immunity. Rather than recognizing antigens specific to an infectious microorganism, they recognize molecules associated with the epithelium as a consequence of infection. Their T-cell receptors may also function as PRRs for recognizing certain PAMPs. As such, they function more as effector cells for innate immunity rather than adaptive immunity. They probably help defend the body by producing cytokines that play a variety of roles in body defense. IELs are also thought to aid in repair of mucous membranes following inflammatory damage. Excessive or inappropriate activation of IELs can also lead to damage of the intestines as in the case of celiac disease.

b. B-1 lymphocytes, or B-1 cells are found mostly in the peritoneal and pleural cavities . B-1 cells have a limited diversity of antigen receptors that initially produce a class of antibody molecule called IgM against common polysaccharide and lipid antigens of microbes and against PAMPs. As such they function more as effector cells for innate immunity rather than adaptive immunity. Antibodies produced by B-1 cells are often called natural antibodies that help to protect against bacteria in body cavities. Similar B-lymphocytes called marginal zone B cells are found in the marginal zone of the white pulp of the spleen. These are thought to make IgM to protect against bacteria that enter the bloodstream.

Summary

1. Most of the T-lymphocytes and B-lymphocytes in the body are involved in the adaptive immune responses wherein specific receptors on T-lymphocytes (T-cell receptors or TCRs) and B-lymphocytes (B-cell receptors or BCRs) recognize specific antigens of specific microbes.
2. Intraepithelial T-lymphocytes and B-1 cells, however, are subpopulations of T-lymphocytes and B-lymphocytes that possess a more limited diversity of receptors and are designed to directly recognize the more common microbes that enter the epidermis or the mucosal epithelia and function more as effector cells for innate immunity rather than adaptive immunity.
3. Intraepithelial T-lymphocytes (IELs) are found in the epidermis of the skin and the mucosal epithelia.
4. It has been proposed that they recognize molecules such as MHC-I molecules and heat shock proteins associated with epithelial cells but expressed only when those cells are infected and trigger apoptosis of these stressed or infected cells. They may also aid in repair of mucous membranes following inflammatory damage.
5. B-1 lymphocytes, or B-1 cells, are found mostly in the peritoneal and pleural cavities.
6. B-1 cells have a limited diversity of antigen receptors that initially produce a class of antibody molecule called IgM against common polysaccharide and lipid antigens of microbes and against PAMPs.
7. Similar B-lymphocytes called marginal zone B cells are found in the spleen.\ and are thought to make IgM to protect against

bacteria that enter the bloodstream.

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11.E: Innate Immunity (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

11.1: The Innate Immune System: An Overview

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe what is meant by the following:
   a. innate immunity
   b. adaptive (acquired) immunity
2. Define the following:
   a. antigen
   b. pathogen-associated molecular patterns or PAMPs
   c. epitope

11.2: Defense Cells in the Blood: The Leukocytes

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. What is the difference between a CBC and a leukocyte differential count?
2. A person has an elevated white blood cell count with anelevated number of band-form neutrophils. What is the significance of this?
3. Match the following descriptions and functions with the type of leukocytes:

   _____ Important phagocytes; 54%-75% of the leukocytes; granules stain poorly; produce enzymes for the synthesis of bradykinins and prostaglandins that promote inflammation.

   _____ Capable of phagocytosis but primarily kill microorganisms and parasitic worms extracellularly; 1%-4% of the leukocytes; large granules stain red; secrete leukotriens and prostaglandins to promote inflammation.

   _____ Not important in phagocytosis; large granules stain a purplish blue; 0%-1% of the leukocytes; release histamine, leukotriens, and prostaglandins to promote inflammation.

   _____ Important in phagocytosis and aid in the adaptive immune responses; produce cytokines; 4%-8% of the leukocytes; differentiate into macrophages and dendritic cells when they leave the blood and enter the tissue.

   _____ Mediate humoral immunity (antibody production); have B-cell receptors (BCR) on their surface for antigen recognition; differentiate into antibody-secreting plasma cells.

   _____ Regulate the adaptive immune responses through cytokine production; have CD4 molecules and TCRs on their surface for antigen recognition.

   _____ Carry out cell-mediated immunity; have CD8 molecules and TCRs on their surface for antigen recognition; differentiate into cytotoxic T-lymphocytes (CTLs).

   _____ Lymphocytes that lack B-cell receptors and T-cell receptors; kill cells to which the antibody IgG has attached as well as human cells lacking MHC-I molecules on their surface.

   a. B-lymphocytes

b. T4-lymphocytes
c. T8-lymphocytes
d. NK cells
e. basophils
f. neutrophils
g. eosinophils
h. monocytes

4. State what type of cell monocytes differentiate into when they enter tissue.
5. Multiple Choice

11.3: Defense Cells in the Tissue: Dendritic Cells, Macrophages, and Mast Cells

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State 3 different functions of macrophages in body defense.
   a.
   b.
   c.
2. Name the cells in the tissue whose primary function is to present antigen to naive T-lymphocytes.
3. Name the cells in the tissue whose primary function is to present antigen to effector T-lymphocytes.
4. State the primary function of mast cells in body defense.

11.3: Immediate Innate Immunity

11.3A: Antimicrobial Enzymes and Antimicrobial Peptides

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching

   ___ Found in in tears, mucous, saliva, plasma, tissue fluid, etc.; breaks down peptidoglycan.

   _____ A protein produced by skin and mucosal epithelial cells. The two peptides produced upon cleavage of this protein are directly toxic to a variety of microorganisms.

   ___ An enzyme that penetrates the bacterial cell wall and hydrolizes the phospholipids in the bacterial cytoplasmic membrane.

   ___ Short cationic peptides that are directly toxic by disrupting the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs. They also activate cells for an inflammatory response.

   a. lysozyme
   b. phospholipase A_2
   c. defensins
   d. cathelicidins
   e. lactotransferrin and transferrin

11.3B: The Complement System

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe how the classical complement pathway is activated.
2. Match the following:

_____ Complement proteins that trigger inflammation

_____ Complement proteins that chemotactically attracting phagocytes to the infection site.

_____ Complement proteins that promote the attachment of antigens to phagocytes (enhanced attachment or opsonization.

_____ Complement proteins that cause lysis of Gram-negative bacteria and human cells displaying foreign epitopes.

a. the membrane attack complex (MAC)
b. C5a. and to a lesser extent, C3a and C4a.
c. C3b, and to a lesser extent, C4b.
d. C5a

3. Briefly describe how the lectin complement pathway is activated.
4. Briefly describe how the alternative complement pathway is activated.

11.3C: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe what is meant by anatomical barriers to infection.
2. List 4 ways in which the body can physically remove microorganisms or their products.
3. Describe how bacterial antagonism by normal microbiota acts as a nonspecific body defense mechanism.

11.4: Early Induced Innate Immunity

11.3A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State the function of pathogen-associated molecular patterns as they relate to innate immunity.
2. Name at least 5 PAMPS associated with bacteria.
3. Name at least 2 PAMPS associated with viruses.
4. Define DAMP.

11.3B: Pattern-Recognition Receptors (PRRs)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State the function of the following as they relate to innate immunity.
   a. pathogen-associated molecular patterns
   b. pattern recognition receptors
   c. endocytic pattern recognition receptors
   d. signaling pattern recognition receptors
   e. danger-associated molecular patterns
   f. danger recognition receptors
   g. inflammasome
2. Briefly describe the major difference between the effect of the cytokines produced in response to PAMPs that bind to cell surface signaling PRRs and endosomal PRRs.

11.3C: Cytokines Important in Innate Immunity

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write

them out. This will not test your understanding of this tutorial.

1. Match the following:

   _____ Cytokines that promote inflammation by enabling white blood cells to adhere to the inner surface of blood vessels, migrate out of the blood vessels into the tissue, and be chemotactically attracted to the injured or infected site.

   _____ Cytokines that prevent viral replication, activate a variety of cells important in body defense, and exhibit some anti-tumor activity.

   _____ A wide variety of intercellular regulatory proteins produced by many different cells in the body that ultimately control every aspect of body defense. Cytokines activate and deactivate phagocytes and immune defense cells, increase or decrease the functions of the different immune defense cells, and promote or inhibit a variety of nonspecific body defenses.

   a. lysozyme
   b. chemokines
   c. cytokines
   d. interferons
   e. human beta-defensins
2. Describe specifically how type-I interferons are able to block viral replication within an infected host cell.

11.3D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe two specific examples of how an improper functioning PRR can lead to an increased risk of a specific infection or disease.
   A.
   B.

11.3E: Phagocytosis

Questions I

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the role of the following as they relate to phagocytosis:

   a. inflammation

   b. lymph nodules

   c. lymph nodes

   d. spleen

Questions II

1. Describe the following steps in phagocytosis:

   a. activation

   b. chemotaxis

c. attachment (both unenhanced and enhanced)

d. ingestion

e. destruction

2. State what happens when either phagocytes are overwhelmed with microbes or they adhere to cells to large to be phagocytosed.
3. Most of the tissue destruction seen during microbial infections is do to _____.

11.3F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching

_____ Recognize stress induced molecules such as MICA and MICB on the surface of tumor cells or infected cells.

_____ Recognize MHC-I molecules usually present on all nucleated cells of the body.

_____ Mechanism by which NK cells kill tumor cells and infected cells.

A. Apoptosis, a programmed cell suicide
B. Killer-activating receptors
C. Killer-inhibitory receptors

2. Epitopes of glycolipid antigens are recognized by iNKT lymphocytes by way of their _____.
3. iNKT cells promote both innate and adaptive immunity and may also regulate immune responses by way of the _____ they produce once activated.

11.3G: Inflammation

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe the following in termsof inflammation:
   a. mechanism for inflammation
   b. benefits of plasma leakage
   c. benefits of diapedesis
   d. healing
2. Briefly describe the process of diapedesis, indicating the role of the following:
   a. P-selectins
   b. integrins
   c. adhesion molecules
3. Briefly describe the problems that arise from chronic inflammation.

11.3H: Nutritional Immunity

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State three different ways the body deprives microorganisms of iron.
   a.
   b.
   c.

11.3I: Fever

1. Describe the mechanism behind fever.
2. State 2 benefits of fever.
   a.
   b.

11.3J: The Acute Phase Response

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the mechanism behind the acute phase response.
2. An acute phase protein that binds to phospholipids in microbial membranes, sticks the micobe to phagocytes, and activates the classical complement pathway is _____.
3. An acute phase protein that binds to mannose in microbial walls, sticks the micobe to phagocytes, and activates the lectin pathway is _____.

11.3K: Intraepithelial T-lymphocytes and B-1 cells

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

_____ These cells have a limited diversity of antigen receptors that initially produce a class of antibody molecule called IgM against common polysaccharide and lipid antigens of microbes and against PAMPs of bacteria that invade body cavities.

____ These cells have a limited diversity of antigen receptors that recognize molecules associated with epithelial cells but expressed only when those cells arestressed or infected. They kill those cells by inducing apoptosis, a programmed cell suicide.

a. gamma:delta T-lymphocytes
b. alpha:beta T-lymphocytes
c. B-1 cells
d. marginal zone B cells

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UNIT 6: ADAPTIVE IMMUNITY

The adaptive immune system is a subsystem of the overall immune system that is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogen growth. Adaptive immunity creates immunological memory after an initial response to a specific pathogen, and leads to an enhanced response to subsequent encounters with that pathogen. This process of acquired immunity is the basis of vaccination.

12: Introduction to Adaptive Immunity

12.1: An Overview of Innate and Adaptive Immunity

12.2: Antigens and Epitopes

12.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses

12.3A: Major Histocompatibility Complex (MHC) Molecules

12.3B: Antigen-Presenting Cells (APCs)

12.3C: T4-Lymphocytes (T4-Cells)

12.3D: T8-Lymphocytes (T8-Cells)

12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

12.3F: B-Lymphocytes (B-Cells)

12.3G: Natural Killer Cells (NK Cells)

12.4: The Lymphoid System

12.5: An Overview of the Steps Involved in Adaptive Immune Responses

12.E: Introduction to Adaptive Immunity (Exercises)

13: Humoral Immunity

13.1: Antibodies (Immunoglobulins)

13.1B: Antibody Structure

13.1C: The 5 Classes (Isotypes) of Human Antibodies

13.1D: Generation of Antibody Diversity

13.1E: Clonal Selection and Clonal Expansion

13.1F: Anamnestic (Memory) Response

13.2: Ways That Antibodies Help to Defend the Body

13.2A: Opsonization

13.2B: Cytolysis by the Membrane Attack Complex (MAC)

13.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells

13.2D: Neutralization of Exotoxins

13.2E: Neutralization of Viruses

13.2F: Preventing Bacterial Adherence

13.2G: Agglutination of Microorganisms

13.2H: Immobilization of Bacteria and Protozoans

13.2I: Promoting an Inflammatory Response

13.3: Naturally and Artificially Acquired Active and Passive Immunity

13.3A: Naturally Acquired Immunity

13.3B: Artificially Acquired Immunity

13.E: Humoral Immunity (Exercises)

14: Cell-Mediated Immunity

14.1: Cell-Mediated Immunity - An Overview

14.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes

14.3: Activating Macrophages and NK Cells

14.4: Stimulating Cells to Secrete Cytokines

14.E: Cell-Mediated Immunity (Exercises)

15: Immunodeficiency

15.1: Primary Immunodeficiency

15.2: Secondary Immunodeficiency

15.E: Immunodeficiency (Exercises)

16: Hypersensitivities

16.1: Immediate Hypersensitivities: Type I

16.2: Immediate Hypersensitivities: Type II

16.3: Immediate Hypersensitivities: Type III

16.4: Immediate Hypersensitivities - Type V

16.5: Delayed Hypersensitivities - Type IV

16.6: Superantigens

16.E: Hypersensitivities (Exercises)

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12: INTRODUCTION TO ADAPTIVE IMMUNITY

12.1: An Overview of Innate and Adaptive Immunity

12.2: Antigens and Epitopes

12.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses

12.3A: Major Histocompatibility Complex (MHC) Molecules

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12.3C: T4-Lymphocytes (T4-Cells)

12.3D: T8-Lymphocytes (T8-Cells)

12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

12.3F: B-Lymphocytes (B-Cells)

12.3G: Natural Killer Cells (NK Cells)

12.4: The Lymphoid System

12.5: An Overview of the Steps Involved in Adaptive Immune Responses

12.E: Introduction to Adaptive Immunity (Exercises)

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12.1: An Overview of Innate and Adaptive Immunity

Compare adaptive (acquired) immunity with innate immunity.

- Define the following:

  a. antigen
  b. immunogen
  c. epitope
  d. humoral immunity
  e. cell-mediated immunity

As mentioned in Unit 5, the body has two immune systems: innate immunity and adaptive immunity. Unit 5 dealt with innate immunity. In Unit 6 we will cover adaptive immunity. Let's first again briefly compare acquired and innate immunity.

Innate Immunity

Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Innate immunity can be divided into immediate innate immunity and early induced innate immunity.

Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood, our found in extracellular tissue fluids, and are secreted by epithelial cells. These include: antimicrobial enzymes and peptides; complement system proteins; and anatomical barriers to infection, mechanical removal of microbes, and bacterial antagonism by normal flora bacteria. These preformed innate defense molecules will be discussed in greater detail later in this unit.

Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs. These recruited defense cells include: phagocytic cells: leukocytes such as neutrophils, eosinophils, and monocytes; tissue phagocytic cells in the tissue such as macrophages; cells that release inflammatory mediators: inflammatory cells in the tissue such as macrophages and mast cells; leukocytes such as basophils and eosinophils; and natural killer cells (NK cells).

Unlike adaptive immunity, innate immunity does not recognize every possible antigen. Instead, it is designed to recognize molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells. These unique microbial molecules are called pathogen-associated molecular patterns or PAMPS and include LPS from the gram-negative cell wall, peptidoglycan and lipotechoic acids from the gram-positive cell wall, the sugar mannose (a terminal sugar common in microbial glycolipids and glycoproteins but rare in those of humans), bacterial and viral unmethylated CpG DNA, bacterial flagellin, the amino acid *N*-formylmethionine found in bacterial proteins, double-stranded and single-stranded RNA from viruses, and glucans from fungal cell walls. In addition, unique molecules displayed on stressed, injured, infected, or transformed human cells also act as PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Most body defense cells have pattern-recognition receptors or PRRs for these common PAMPS (Figure 12.1.1) and so there is an immediate response against the invading microorganism. Pathogen-associated molecular patterns can also be recognized by a series of soluble pattern-recognition receptors in the blood that function as opsonins and initiate the complement pathways. In all, the innate immune system is thought to recognize approximately 10^3 of these microbial molecular patterns.

For More Information: Leukocytes from Unit 5

Examples of innate immunity include anatomical barriers, mechanical removal, bacterial antagonism, antigen-nonspecific

defense chemicals, the complement pathways, phagocytosis, inflammation, fever, and the acute-phase response. In this current unit we will look at each of these in greater detail.

Adaptive Immunity

Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life. There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. humoral immunity: humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes.
2. cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes.

During adaptive immunity, antigens are transported to lymphoid organs where they are recognized by naive B-lymphocytes and T-lymphocytes. These activated B- and T-lymphocytes subsequently proliferate and differentiate into effector cells. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as nonself and stimulates an adaptive immune response. For simplicity we will use the term antigen when referring to both antigens and immunogens. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes. The size of an epitope is generally thought to be equivalent to 5-15 amino acids in the case of protein antigens (Figure 12.1.2); 3-4 sugar residues in the case of polysaccharide antigens (Figure 12.1.3).

For More Information: Antigens and Immunogens

For More Information: Antibodies from Unit 6

The body recognizes an antigen as foreign when epitopes of that antigen bind to epitope-specific receptor molecules on the surface of B-lymphocytes and/or T-lymphocytes. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor (BCR) and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

- B-cell receptors (BCRs) can bind directly to epitopes on peptide, protein, polysaccharide, nucleic acid, and lipid antigens (Figure 12.1.4).
- T-cell receptors (TCRs) of most T4-lymphocytes and T8-lymphocytes can only recognize peptide epitopes from protein antigens presented by the body's own cells by way of special molecules called MHC molecules (Figure 12.1.4).

It is estimated that the human body has the ability to recognize 10^7 or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor. Among this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters. With the adaptive immune responses, the body is able to recognize any conceivable antigen it may eventually encounter.

The downside to the specificity of adaptive immunity is that only a few B-cells and T-cells in the body recognize any one epitope. These few cells then must rapidly proliferate in order to produce enough cells to mount an effective immune response against that particular epitope, and that typically takes several days. During this time the pathogen could be causing considerable harm, and that is why innate immunity is also essential.

Flash animation of epitopes reacting with a specific TCR on a T8-lymphocyte.

Adaptive immunity usually improves upon repeated exposure to a given infection and involves the following:

- antigen-presenting cells (APCs) such as macrophages and dendritic cells;
- the activation and proliferation of antigen-specific B-lymphocytes;
- the activation and proliferation of antigen-specific T-lymphocytes; and
- the production of antibody molecules, cytotoxic T-lymphocytes (CTLs), activated macrophages, and cytokines.

Acquired immunity includes both humoral immunity and cell-mediated immunity and will be the topic of Unit 5.

Concept Map for Innate Versus Adaptive Immunity

We will now take a closer look at adaptive immunity.

Summary

1. The body has two immune systems: the innate immune system and the adaptive immune system.
2. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe.
3. Innate immunity is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.
4. Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood and in extracellular tissue fluids.
5. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs.
6. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen.
7. Adaptive immunity is the immunity one develops throughout life.
8. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes.
9. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes.

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12.2: Antigens and Epitopes

Define antigen and immunogen.

- State what antigens are composed of chemically.
- List 3 characteristics an antigen must have to be immunogenic.
- Define epitope.
- Briefly describe how the body recognizes an antigen as foreign.
- Compare B-cell receptors and T-cell receptors in terms of how they recognize epitopes.
- In terms of infectious diseases, list 2 categories of microbial materials that may act as an antigen.
- List 3 groups of noninfectious materials that may act as an antigen.
- Define the following:

  a. endogenous antigen
  b. exogenous antigen
  c. autoantigen
  d. hapten

An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response. For simplicity, both antigens and immunogens are usually referred to as antigens.

To be immunogenic, an antigen must possess three characteristics:

- be of high molecular weight,
- exhibit chemical complexity, and
- exhibit foreignness (recognized as non-self by the body).

Chemically, antigens are large molecular weight proteins (including conjugated proteins such as glycoproteins, lipoproteins, and nucleoproteins) and polysaccharides (including lipopolysaccharides). These protein and polysaccharide antigens are found on the surfaces of viruses and cells, including microbial cells (bacteria, fungi, protozoans) and human cells.

Epitopes of an antigen

The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes, as well as with free antibody molecules, are called epitopes or antigenic determinants. The size of an epitope is generally thought to be equivalent to 5-15 amino acids or 3-4 sugar residues.

Some antigens, such as polysaccharides, usually have many epitopes, but all of the same specificity. This is because polysaccharides may be composed of hundreds of sugars with branching sugar side chains, but usually contain only one or two different sugars. As a result, most "shapes" along the polysaccharide are the same (see Figure 12.2.1).

Other antigens such as proteins usually have many epitopes of different specificities. This is because proteins are usually hundreds of amino acids long and are composed of 20 different amino acids. Certain amino acids are able to interact with other amino acids in the protein chain and this causes the protein to fold over upon itself and assume a complex three-dimensional shape. As a result, there are many different "shapes" on the protein (see Figure 12.2.2). That is why proteins are more immunogenic than polysaccharides; they are chemically more complex.

A microbe, such as a single bacterium, has many different proteins (and polysaccharides) on its surface that collectively form its various structures, and each different protein may have many different epitopes. Therefore, immune responses are directed against many different epitopes of many different antigens of the same microbe. (For example, a bacterial cell wall alone may contain over 100 different epitopes.) Even simple viruses possess many different epitopes. (see Figure 12.2.3).

Recognizing an antigen as foreign

As we saw earlier in Unit 5, the B-lymphocytes and T-lymphocytes are the cells that carry out the immune responses. The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope (similar to interlocking pieces of a puzzle).

a. B-cell receptors

The antigen receptors on the cytoplasmic membrane of B-lymphocytes are called B-cell receptors and are actually antibody molecules made by that cell and anchored to the outer surface of its cytoplasmic membrane. As will be seen in a later section, antibodies are "Y"-shaped macromolecules composed of four glycoprotein chains connected to one another by disulfide (S-S) bonds and noncovalent bonds (see Figure 12.2.4). Additional S-S bonds fold the individual glycoprotein chains into a number of distinct globular domains (see Figure 12.2.5).

The two tips of the "Y" are referred to as the Fab portions of the antibody (see Figure 12.2.4 and Figure 12.2.5). The first 110 amino acids or first domain of both the heavy and light chain of the Fab region of the antibody provide specificity for binding an epitope on an antigen. Because they recognize molecular shapes that occur as a result of the 3-dimensional folding of an antigen, B-cell receptors can bind directly to epitopes on peptide, protein, polysaccharide, nucleic acid, and lipid antigens.

The bottom part of the "Y", the C terminal region of each glycoprotein chain, is called the Fc portion. The Fc portion has a constant amino acid sequence that defines the class and subclass of each antibody. The terminal portion of the Fc region of the B-cell receptor is the part that becomes anchored to the cytoplasmic membrane of B-lymphocyte (see Figure 12.2.6).

b. T-cell receptors

The receptors on the membrane of T-lymphocytes are called T-cell receptors or TCRs. They are analogous to the B-cell receptor, but are composed of just two glycoprotein chains, each having a variable domain and a constant domain (see Figure 12.2.7).

Unlike B-cell receptors that can directly bind to epitopes on antigens, the T-cell receptor or TCR of most T4-lymphocytes and T8-lymphocytes can only recognize peptide epitopes from protein antigens presented by the body's own cells by way of special molecules called MHC molecules as seen in Figure 12.2.6. The terminal portion of the variable domains provides specificity for binding peptides of protein antigens after the protein has been unfolded, broken into peptides, and bound to a MHC molecule, while the terminus of the constant region becomes anchored to the cytoplasmic membrane of the T-lymphocyte.

The TCR of $CD4^-CD8^-$ T-lymphocytes and non-MHC restricted $CD4^+$ and $CD8^+$ lymphocytes can recognize epitopes of lipid or glycolipid antigens after they have been attached to CD1 molecules on antigen-presenting cells or in some cases, epitopes directly on antigens.

It is estimated that the human body has the ability to recognize 10^7or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor. Among this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters. With the adaptive immune responses, the body is able to recognize any conceivable antigen it may eventually encounter.

Flash animation of epitopes reacting with specific B-cell receptors on B-lymphocytes.

html5 version of animation for iPad showing epitopes reacting with specific B-cell receptor on a B-lymphocytes.

Flash animation showing epitopes reacting with a specific TCR on a T8-lymphocyte.

html5 version of animation for iPad showing epitopes reacting with a specific TCR on a T8-lymphocyte.

For More Information: B-Lymphocytes from Unit 6

For More Information: T4-Lymphocytes from Unit 6

For More Information: T8-Lymphocytes from Unit 6

Substances that act as antigens

In terms of infectious diseases, the following may act as antigens:

a. microbial structures, such as bacterial and fungal cell walls, protozoan cell membranes, bacterial and fungal capsules, microbial flagella, bacterial pili, viral capsids, viral envelope-associated glycoproteins, etc.; and

b. microbial toxins

Certain non-infectious materials may also act as antigens if they are recognized as "nonself" by the body. These include:

a. allergens, including dust, pollen, hair, foods, dander, bee venom, drugs, and other agents causing allergic reactions;

b. foreign tissues and cells from transplants and transfusions; and

c. the body's own cells that the body fails to recognize as "normal self," such as cancer cells, infected cells, cells involved in autoimmune diseases.

There are three broad categories of antigens: endogenous antigens, exogenous antigens, and autoantigens.

1. Endogenous antigens are proteins found within the cytosol of human cells. Examples of endogenous antigens include:

a. viral proteins produced during viral replication;
b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication;
c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells;
d. tumor antigens produced by cancer cells; and
e. self-peptides from host cellular proteins.

2. Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses. These exogenous antigens enter macrophages, dendritic cells, and B-lymphocytes through phagocytosis or pinocytosis.

3. Autoantigens are any of an organism’s own antigens (self-antigens) that stimulate an autoimmune reaction, that is humoral immunity or cell-mediated against self.

A hapten is a small molecule that by itself is not immunogenic but can act as an antigen when it binds to a larger protein molecule. The hapten then acts as an epitope on the protein. For example with penicillin and poison ivy allergies, the penicillin molecules and the oil urushiol from the poison ivy plant function as haptens, binding to tissue proteins to form an antigen and stimulating an allergic immune response.

How is the body able to distinguish epitopes of microorganisms from “self” epitopes present as a part of our body?

- What is the difference between how B-lymphocytes and T-lymphocytes recognize antigens?

Summary

1. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes.
2. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response.
3. Chemically, antigens are large molecular weight proteins and polysaccharides.
4. The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes, as well as with free antibody molecules, are called epitopes.
5. The size of an epitope is generally thought to be equivalent to 5-15 amino acids or 3-4 sugar residues.
6. Polysaccharides antigens usually have many epitopes but all of the same specificity.
7. Proteins antigens usually have many epitopes of different specificities.
8. Immune responses are directed against many different epitopes of many different antigens of the same microbe.
9. The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope.
10. The antigen receptors on the cytoplasmic membrane of B-lymphocytes are called B-cell receptors and are actually antibody molecules made by that cell and anchored to the outer surface of its cytoplasmic membrane and is composed of composed of four interconnected glycoprotein chains.
11. The receptors on the membrane of T-lymphocytes are called T-cell receptors or TCRs and are composed of just two glycoprotein chains.
12. During its development, each different B-lymphocyte and T-lymphocyte becomes genetically programmed to produce a B-cell receptor or T-cell receptor with a unique three-dimensional shape.
13. The body produces 10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor and with this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters.
14. In terms of infectious diseases, microbial structures and microbial toxins act as antigens.
15. Certain noninfectious materials also act as antigens, including allergens, foreign tissues and cells from transplants and transfusions, and the body's own cells that the body fails to recognize as "normal self," such as cancer cells, infected cells, and cells involved in autoimmune diseases.
16. Endogenous antigens are antigens found within the cytosol of human cells such as viral proteins, proteins from intracellular bacteria, and tumor antigens.
17. Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses.
18. Autoantigens are any of an organism's own antigens (self-antigens) that stimulate an autoimmune reaction.

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12.3: MAJOR CELLS AND KEY CELL SURFACE MOLECULES INVOLVED IN ADAPTIVE IMMUNE RESPONSES

We will now take a look at major cells and key cell-surface molecules involved in adaptive immune responses.



- Topic hierarchy

12.3A: Major Histocompatibility Complex (MHC) Molecules

12.3B: Antigen-Presenting Cells (APCs)

12.3C: T4-Lymphocytes (T4-Cells)

12.3D: T8-Lymphocytes (T8-Cells)

12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

12.3F: B-Lymphocytes (B-Cells)

12.3G: Natural Killer Cells (NK Cells)

Template:HideTOC

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12.3A: Major Histocompatibility Complex (MHC) Molecules

Learning Objectives

- State which body cells display MHC-I surface molecules and which cells normally display MHC-II surface molecules.
- Define endogenous antigen and exogenous antigen and state which class of MHC molecule primarily binds each.
- State which type of T-lymphocyte recognizes epitopes from protein antigens on MHC-I molecules and which type recognizes epitopes from protein antigens on MHC-II molecules.
- State the role of proteasomes in binding of peptides from endogenous antigens by MHC-I molecules.
- State the role of lysosomes in binding of peptides from exogenous antigens by MHC-II molecules.

The Roles of MHC Molecules In Adaptive Immune Responses

MHC molecules enable T-lymphocytes to recognize epitopes of antigens and discriminate self from non-self. Unlike B-cell receptors on B-lymphocytes that are able to directly bind epitopes on antigens, the T-cell receptors (TCRs) of T-lymphocytes can only recognize epitopes - typically short chains of amino acids called peptides - after they are bound to MHC molecules (Figure 12.3A.1).

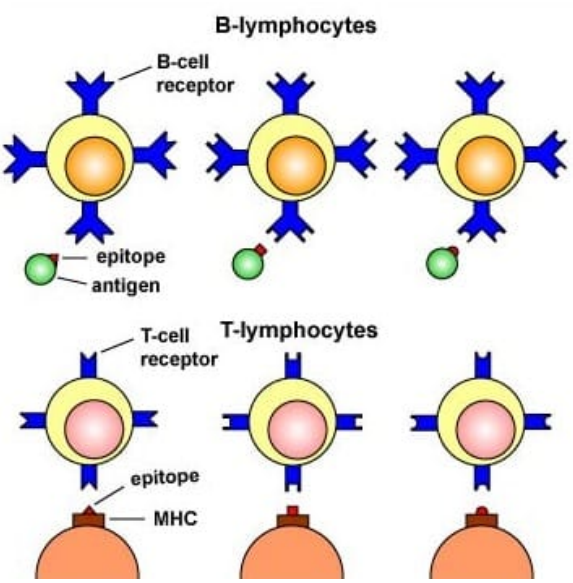


Figure 12.3A.1: Epitope-Specific Receptors on the Surface of B- and T-Lymphocytes. B-lymphocytes have B-cell receptors that recognize epitopes directly on antigens. T-lymphocytes have TCR molecules that recognize epitopes only after they have been placed on cells of the body by way of MHC molecules.

The MHC genes are the most polymorphic genes in the human genome, possessing many alleles for each gene. The MHC genes are co-dominantly expressed so that an individual expresses the alleles inherited from each parent. In this way, the number of MHC molecules that bind peptide for presentation to T-lymphocytes is maximized. In addition, each MHC molecule is able to bind a wide variety of different peptides, both self-peptides and foreign peptides. There are two classes of MHC molecules: MHC-I and MHC-II.

- MHC-I molecules present epitopes to T8-lymphocytes.
- MHC-II molecules presents epitopes to T4-lymphocytes .

The expression of MHC molecules is increased by cytokines produced during both innate immune responses and adaptive immune responses. Cytokines such as interferon-alpha, interferon-beta, interferon-gamma, tumor necrosis factor increase the expression of MHC-I molecules, while interferon-gamma is the main cytokine to increase the expression of MHC-II molecules.

MHC-I molecules

MHC-I molecules are designed to enable the body to recognize infected cells and tumor cells and destroy them with cytotoxic T-lymphocytes or CTLs. CTLs are effector defense cells derived from naive T8-lymphocytes. MHC-I molecules are:

- Made by all nucleated cells in the body.
- Possess a deep groove that can bind peptide epitopes, typically 8-11 amino acids long, typically from endogenous antigens .
- Present MHC-I/peptide complexes to naive T8-lymphocytes and cytotoxic T-lymphocytes possessing a complementary-shaped T-cell receptor or TCR.
- Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of exogenous antigens to MHC-I molecules for eventual presentation to naive T8-lymphocytes.

Endogenous antigens are proteins found within the cytosol of human cells. Examples of endogenous antigens include:

a. Viral proteins produced during viral replication;
b. Proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication;
c. Proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells;
d. Tumor antigens produced by cancer cells; and
e. Self-peptides from host cellular proteins.

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. The body's own cytosolic proteins are also degraded into peptides by proteasomes.

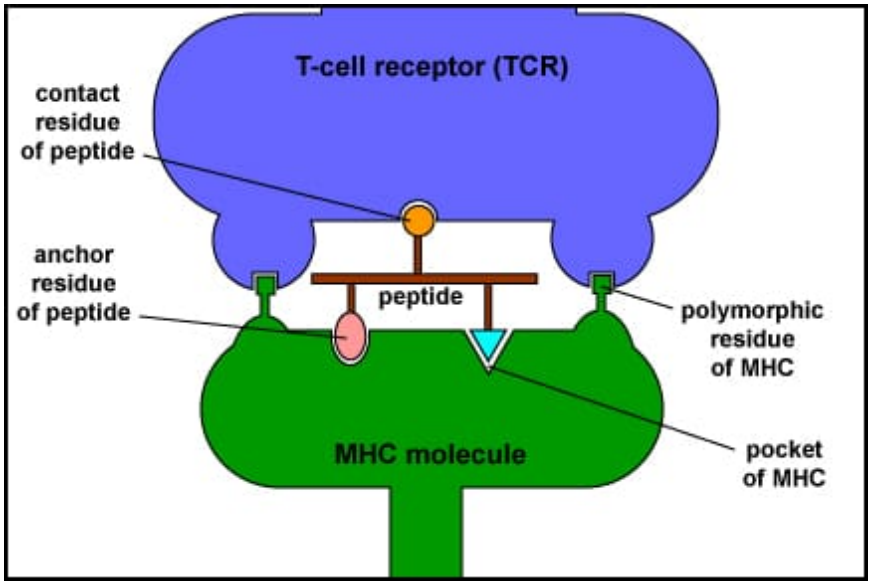


Figure 12.3A.2: MHC Molecule with Bound Peptide Binding to a Complementary T-Cell Receptor. This illustration shows a T-cell receptor (TCR) on the surface of a T-lymphocyte recognizing two polymorphic residues of a MHC molecule and one residue of its bound peptide epitope.

These peptide epitopes are then attached to a groove of MHC-I molecules that are then transported to the surface of that cell where they can be recognized by a complementary-shaped T-cell receptor (TCR) and a CD8 molecule, a co-receptor, on the surface of either a naive T8-lymphocyte or a cytotoxic T-lymphocyte (CTL). The TCRs recognize both the foreign peptide antigen and the MHC molecule (Figure 12.3A.2). TCRs, however, will not recognize self-peptides bound to MHC-I. As a result, normal cells are not attacked and killed.

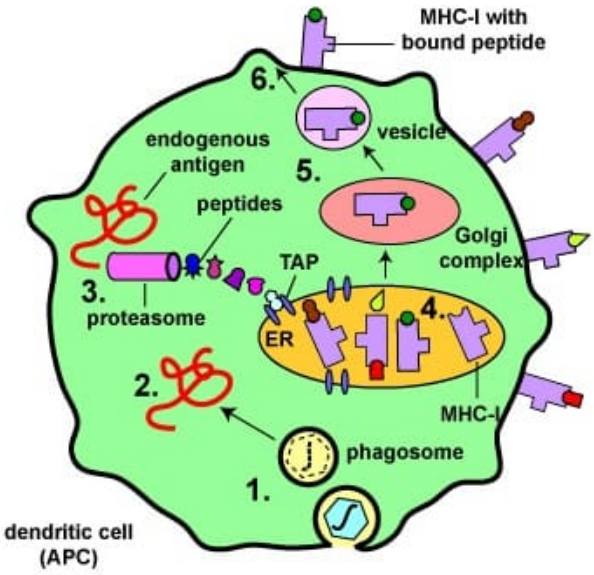


Figure 12.3A.3: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Molecules by a Dendritic Cell.Endogenous antigens are those located within the cytosol of the cells of the body. Examples include: a. viral proteins produced during viral replication, b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication, c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells, d. tumor antigens produced by cancer cells, e. and self peptides from human cell proteins.

Dendritic cells bind epitopes from endogenous antigens to MHC-I molecules and present them to naive T8-lymphocytes in order to activate these naive T8-lymphocytes.

1. Antigens are engulfed by dendritic cells and placed in a phagosome. Some of the proteins escape from the phagosome into the cytosol of the dendritic cell where they become endogenous antigens.
2. These endogenous antigens pass through proteasomes where they are degraded into a series of peptides.
3. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP.
4. The peptides then bind to the grooves of newly synthesized MHC-I molecules.
5. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex.
6. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by naive T8-lymphocytes by way of TCRs and CD8 molecules having a complementary shape.

Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of exogenous antigens to MHC-I molecules for eventual presentation to naive T8-lymphocytes.

MHC-I molecule with bound peptide on the surface of antigen-presenting dendritic cells (Figure 12.3A.3) can be recognized by a complementary-shaped TCR/CD8 on the surface of a naive T8-lymphocyte to initiate cell-mediated immunity (Figure 12.3A.4). (Certain dendritic cells, as discussed later, can also cross-present exogenous antigens to MHC-I molecules).

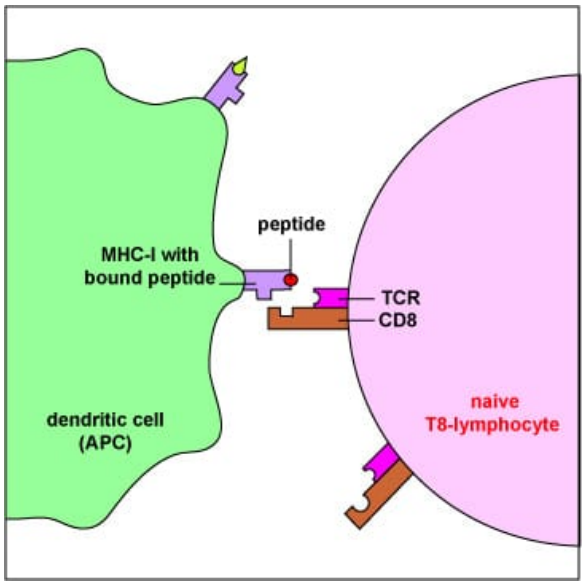


Figure 12.3A.4: An Antigen-Presenting Dendritic Cell Presenting MHC-I with Bound Peptide to a Naive T8-lymphocyte having a Complementary T-Cell Receptor. Antigen-presenting dendritic cells produce both MHC-I and MHC-II molecules. These APCs can phagocytose infected cells and tumor cells, place them in phagosomes, and degrade them with lysosomes. During this process, some of the proteins escape from the phagosome into the surrounding cytosol. Here they can be degraded into peptides by proteasomes, bound to MHC-I molecules, and placed on the surface of the dendritic cell. Now the peptide/MHC-I complexes can be recognized by a naive T8-lymphocyte having a complementary shaped T-cell receptor (TCR) and CD8 molecule. This activates the naive T8-lymphocyte enabling it to eventually proliferate and differentiate into cytotoxic T-lymphocytes (CTLs).

MHC-I molecule with bound peptide on the surface of infected cells and tumor cells (Figure 12.3A.5) can be recognized by a complementary-shaped TCR/CD8 on the surface of a cytotoxic T-lymphocyte or CTL to initiate destruction of the cell containing the endogenous antigen (Figure 12.3A.6). (CTLs are effector cells derived from naive T8-lymphocytes.)

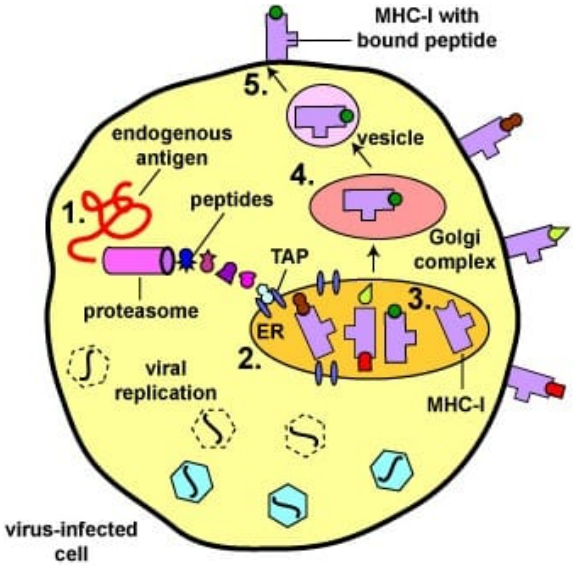


Figure 12.3A.5: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Molecules by a Virus-Infected Cell. Endogenous antigens are those being produced within the cytosol of the cells of the body. Examples include: a. viral proteins produced during viral replication, b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication, c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cellsd. tumor antigens produced by cancer cells, e. and self peptides from human cell proteins. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules.

Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

1. During viral replication within the host cell, endogenous antigens, such as viral proteins, pass through proteasomes where they are degraded into a series of peptides.
2. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP.
3. The peptides then bind to the grooves of newly synthesized MHC-I molecules.
4. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex.
5. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.

MHC-I molecules are coded for by three MHC-I genes, *HLA-A*, *HLA-B*, and *HLA-C*. As mentioned above, however, there are many different alleles for each gene that a person inherits. In this way, the number of MHC-I molecules that bind peptides for presentation to T-8 lymphocytes is maximized. The expression of MHC-I molecules on all cell types is increased by the cytokines interferon-alpha (IFN-a) and interferon-beta (IFN-ß).

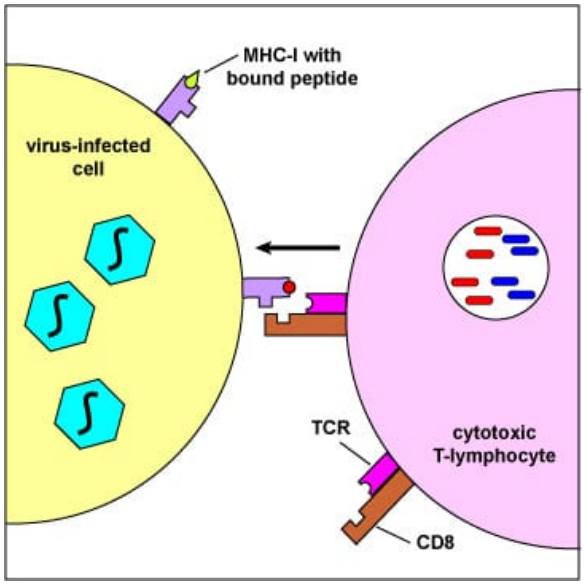


Figure 12.3A.6: A Cytotoxic T-lymphocyte Recognizing a Virus-Infected Cell. Endogenous antigens are those being produced within the cytosol of the cells of the body. Examples include proteins from replicating viruses, proteins from intracellular bacteria, and tumor antigens. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

Exercise: Think-Pair-Share Questions

All nucleated cells produce MHC-I molecules. MHC-I molecules bind peptide epitopes of antigens found within our cells. Peptide epitopes bound to MHC-I molecules are recognized by TCRs and CD8 molecules on the surfaces of naive T8-lymphocytes and on cytotoxic T-lymphocytes (CTLs).

Why is it important that all nucleated cells in our body are able to produce MHC-I molecules?

MHC-II molecules

MHC-II molecules are designed to enable T4-lymphocytes to recognize epitopes of exogenous antigens and discriminate self from non-self. MHC-II molecules are:

- Made by antigen-presenting cells or APCs, such as dendritic cells, macrophages, and B-lymphocytes .
- Possess a deep groove that can bind peptide epitopes, often 10-30 amino acids long but with an optimum length of 12-16 amino acids, typically from exogenous antigens. The peptides interact along their entire length with the groove.
- Present MHC-II/peptide complexes to naive T4-lymphocytes or effector T4-lymphocytes that have a complementary shaped T-cell receptor or TCR.
- Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of endogenous antigens to MHC-II molecules for eventual presentation to naive T4-lymphocytes.

Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses. These exogenous antigens enter macrophages, dendritic cells, and B-lymphocytes through phagocytosis. The microbes are engulfed and placed in a phagosome which then fuses with lysosomes. Following this fusion, the phagolysosome becomes acidified. Acidification, in turn, activates the proteases within the phagolysosome enabling protein antigens from the microbe to be degraded into a series of short peptides. These peptide epitopes are then attached to MHC-II molecules and are then transported to the surface of the antigen-presenting cell (APC) (Figure 12.3A.7). (Certain dendritic cells, as discussed later, can also cross-present endogenous antigens to MHC-II molecules.)

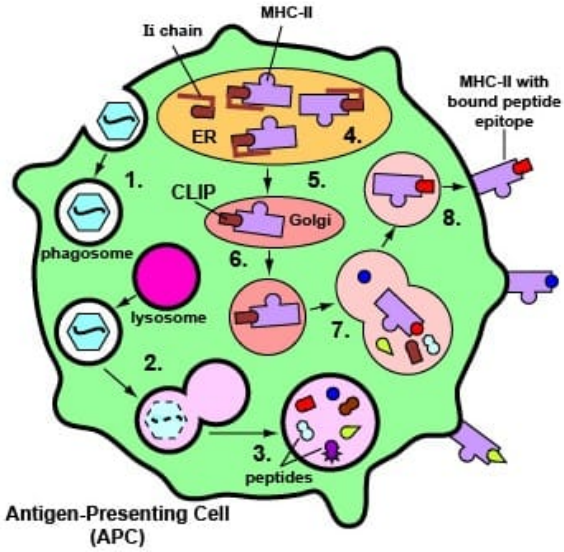


Figure 12.3A.7: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules. 1. Exogenous antigens, such as viruses, are engulfed and placed in a phagosome.2. Lysosomes fuse with the phagosome forming an phagolysosome. 3. Protein antigens are degraded into a series of peptides. 4. MHC-II molecules are synthesized in the endoplasmic reticulum and transported to the Golgi complex. Once assembled, within the endoplasmic reticulum, a protein called the invarient chain (Ii) attaches to the the peptide-binding groove of the MHC-II molecules and in this way prevents peptides designated for binding to MHC-I molecules within the ER from attaching to the MHC-II. 5. As the MHC-II molecules with bound Ii chain are transported to the Golgi complex, the Ii is cleaved, leaving a short peptide called CLIP in the groove of the MHC molecule. 6&7. The vesicles containing the MHC-II molecules fuse with the peptide-containing phaglysosomes. The CLIP peptide is removed from the MHC=II molecules and the peptide epitopes are now free to bind to the grooves of the MHC-II molecules. 8. The MHC-II molecules with bound peptides are transported to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-II complexes can be recognized by T4-lymphocytes by way of TCRs and CD4 molecules having a complementary shape. (Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of endogenous antigens to MHC-II molecules for eventual presentation to naive T4-lymphocytes.)

Some pathogens, such as *Mycobacterium tuberculosis, Mycobacterium leprae*, and *Leishmania*, are able to grow in the endocytic vesicles of macrophages without being killed by lysosomes. These macrophages can, however, become activated by T4-effector lymphocytes called T_H1 cells and subsequently use intravesicular proteases to degrade the proteins from these pathogens into peptides for presentation to MHC-II molecules that pass through on their way to the cell surface.

Here the MHC-II molecules with bound peptides can be recognized by a complementary-shaped T-cell receptor and a CD4 molecule, a co-receptor, on the surface of a T4-lymphocyte (Figure 12.3A.8). T4-lymphocytes are the cells the body uses to

regulate both humoral immunity and cell-mediated immunity.

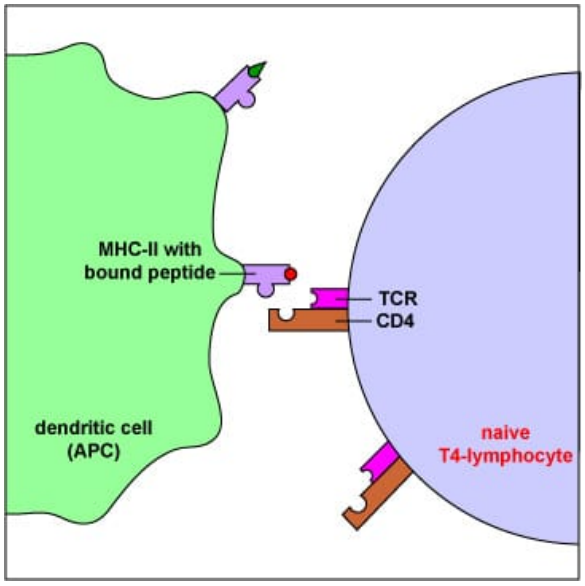


Figure 12.3A.8: A T4-Lymphocyte Recognizing Epitope/MHC-II on an Antigen-Presenting Dendritic Cell.Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting dendritic cells through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

MHC-II molecules are coded for by three MHC-II genes, *HLA-DR*, *HLA-DP*, and *HLA-DQ*. Interferon-gamma (IFN- ?) increases the expression of both MHC-I and MHC-II molecules.

Think-Pair-Share Questions

Only antigen-presenting cells such as dendritic cells, macrophages, and B-lymphocytes produce MHC-II molecules. Peptide epitopes bound to MHC-II molecules are recognized by TCRs and CD4 molecules on the surfaces of naive T4-lymphocytes and on effector T4-lymphocytes.

Why don't all nucleated cells in our body produce MHC-II molecules as well as MHC-I molecules?

Why is it important for dendritic cells to produce both MHC-I and MHC-II molecules?

Summary

1. MHC molecules enable T-lymphocytes to recognize epitopes and discriminate self from non-self.
2. T-cell receptors (TCRs) of T-lymphocytes can only recognize epitopes - typically short chains of amino acids called peptides - after they are bound to MHC molecules.
3. MHC-I presents epitopes to T8-lymphocytes; MHC-II presents epitopes to T4-lymphocytes.
4. MHC-I molecules are designed to enable the body to recognize infected cells and tumor cells and destroy them with cytotoxic T-lymphocytes or CTLs. (CTLs are effector defense cells derived from naïve T8-lymphocytes.)
5. MHC-I molecules are made by all nucleated cells in the body; bind peptide epitopes typically from endogenous antigens; present MHC-I/peptide complexes to naive T8-lymphocytes and cytotoxic T-lymphocytes possessing a complementary-shaped T-cell receptor or TCR.
6. Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of exogenous antigens to MHC-I molecules for eventual presentation to naive T8-lymphocytes.
7. Endogenous antigens are proteins found within the cytosol of human cells and include viral proteins produced during viral replication, proteins produced by intracellular bacteria, proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells, and tumor antigens produced by cancer cells.

8. During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. The resulting peptide epitopes are then attached to MHC-I molecules that are then transported to the surface of that cell.
9. Exogenous antigens are antigens that enter from outside the body such as bacteria, fungi, protozoa, and free viruses.
10. MHC-II molecules are made by antigen-presenting cells or APCs, such as dendritic cells, macrophages, and B-lymphocytes; bind peptide epitopes typically from exogenous antigens; and present MHC-II/peptide complexes to naive T4-lymphocytes or effector T4-lymphocytes that have a complementary shaped T-cell receptor or TCR.
11. Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of endogenous antigens to MHC-II molecules for eventual presentation to naive T4-lymphocytes.
12. Exogenous antigens enter antigen-presenting macrophages, dendritic cells, and B-lymphocytes through phagocytosis, and are engulfed and placed in a phagosome where protein antigens from the microbe are degraded by proteases into a series of peptides. These peptides are then attached to MHC-II molecules that are then put on the surface of the APC.

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12.3B: Antigen-Presenting Cells (APCs)

Describe the overall function of antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B-lymphocytes in terms of the following:

a. how they "process" exogenous antigens
b. how they "process" endogenous antigens
c. the types of MHC molecule to which they attach peptides
d. the role of proteasomes in the binding of peptides from endogenous antigens by MHC-I molecules.
e. the role of lysosomes in the binding of peptides from exogenous antigens by MHC-II molecules.
f. the types of cells to which they present peptides

- Name the primary type of cell that functions as an antigen-presenting cell to naive T4-lymphocytes and naive T8-lymphocytes.
- State the role of T4-effector cells in activating macrophages.
- State the role of T4-effector cells in the proliferation and differentiation of activated B-lymphocytes.

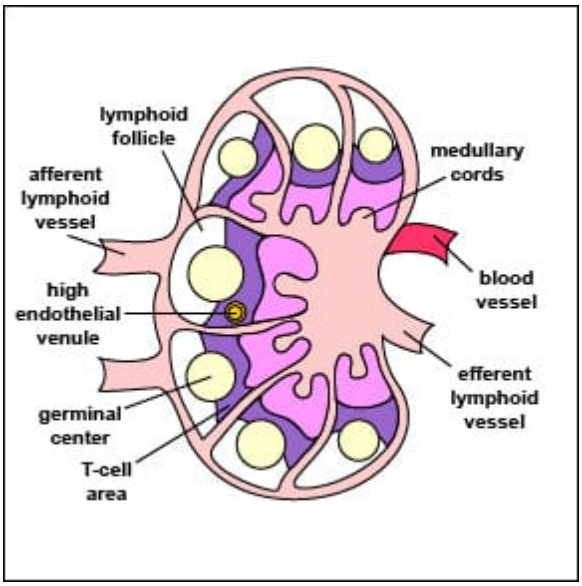


Figure 12.3B.1: Structure of a Lymph Nodes Antigens enter lymph nodes through afferent lymphoid vessels. Antigen-presenting dendritic cells, B-lAntigens enter lymph nodes through afferent lymphoid vessels. Antigen-presenting dendritic cells enter the lymph node through afferent lymphatic vessels while naive B-lymphocytes, and naive T-lymphocytes enter through high endothelial venules. Non-activated and effector lymphocytes leave the lymph node through efferent lymphatic vessels. Naive B-lymphocytes become activated, proliferate, and differentiate into plasma cells in the germinal centers of lymphoid follicles while naive T-lymphocytes become activated, proliferate and differentiate into T-effector lymphocytes in the T-cell area.

The primary function of dendritic cells, then, is to capture and present protein antigens to naive T-lymphocytes. (Naive lymphocytes are those that have not yet encountered an antigen.) Since dendritic cells are able to express both MHC-I and MHC-II molecules, they are able to present antigens to both naive T8-lymphocytes and naive T4-lymphocytes.

You Tube movie of a dendritic cell engulfing melanoma cells (red).

These interactions enable the naiveT4-lymphocyte or T8-lymphocyte to become activated, proliferate, and differentiate into effector lymphocytes. (Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.)

1. MHC-II presentation of protein antigens to naive T4-lymphocytes

a. MHC-II presentation of exogenous antigens to naive T4-lymphocytes

Immature dendritic cells take in protein antigens for attachment to MHC-II molecules and subsequent presentation to naive T4-lymphocytes by:

1. Receptor-mediated phagocytosis, e.g., PAMPs binding to endocytic PRRs, IgG or C3b attachment of microbes to phagocytes during opsonization (see Figure 12.3B.2).

2. Macropinocytosis, a process where large volumes of surrounding fluid containing microbes are engulfed. This also enables dendritic cells to take in some encapsulated bacteria that might resist classical phagocytosis (see Figure 12.3B.3).

The binding of microbial PAMPs to the PRRs of the immature dendritic cell activates that dendritic cell and promotes production of the chemokine receptor CCR7 that directs the dendritic cell into local lymphoid tissue. Following maturation, the dendritic cell can now present protein epitopes bound to MHC molecules to all the various naive T-lymphocytes passing through the lymphoid system (See Figure 12.3B.4 and Figure 12.3B.5).

The MHC-II molecules bind peptide epitopes from exogenous antigens and place them on the surface of the dendritic cell (see Figure 12.3B.6). Here the MHC-II/peptide complexes can be recognized by complementary shaped TCRs and CD4 molecules on naive T4-lymphocytes (see Figure 12.3B.7).

Flash animation of MHC-II molecules binding epitopes from exogenous antigens.

html5 version of animation for iPad showing MHC-II molecules binding epitopes from exogenous antigens.

Flash animation of a naive T4-lymphocyte recognizing epitopes bound to MHC-II molecules on an antigen-presenting dendritic cell.

html5 version of animation for iPad showing a naive T4-lymphocyte recognizing epitopes bound to MHC-II molecules on an antigen-presenting dendritic cell.

b. MHC-II cross-presentation of endogenous antigens to naive T4-lymphocytes

While most dendritic cells present exogenous antigens to naive T4-lymphocytes, certain dendritic cells are capable of cross-presentation of endogenous antigens to naive T4-lymphocytes. In this way, T4-lymphocytes can play a role in defending against both exogenous and endogenous antigens. This is done via autophagy, the cellular process whereby the cell's own cytoplasm is taken into specialized vesicles called autophagosomes (See Figure 12.3B.8). The autophagosomes subsequently fuse with lysosomes containing proteases that will degrade the proteins in the autophagosome into peptides. From here, the peptides are transported into the vesicles containing MHC-II molecules where they can bind to the MHC-II groove, be transported to the surface of the denritic cell, and interact with the TCRs and CD4 molecules of naive T4-lymphocytes (See Figure 12.3B.8).

2. MHC-I presentation of protein antigens to naive T8-lymphocytes

Immature dendritic cells take in protein antigens for attachment to MHC-I molecules and subsequent presentation to naive T8-lymphocytes.

a. MHC-I presentation of endogenous antigens to naive T8-lymphocytes

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. The body's own cytosolic proteins are also degraded into peptides by proteasomes.

These peptide epitopes are then attached to a groove of MHC-I molecules that are then transported to the surface of that

cell where they can be recognized by a complementary-shaped T-cell receptor (TCR) and a CD8 molecule, a co-receptor, on the surface of either a naive T8-lymphocyte or a cytotoxic T-lymphocyte (CTL). The TCRs recognize both the foreign peptide antigen and the MHC molecule. TCRs, however, will not recognize self-peptides bound to MHC-I. As a result, normal cells are not attacked and killed.

MHC-I molecule with bound peptide on the surface of antigen-presenting dendritic cells ; see Figure 12.3B.9 can be recognized by a complementary-shaped TCR/CD8 on the surface of a naive T8-lymphocyte to initiate cell-mediated immunity (see Figure 12.3B.10).

Flash animation of MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting cell.

Flash animation of a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

html5 version of animation for iPad showing a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

b. MHC-I cross-presentation of exogenous antigens to naive T8-lymphocytes

While most dendritic cells present endogenous antigens to naive T8-lymphocytes, certain dendritic cells are capable of cross-presentation of exogenous antigens to naive T8-lymphocytes. In this way, T8-lymphocytes can play a role in defending against both exogenous and endogenous antigens. There are two proposed mechanisms for cross-presentation of exogenous antigens to T8-lymphocytes:

1. The dendritic cell engulfs the exogenous antigen and places it in a phagosome which then fuses with a lysosome to form a phagolysosome. The antigen is partially degraded in the phagolysosome where proteins are translocated into the cytoplasm where they are processed into peptides by proteasomes, enter the endoplasmic reticulum, and are bound to MHC-I molecules (see Figure 12.3B.11).

2. The dendritic cell engulfs the exogenous antigen and places it in a phagosome which then fuses with a lysosome to form a phagolysosome. The protein antigens are degraded into peptides within the phagolysosome which then directly fuses with vesicles containing MHC-I molecules to which the peptides subsequently bind (see Figure 12.3B.12).

In addition, dendritic cells are very susceptible to infection by many different viruses. Once inside the cell, the viruses become endogenous antigens in the cytosol. Once in the cytosol, the viral proteins from the replicating viruses are degraded into peptides by proteasomes where they subsequently bind to MHC-I molecules.

The binding of microbial PAMPs to the PRRs of the immature dendritic cell activates that dendritic cell and promotes production of the chemokine receptor CCR7 that directs the dendritic cell into local lymphoid tissue. Following maturation, the dendritic cell can now present protein epitopes bound to MHC molecules to all the various naive T-lymphocytes passing through the lymphoid system.

To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the University of Illinois College of Medicine.

To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

Why is this essential for effective adaptive immunity ?

For a Summary of Key Surface Molecules and Cellular Interactions of Antigen-Presenting Dendritic Cells, see Figure 12.3B.13 .

Concept Map for Antigen-Presenting Cells (APCs)

Macrophages

As we learned in Unit 5, when monocytes leave the blood and enter the tissue, they become activated and differentiate into macrophages. Those that have recently left the blood during inflammation and move to the site of infection are sometimes referred to as wandering macrophages. In addition, the body has macrophages already stationed throughout the tissues and organs of the body. These are sometimes referred to as fixed macrophages. Many fixed macrophages are part of the mononuclear phagocytic (reticuloendothelial) system. They, along with B-lymphocytes and T-lymphocytes, are found supported by reticular fibers in lymph nodules, lymph nodes, and the spleen where they filter out and phagocytose foreign matter such as microbes. Similar cells derived from stem cells, monocytes, or macrophages are also found in the liver (Kupffer cells), the kidneys (mesangial cells), the brain (microglia), the bones (osteoclasts), the lungs (alveolar macrophages), and the gastrointestinal tract (peritoneal macrophages).

The primary function of macrophages, then, is to capture and present protein antigens to effector T-lymphocytes. (Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.)

The MHC-II molecules bind peptide epitopes from exogenous antigens and place them on the surface of the macrophages. Here the MHC-II/peptide complexes can be recognized by complementary shaped T-cell receptors (TCRs) and CD4 molecules on an effector T4-lymphocytes ; see Fig.14.

Effector T4-lymphocytes called T_H1 cells coordinate immunity against intracellular bacteria and promote opsonization by macrophages.

1. They produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis, Mycobacterium leprae, Leishmania donovani*, and *Pneumocystis jiroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness (see Figure 12.3B.14).

2. They produce cytokines that promote the production of opsonizing and complement activating IgG that enhances phagocytosis (see Figure 12.3B.15).

3. They produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so they can be engulfed and killed by macrophages.

4. They produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.

5. They produce the chemokine CXCL2 to attract macrophages to the infection site.

Flash animation of the activation of a macrophage by a T_H1 cell.

html5 version of animation for iPad showing the activation of a macrophage by a T_H1 cell.

There is growing evidence that monocytes and macrophages can be “trained” by an earlier infection to do better in future infections, that is, develop memory. It is thought that microbial pathogen-associated molecular patterns (PAMPs) binding to pattern-recognition (PRRs) on monocytes and macrophages triggers the cell’s epigenome to reprogram or train that cell to react

better against new infections.

For a Summary of Key Surface Molecules and Cellular Interactions of Antigen-Presenting Macrophages, see Figure 12.3B.16.

Concept Map for Antigen-Presenting Cells (APCs)

B-lymphocytes

Like all lymphocytes, B-lymphocytes circulate back and forth between the blood and the lymphoid system of the body. B-lymphocytes are able to capture and present peptide epitopes from exogenous antigens to effector T4-lymphocytes. The MHC-II molecules bind peptide epitopes from exogenous antigens and place them on the surface of the B-lymphocytes. Here the MHC-II/peptide complexes can be recognized by complementary shaped T-cell receptors (TCRs) and CD4 molecules on an effector T4-lymphocytes (see Figure 12.3B.17). This interaction eventually triggers the effector T4-lymphocyte to produce and secrete various cytokines that enable that B-lymphocyte to proliferate and differentiate into antibody-secreting plasma cells (see Figure 12.3B.18).

Flash animation of the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.

Flash animation of an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

html5 version of animation for iPad showing the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte

html5 version of animation for iPad showing an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

For a Summary of Key Surface Molecules and Cellular Interactions of Antigen-Presenting B-Lymphocytes, see Figure 12.3B.19.

Summary

1. Antigen-presenting cells (APCs) include dendritic cells, macrophages, and B-lymphocytes.
2. APCs express both MHC-I and MHC-II molecules and serve two major functions during adaptive immunity: they capture and process antigens for presentation to T-lymphocytes, and they produce signals required for the proliferation and differentiation of lymphocytes.
3. Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells and are located under the surface epithelium of the skin, the mucous membranes of the respiratory tract, genitourinary tract, and the gastrointestinal tract, and throughout the body's lymphoid tissues and in most solid organs.
4. The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes which enables the naïve T4-lymphocytes or T8-lymphocytes to become activated, proliferate, and differentiate into effector cells.
5. Naïve lymphocytes are B-lymphocytes and T-lymphocytes that have not yet reacted with an epitope of an antigen.
6. Dendritic cells use MHC-II molecules to present protein antigens to naïve T4-lymphocytes and MHC-I molecules to present protein antigens to naïve T8-lymphocytes.
7. When monocytes leave the blood and enter the tissue, they become activated and differentiate into macrophages.
8. When functioning as APCs, macrophages capture and present peptide epitopes from exogenous antigens to effector T4-lymphocytes.
9. Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.
10. B-lymphocytes mediate antibody production.
11. When functioning as APCs, B-lymphocytes are able to capture and present peptide epitopes from exogenous antigens to effector T4-lymphocytes.
12. To activate naïve T4-lymphocytes, dendritic cells engulf exogenous antigens, place them in a phagosome, degrade protein antigens into peptides via lysosomes, bind those peptides to MHC-II molecules and transport them to the surface of the

dendritic cell where they can be recognized by the T-cell receptors and CD4 molecules of naïve T4-lymphocytes.

13. To activate naïve T8-lymphocytes, dendritic cells degrade endogenous protein antigens into peptides via their proteasomes, bind those peptides to MHC-I molecules and transport them to the surface of the dendritic cell where they can be recognized by the T-cell receptors and CD8 molecules of naïve T8-lymphocytes.

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12.3C: T4-Lymphocytes (T4-Cells)

Describe the overall function of T4-lymphocytes and their activation in terms of the following:

a. the role of their TCRs and CD4 molecules
b. what they recognize on antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B-lymphocytes.
c. the role of antigen-presenting dendritic cells in the activation of naive T4-lymphocytes.

- Compare T_H1, T_H2, T_H17, T_{reg}, and T_{FH} lymphocytes in terms of their primary function(s) in immunity.

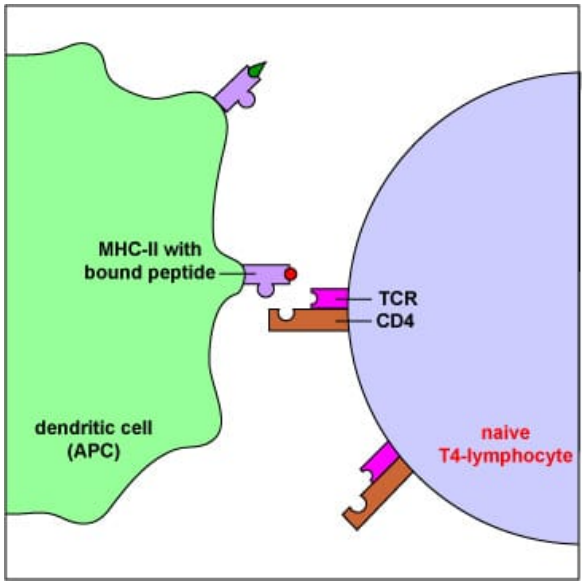


Figure 12.3C.6: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

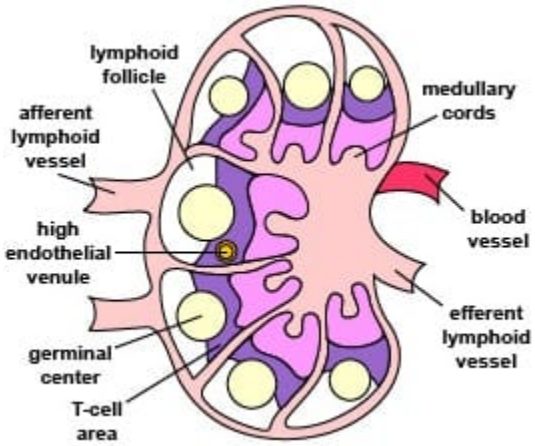


Figure 12.3C.8: Transient binding of T4-Lymphocytes to Dendritic Cells.As naive T4-lymphocytes migrate through the cortical region of lymph nodes, they use surface cell adhesion molecules such as LFA-1 and CD2 to bind transiently to corresponding receptors such as ICAM-1, ICAM-2 and CD58 on the surface of dentritic cells. This transient binding allows time for the TCRs on the T8-lymphocyte to sample large numbers of MHC-II/peptide complexes on the antigen-presenting dendritic cells.

- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the

University of Illinois College of Medicine.
- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

Those naive T4-lymphocytes not activated by epitopes of antigens on the dendritic cells exit the lymph node (or other lymphoid tissue) and eventually re-enter the bloodstream. However, if a TCR and CD4 molecule of the naive T4-lymphocyte detects a corresponding MHC-II/peptide complex on a mature dendritic cell, this will send a first signal for the activation of that naive T-lymphocyte. Next, a second signal that promotes survival of that T-lymphocyte is sent when co-stimulatory molecules such as B7.1 and B7.2 on the dendritic cell bind to CD28 molecules on the T4-lymphocyte. Finally, the dendritic cell produces cytokines such as interleukin-6 (IL-6), IL-4, IL-12, and T-cell growth factor-beta (TGF-ß) that contribute to proliferation of the T4-lymphocytes and their differentiation into effector T4-lymphocytes, the cells the body uses to regulate both humoral immunity and cell-mediated immunity through the cytokines they produce. (Activated T4-lymphocytes remain in the lymph node as they proliferate (clonal expansion) and only leave the lymphoid tissues and re-enter the bloodstream after they have differentiated into effector T4-lymphocytes.)

CD28-dependent co-stimulation of the T4-lymphocyte also stimulates it to synthesize the cytokine interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor. The binding of IL-2 to its high affinity receptor allows for cell proliferation and formation of a clone of thousands of identical T4-lymphocytes after several days. IL-2 also contributes to survival of those activated T4-lymphocytes and their differentiation into T4-effector cells. In addition, some of the T4-lymphocytes differentiate into circulating T4-memory cells. Circulating T4-memory cells allow for a more rapid and greater production of effector T4-lymphocytes upon subsequent exposure to the same antigen.

Differentiation of naive T4-lymphocyte into T4-effector lymphocytes

Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Immune reactions are typically dominated by five primary types: T_H1 cells, T_H2 cells, T_H17 cells, T_{reg} cells, and T_{FH} cells.

CD4 T_H1 cells

Coordinate immunity against intracellular bacteria and promote opsonization. They:

1. Produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis, Mycobacterium leprae, Leishmania donovani*, and *Pneumocystis jjroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness.
2. They produce cytokines that promote the production of opsonizing antibodies that enhance phagocytosis (Figure 12.3C.9).
3. Produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so the can be engulfed and killed by macrophages.
4. Produce the cytokine interleukin-2 (IL-2) that induces T-lymphocyte proliferation.
5. Produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.
6. Produces the chemokine CXCL2 to attract macrophages to the infection site.
7. Produce cytokines that block the production of T_H2 cells.

CD4 T_H2 cells

Coordinate immunity against helminths and microbes that colonize mucous membranes

1. Produce the cytokine interleukin-4 (IL-4) that promotes the production of the antibody isotype IgE in response to helminths and allergens. IgE is able to stick eosinophils to helminths for extracellular killing of the helminth (Figure 12.3C.10); it also promotes many allergic reactions.
2. Produce cytokines that attract and activate eosinophils and mast cells.
3. Promote the production of antibodies that neutralize microbes (Figure 12.3C.11) and toxins (Figure 12.3C.12) preventing their attachment to host cells.
4. Produce cytokines that function as B-lymphocyte growth factors such as IL-4, IL-5, IL-9. and IL-13 (Figure 12.3C.13).
5. Produce interleukin-22 (IL-22) that promotes the removal of microbes in mucosal tissues.

6. Produce cytokines that block the production of T_H1 cells.

CD4 T_H17 cells

Promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes

Produce cytokines like interleukin-17 (IL-17) and interleukin-6 (IL-6) that trigger local epithelial cells and fibroblasts to produce chemokines that recruit neutrophils to remove extracellular pathogens.

CD4 T_{reg} cells

Suppress immune responses

1. Produce inhibitory cytokines such as Interleukin-10 (IL-10) and TGF-ß that help to limit immune responses and prevent autoimmunity by suppressing T-lymphocyte activity.
2. Promoting anamnestic response (immunologic memory) to resist repeat infections by the same microbe.
3. Protecting beneficial normal flora in the intestines from being destroyed by the immune system.
4. Aiding in sustaining pregnancy so that the immune system doesn't recognize a fetus as foreign and try to destroy it.
5. Controlling established inflammation in tissues.

T_{FH} cells

Promote humoral immunity by stimulating antibody production and antibody isotype switching by B-lymphocytes

1. T follicular helper cells (T_{FH} cells) are located in lymphoid follicles.
2. T_{FH} cells are now thought to be the primary effector T-lymphocytes that stimulate antibody production and isotype switching by B-lymphocytes. They are able to produce cytokines that are characteristic of both T_H2 cells and T_H1 cells.
3. T_{FH} cells producing (IFN-?) promote the production of opsonizing antibodies; those producing IL-4 promote the production of IgE.

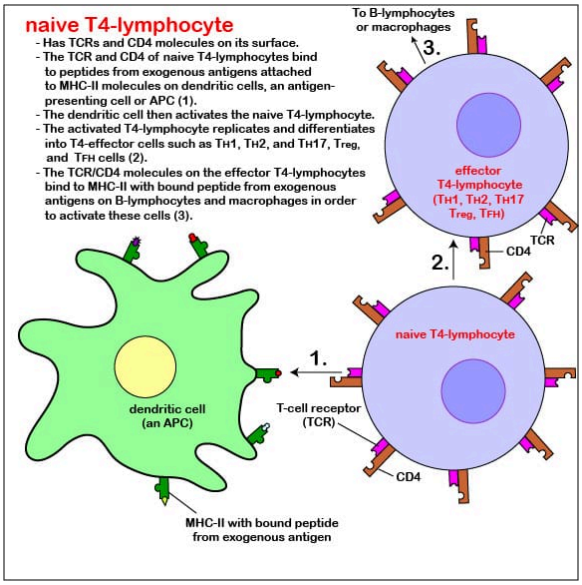


Figure 12.3C.14: A Summary of Key Surface Molecules and Cellular Interactions of Naive T4-Lymphocytes

Macrophages and B-lymphocytes are antigen-presenting cells but they do not activate naive T4- and T8-lymphocytes. Why must macrophages and B-lymphocytes be antigen-presenting cells?

Regulation of effector T4-lymphocyte activity: A role for commensals and helminths?

It is now recognized that genes associated with the normal flora (microbiota) of the intestinal tract aid in digestion of many foods (especially plant polysaccharides that would normally be indigestible by humans), may play a role in normal growth and regulating appetite, and also help to regulate immune defenses. There is ever growing evidence that commensal bacteria of the gastrointestinal tract, as well as parasitic gastrointestinal helminths, may have coevolved with the human body over the past 200,000 year in such a way that genes from the human microbiota may play a significant role in regulating the human immune responses by providing a series of checks and balances that prevent the immune system from being too aggressive and causing an autoimmune attack upon the body's own cells, while still remaining aggressive enough to recognize and remove harmful pathogens. As exposure to and colonization with these once common human organisms has drastically changed over time as a result of less exposure to mud, animal and human feces,and helminth ova, coupled with ever increasing antibiotic use, improved sanitation, changes in the human diet, increased rate of cesarean sections, and improved methods of processing and preserving of food, the rate of allergies, allergic asthma, and autoimmune diseases (inflammatory bowel disease, Crone's disease, type-1 diabetes, and multiple sclerosis for example) has dramatically increased in developed countries while remaining relatively low in undeveloped and more agrarian parts of the world.

Numerous experiments in germ-free mice (mice with no intestinal commensals) have shown them to be much more susceptible to allergic asthma and autoimmune diseases such as colitis then normal mice. Feeding commensals or nematode ova to newborn germ-free mice, in turn, reduces the occurrence to these disorders. An imbalance in the relationship between proinflammatory T_H17 cells and inflammation-suppressing T_{reg} cells appears to increase the risk of inflammatory autoimmune diseases, while an imbalance between T_H1 and T_H2 cells seems to contribute to the risk of allergies and asthma. For example, a common commensal colon bacterium *Bacteroides fragilis* produces a molecule called polysaccharide A that dendritic cells engulf, process and present to naive T4-lymphocytes. This interaction stimulates the differentiation of the naive T4-lymphocytes into anti-inflammatory T_{reg} cells that suppress the activity of proinflammatory T_H17 cells. Without colonization with *B. fragilis*, the proinflammatory T_H17 cells are not suppressed and there is an increased risk of inflammatory autoimmune diseases.

Normal intestinal microbiota also appear to regulate the intestinal levels of the invariant natural killer (iNKT) cells discussed under innate immune responses in Unit 4. iNKT cells recognize endogenous and exogenous lipid antigens presented on CD1d molecules by dendritic cells and in response, secrete proinflammatory cytokines. Germ free mice show an accumulation of iNKT cells in the colon and in the lungs and have an increased risk of intestinal bowel disease and allergic asthma. Neonatal germ free mice that were subsequently colonized with normal microbiota were protected from this iNKT cell accumulation and the resulting inflammatory pathology.

For More Information: MHC Molecules from Unit 6

For More Information: B-Lymphocytes from Unit 6

For More Information: Macrophages and NK cells from Unit 6

For More Information: Cytotoxic T-Lymphocytes from Unit 6

Summary

1. T-lymphocytes refer to lymphocytes that are produced in the bone marrow but require interaction with the thymus for their maturation.

2. The primary role of T4-lymphocytes is to regulate the body's immune responses through the production of cytokines.
3. T4-lymphocytes display CD4 molecules and T-cell receptors (TCRs) on their surface.
4. The TCR on T4-lymphocytes, in cooperation with CD4, typically bind peptides from exogenous antigens bound to MHC-II molecules.
5. During its development, each T4-lymphocyte becomes genetically programmed to produce a TCR with a unique specificity that is able to bind an epitope/MHC-II complex on an APC such as a dendritic cell, a macrophage, or a B-lymphocyte possessing a corresponding shape.
6. To become activated, naive T4-lymphocytes migrate through lymph nodes where the TCRs on the T4-lymphocyte are able to sample large numbers of MHC-II/peptide complexes on the antigen-presenting dendritic cells for ones that “fit”, thus enabling activation of that naïve T4-lymphocyte.
7. After activation, the dendritic cell produces cytokines that contribute to proliferation of the T4-lymphocytes and their differentiation into effector T4-lymphocytes, the cells the body uses to regulate both humoral immunity and cell-mediated immunity through the cytokines they produce.
8. Some of the T4-lymphocytes differentiate into circulating T4-memory cells that enable a more 9.rapid and greater production of effector T4-lymphocytes upon subsequent exposure to the same antigen.
9. Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Immune reactions are typically dominated by five primary types: TH1 cells, TH2 cells, TH17 cells, Treg cells, and TFH cells.
10. CD4 TH1 cells coordinate immunity against intracellular bacteria and promote opsonization.
11. CD4 TH2 cells coordinate immunity against helminths and microbes that colonize mucous membranes.
12. CD4 TH17 cells promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes.
13. CD4 Treg cells suppress immune responses.
14. TFH cells promote humoral immunity by stimulating antibody production and antibody isotype switching by B-lymphocytes.
15. There is ever growing evidence that commensal bacteria of the gastrointestinal tract, as well as parasitic gastrointestinal helminths, may have coevolved with the human body over the past 200,000 year in such a way that genes from the human microbiota may play a significant role in regulating the human immune responses by providing a series of checks and balances that prevent the immune system from being too aggressive and causing an autoimmune attack upon the body's own cells, while still remaining aggressive enough to recognize and remove harmful pathogens.

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12.3D: T8-Lymphocytes (T8-Cells)

Describe the overall function of T8-lymphocytes and their activation in terms of the following:

a. the role of their TCRs and CD8 molecules
b. how they are activated by antigen-presenting dendritic cells
c. the type of effector cells into which activated T8-lymphocytes differentiate
d. what CTLs recognize on infected cells and tumor cells
e. how CTLs kill infected cells and tumor cells

- State the overall function of T8-lymphocytes in adaptive immunity.

The primary role of T8-lymphocytes (T8-Cells; $CD8^+$ Cells; Cytotoxic T-Lymphocytes) is to kill infected cells and tumor cells by inducing apoptosis of those cells. Once naive T8-lymphocytes are activated by dendritic cells , they proliferate and differentiate into T8-effector lymphocytes called cytotoxic T-lymphocytes (CTLs) that bind to and kill infected cells and tumor cells.

T8-lymphocytes are T-lymphocytes displaying a surface molecule called CD8. T8-lymphocytes also have on their surface, T-cell receptors or TCRs similar to those on T4-lymphocytes. The TCR on T8-lymphocytes, in cooperation with CD8, bind peptides from endogenous antigens bound to MHC-I molecules .

During its development, each T8-lymphocyte becomes genetically programmed, by gene-splicing reactions similar to those in B-lymphocytes and T4-lymphocytes, to produce a TCR with a unique shape capable of binding epitope/MHC-I complex with a corresponding shape. It is estimated that the human body has the ability to recognize 10^7 or more different epitopes . In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of T-lymphocytes, each with a unique T-cell receptor. In this variety of T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, peptides of any antigen the immune system eventually encounters.

Activation of a naive T8-lymphocyte by a dendritic cell

One of the body's major defenses against viruses, intracellular bacteria, and cancers is the destruction of infected cells and tumor cells by cytotoxic T-lymphocytes or CTLs . These CTLs are effector cells derived from naive T8-lymphocytes during cell-mediated immunity. However, in order to become CTLs, naive T8-lymphocytes must become activated by dendritic cells as shown in Figure $12.3D.1$ and Figure $12.3D.2$.

Flash animation of MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the University of Illinois College of Medicine.
- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

Certain dendritic cells are capable of cross-presentation of exogenous antigens to naive T8-lymphocytes . In this way, T8-lymphocytes can play a role in defending against both exogenous and endogenous antigens.

Naive T-lymphocytes circulate in the blood. In response to chemokines produced by lymphoid tissues, they leave the vascular endothelium in regions called high endothelial venules and enter lymph nodes (see Figure $12.3D.3$) or other lymphoid tissues, a process called diapedesis .

As naive T8-lymphocytes migrate through the cortical region of lymph nodes, they use surface cell adhesion molecules such as LFA-1 and CD2 to bind transiently to corresponding receptors such as ICAM-1, ICAM-2 and CD58 on the surface of dendritic cells. This transient binding allows time for the TCRs on the T8-lymphocyte to sample large numbers of MHC-I/peptide complexes on the antigen-presenting dendritic cells (see Figure 12.3D.4).

Flash animation of the activation of a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

html5 version of animation for iPad showing the activation of a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

Those naive T8-lymphocytes not activated by epitopes of antigens on the dendritic cells exit the lymph node (or other lymphoid tissue) and eventually re-enter the bloodstream. However, if a TCR and CD8 molecule of the naive T8-lymphocyte detects a corresponding MHC-I/peptide complex on a mature dendritic cell, this will send a first signal for the activation of that naive T-lymphocyte. Next, a second signal that promotes survival of that T-lymphocyte is sent when co-stimulatory molecules such as B7.1 and B7.2 on the dendritic cell bind to CD28 molecules on the T8-lymphocyte. Finally, the dendritic cell produces cytokines such as interleukin-6 (IL-6), IL-4, IL-12, and T-cell growth factor-beta (TGF-ß) that contribute to proliferation of the T8-lymphocytes and their differentiation into effector T8-lymphocytes called cytotoxic T-lymphocytes (CTLs) that are able to bind to and kill infected cells and tumor cells displaying the same peptide/MHC-I complex on their surface. (Activated T8-lymphocytes remain in the lymph node as they proliferate (clonal expansion) and only leave the lymphoid tissues and re-enter the bloodstream after they have differentiated into CTLs.)

While activated T8-lymphocytes produce interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor themselves, in most cases it is the IL-2 produced by effector T4-lymphocytes that enables cell proliferation and formation of a clone of thousands of identical T8-lymphocytes after several days. IL-2 also contributes to survival of those activated T8-lymphocytes and their differentiation into T8-effector cells called a cytotoxic T-lymphocytes or CTLs .

CTLs leave the secondary lymphoid organs and enter the bloodstream where they can be delivered anywhere in the body via the circulatory system and the inflammatory response. In addition, some of the T8-lymphocytes differentiate into circulating T8-memory cells . Circulating T8-memory cells allow for a more rapid and greater production of CTLs upon subsequent exposure to the same antigen.

Marking an infected cell or tumor cell for destruction by cytotoxic T-lymphocytes (CTLs)

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes . Other endogenous antigens such as proteins released into the cytosol from the phagosomes of antigen-presenting cells, such as macrophages and dendritic cells as well, as a variety of the human cell's own proteins (self-proteins) are also degraded by proteasomes. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides, typically 8-11 amino acids long (see Figure 12.3D.5).

A transporter protein called TAP located in the membrane of the cell's endoplasmic reticulum then transports these peptide epitopes into the endoplasmic reticulum where they bind to the grooves of various newly made MHC-I molecules. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles. The exocytic vesicles carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they become anchored to its surface (see Figure 12.3D.6). A single cell may have up to 250,000 molecules of MHC-I with bound epitope on its surface.

Flash animation of MHC-I molecules binding epitopes from endogenous antigens in an infected cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens in an infected cell.

CTLs binding to infected cells or tumor cells and inducing apoptosis

CTLs are, by way of their TCRs and CD8 molecules, able to recognize infected cells and tumor cells displaying MHC-I molecules with bound peptides on their surface (see Figure 12.3D.7) and destroy them through apoptosis , a programmed cell suicide.

Apoptosis involves a complex of intracellular granules. This complex of granules in a protected state including:

1. Pore-forming proteins called perforins ;
2. Proteolytic enzymes called granzymes ; and
3. A proteoglycan called granulysin.

When the TCR and CD8 of the CTL binds to the MHC-I/epitope on the surface of the virus-infected cell or tumor cell (see Figure 12.3D.7), this sends a signal through a CD3 molecule which triggers the release of the perforins/granzymes/granulysin complexes from the CTL.

The exact mechanism of entry of the granzymes into the infected cell or tumor cell is still debated. It is, however, dependent on perforins. Possibilities include:

- The perforins/granzymes/granulysin complex may be taken into the target cell by receptor-mediated endocytosis . The perforin molecules may then act on the endosomal membrane allowing granzymes to enter the cytosol.
- The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol (see Figure 12.3D.7).

Killing of the infected cell or tumor cell by apoptosis involves a variety of mechanisms:

- Certain granzymes can activate the caspase enzymes that lead to apoptosis of the infected cell. The caspases are proteases that destroy the protein structural scaffolding of the cell - the cytoskeleton - and nucleases that degrade both the target cell's nucleoprotein and any microbial DNA within the cell (see Figure 12.3D.8).
- Granzymes cleave a variety of other cellular substrates that contribute to cell death.
- The perforin molecules may also polymerize and form pores in the membrane of the infected cell, similar to those produced by MAC. This can increase the permeability of the infected cell and contribute to cell death. If enough perforin pores form, the cell might not be able to exclude ions and water and may undergo cytolysis.
- Granulysin has antimicrobial actions and can also induce apoptosis.
    - Electron micrograph of a CTL binding to a tumor cell.
    - Electron micrograph showing a killed tumor cell.

Flash animation of a CTL triggering apoptosis by way of perforins and granzymes.

html5 version of animation for iPad showing a CTL triggering apoptosis by way of perforins and granzymes.

Flash animation of CTL-induced apoptosis of a virus-infected cell.

html5 version of animation for iPad showing CTL-induced apoptosis of a virus-infected cell.

YouTube animation illustrating the MHC-I system marking an infected cell for destruction and its subsequent killing by CTLs.
Howard Hughes Medical Institute.

Movie illustrating apoptosis. Found on You Tube.

Concept Map for T-lymphocytes

TPS Question: T8-Lymphocytes

For a Summary of Key Surface Molecules and Cellular Interactions of Naive T8-Lymphocytes, see Figure 12.3D.9.

Summary

1. T-lymphocytes refer to lymphocytes that are produced in the bone marrow but require interaction with the thymus for their maturation.
2. The primary role of T8-lymphocytes is to kill infected cells and tumor cells by inducing apoptosis of those cells.
3. Once naive T8-lymphocytes are activated by dendritic cells, they proliferate and differentiate into T8-effector lymphocytes called cytotoxic T-lymphocytes (CTLs) that bind to and kill infected cells and tumor cells.
4. T8-lymphocytes display CD8 molecules and T-cell receptors (TCRs) on their surface.
5. The TCR on T8-lymphocytes, in cooperation with CD8, typically bind peptides from endogenous antigens bound to MHC-I molecules.
6. During its development, each T8-lymphocyte becomes genetically programmed, by gene-splicing reactions similar to those in B-lymphocytes and T4-lymphocytes, to produce a TCR with a unique shape capable of binding epitope/MHC-I complex with a corresponding shape.
7. To become activated, naive T8-lymphocytes migrate through lymph nodes where the TCRs on the T8-lymphocyte are able to sample large numbers of MHC-I/peptide complexes on the antigen-presenting dendritic cells for ones that “fit”, thus enabling activation of that naïve T8-lymphocyte.
8. After activation, the dendritic cell produces cytokines that contribute to proliferation of the T8-lymphocytes and their differentiation into effector T4-lymphocytes called cytotoxic T-lymphocytes (CTLs) that are able to bind to and kill infected cells and tumor cells displaying the same peptide/MHC-I complex on their surface.
9. Some of the T8-lymphocytes differentiate into circulating T8-memory cells that enable a more rapid and greater production of CTLs upon subsequent exposure to the same antigen.
10. During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes.
11. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides that are transported into the endoplasmic reticulum where they bind to newly made MHC-I molecules.
12. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles that carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they become anchored to its surface.
13. CTLs are, by way of their TCRs and CD8 molecules, are then able to recognize infected cells and tumor cells displaying MHC-I molecules with bound peptides on their surface. This sends a signal that triggers the release of the perforins/granzymes/granulysin complexes from the CTL to destroy the infected cell or tumor cell through apoptosis.
14. The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol, and certain granzymes activate the caspase enzymes that lead to apoptosis of the infected cell or tumor cell by destroying the cytoskeleton of the cell and degrading both the target cell's nucleoprotein and any microbial DNA within the cell.

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12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

Describe the overall function of iNKT cells and their activation in terms of the following:

a. the role of their TCRs
b. how they are activated by antigen-presenting cells
c. how they promote both innate and adaptive immunity and may also help to regulate the immune responses

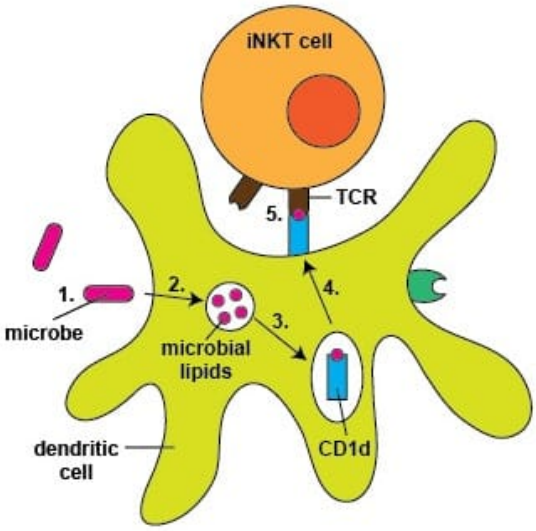


Figure $12.3E.1$: An iNKT-Lymphocyte Recognizing Microbial Glycolipid Antigen Bound to a CD1d Molecule on a Dendritic Cell. 1. Antigen-presenting dendritic cells engulf certain microbes or microbial glycolipids (exogenous glycolipids). 2. The glycolipids are degrade into epitopes by lysosomes. 3. The glycolipid epitopes are then bound to CD1d molecules produced in the endoplasmic reticulum by the dendritic cell. 4. The glycolipid epitope/CD1d complexes are transported by the Golgi apparatus to the surface of the dendritic cell. 5. Here the glycolipid epitope can be presented to theTCR of iNKT cells to induce iNKT cell activation.

Once activated, the iNKT cells rapidly produce large quantities of both T_H1 cell and T_H2 cell cytokines, including interferon-gamma (IFN-?), interleukin-4 (IL-4), interleukin-2 (IL-2), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-a), interleukin-13 (IL-13), and chemokines. Through the rapid productions of such cytokines, iNKT cells are able to promote and suppress different innate and adaptive immune responses. For example, large amounts of IFN-? are produced by activated iNKT cells. IFN-? activates NK cells and macrophages as a part of innate immunity; it also promotes the maturation of dendritic cells so that they induce a T_H1 cell response to induce adaptive immunity.

It has been proposed that if the iNKT cell is repeatedly stimulated by the body's own glycolipids in the ab sense of microbes that this might stimulate the iNKT cell /dendritic cell interaction to produce tolerizing signals that inhibit the T_H1 cell response and possibly stimulate the production of regulatory T-lymphocytes (T_{reg} cells). In this way it might suppress autoimmune responses and prevent tissue damage.

There is also growing evidence that early childhood exposure to microbes is associated with protection against allergic diseases, asthma, and inflammatory diseases such as ulcerative colitis. It has been found that germ-free mice have large accumulations of mucosal iNKT cells in the lungs and intestines and increased morbidity from allergic asthma and inflammatory bowel disease. However, colonization of neonatal germ-free mice with normal microbiota resulted in mucosal iNKT cell tolerance to these diseases. It has been proposed that microbes the human body has been traditionally exposed to from early childhood throughout most of human history might play a role in developing normal iNKT cell numbers and iNKT cell responses.

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12.3F: B-Lymphocytes (B-Cells)

Learning Objectives

Describe the overall function of B-lymphocytes and their activation by T-dependent antigens in terms of the following:

a. the antigen receptor on their surface
b. how they "process" exogenous antigens
c. the type of MHC molecule to which they attach peptides
d. the role of lysosomes in binding of peptides from exogenous antigens by MHC-II molecules.
e. the type of cell to which they present peptides
f. the types of cells into which activated B-lymphocytes differentiate

B-lymphocytes (B-cells) are responsible for the production of antibody molecules **during adaptive immunity**. Antibodies are critical in removing extracellular microorganisms and toxins. B-lymphocytes refer to lymphocytes that are produced in the bone marrow and require bone marrow stromal cells and their cytokines for maturation. During its development, each B-lymphocyte becomes genetically programmed through a series of gene-splicing reactions to produce an antibody molecule with a unique specificity - a specific 3-dimensional shape capable of binding a specific epitope of an antigen (Figure $12.3F.1$).

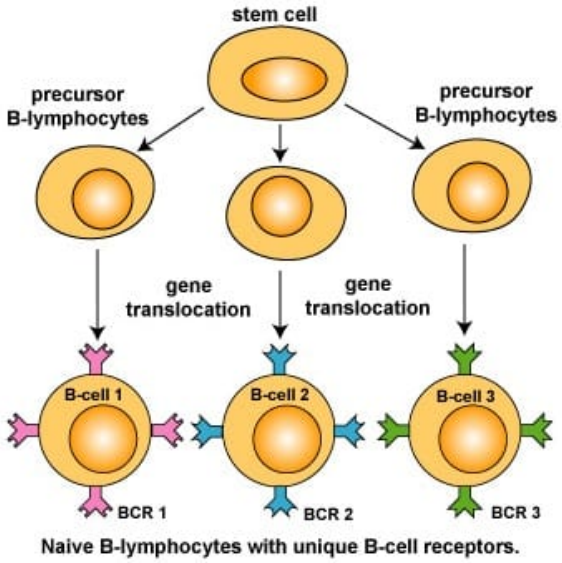


Figure $12.3F.1$: B-Lymphocyte Precursors Making B-Cell Receptors (BCRs). During its development, each B-lymphocyte becomes genetically programmed, through a process called gene translocation, to make a unique B-cell receptor. Molecules of that B-cell receptor are placed on its surface where it can react with epitopes of an antigen.

It is estimated that the human body has the ability to recognize 10^7 or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of B-lymphocytes, each with a unique B-cell receptor or BCR. In this variety of B-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters.

Typically, over 100,000 identical molecules of that unique antibody are placed on the surface of the B-lymphocyte where they can function as B-cell receptors capable of binding specific epitopes of a corresponding shape (Figure $12.3F.2$). Naive B-lymphocytes can be activated by both T-dependent antigens and T-independent antigens.

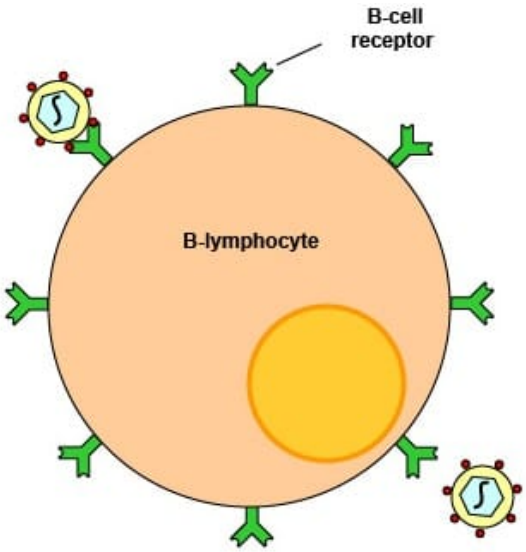


Figure 12.3F.2: A B-lymphocyte Recognizing Epitopes of a Virus by way of B-cell Receptors. Epitopes of the virus bind to a B-lymphocyte by way of a specific B-cell receptor.

Activation of naive B-lymphocytes by T-dependent antigens

In order for naive B-lymphocytes to proliferate, differentiate, and mount an antibody response against T-dependent antigens, such as most proteins, these B-lymphocytes must interact with effector T4-lymphocytes called T_{FH} cells. All classes of antibody molecules can be made against T-dependent antigens and there is usually a memory response against such antigens.

B-Lymphocytes and T4-lymphocytes encounter antigens in secondary lymphoid organs such as the lymph nodes and the spleen. Using a lymph node as an example (Figure 12.3F.3A), soluble antigens, such as microbial polysaccharides and proteins and toxins, as well as **microbes such as bacteria and viruses**, **enter the lymph node** through afferent lymphatic vessels. By this time, complement pathway activation has coated these soluble antigens or microbes with opsonins such as C3b, which in turn can be degraded to C3d.

Located within the lymphoid tissues are specialized macrophages and specialized dendritic cells called follicular dendritic cells (FDCs). These macrophages have poor endocytic ability and produce few lysosomes. The FDCs are nonphagocytic. Both cell types, however, have complement receptors called CR1 and CR2 that bind to the C3b and C3d, enabling the antigens and microbes to stick to the surface of the macrophages and FDCs. However,because of the poor endocytic ability of the macrophages and the lack of endocytosis by the FDCs, the antigens and microbes are not engulfed but rather remain on the surface of the cells. In addition, the macrophages can transfer their bound antigens or microbes to FDCs (Figure 12.3F.3B).

Here the antigens and microbes in the lymph node can bind to complementary-shaped BCRs on naive B-lymphocytes **directly, by way of macrophages, or via the FDCs** (Figure 12.3F.3B).

Circulating naive B-lymphocytes, as a result of chemotaxis, enter lymph nodes through high endothelial venules. Any naive B-lymphocyte that bind antigens become activated and remain in the lymphoid nodes to proliferate and differentiate. Any B-lymphocytes not activated leave the lymphoid node through efferent lymphatic vessels and are returned to the bloodstream.

The first signal for the activation of a naive B-lymphocyte occurs when BCRs on the surface of the B-lymphocyte bind epitopes of antigens having a corresponding shape. A second signal is also needed for the activation of the naive B-lymphocyte. This is provided when the complement protein C3d on the microbial surface or soluble antigen binds to a complement receptor called CR2 on the surface of the naive B-lymphocyte.

Once bound, the antigen is engulfed, placed in a phagosome , and degraded with lysosomes. During this process, protein antigens are broken down into a series of peptide epitopes.These peptides eventually bind to grooves in MHC-II molecules that are then transported to the surface of the B-lymphocyte (Figure 12.3F.4).

Meanwhile, naïve T4-lymphocytes are being activated by epitopes of antigens bound to MHC-II molecules on antigen-presenting

dendritic cells in the T-cell area of the lymph node and subsequently proliferate and differentiate into T4-effector lymphocytes such as T_{FH} cells which remain in the lymph node. The T-cell receptors and CD4 molecules on T_{FH} cells bind to the MHC-II molecules with bound peptide epitope on the B-lymphocyte. The binding of co-receptor molecules such as CD40L and CD28 on the surface of the effector T4-lymphocyte to the corresponding molecules CD40 and B7 on the surface of the B-lymphocyte further contribute to the interaction between these two cells (Figure 12.3F.5). This enables the T_{FH} cells to produce cytokines such as interleukin-2 (IL-2) , interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-6 (IL-6) (Figure 12.3F.5).

Flash animation of the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.
Flash animation of an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

html5 version of animation for iPad showing the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte

html5 version of animation for iPad showing an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

Collectively these cytokines:

a. Enable activated B-lymphocytes to proliferate.
b. Stimulate activated B-lymphocytes to synthesize and secrete antibodies.
c. Promote the differentiation of B-lymphocytes into antibody-secreting plasma cells. See Figure 12.3F.6.
d. Enable antibody producing cells to switch the class or isotype of antibodies being produced.

YouTube animation illustrating production of antibodies by B-lymphocytes.

YouTube animation illustrating production of antibodies by B-lymphocytes against Streptococcus pyogenes.

Effector T4-lymphocytes also enable B-lymphocytes to undergo affinity maturation through a high rate of somatic mutation. This allows the B-lymphocytes to eventually "fine-tune" the shape of the antibody for better fit with the original epitope. After mutation, some antibodies fit better, some worse. To select for B-lymphocytes displaying antibodies with a better fit, the variant B-lymphocytes interact with cells called follicular dendritic cells (FDCs) in the germinal centers of the secondary lymphoid organs. The FDCs display the same antigens that activated the original B-lymphocyte. If the B-lymphocytes have high affinity antibodies for the antigen on the FDC, they are selected to survive. Those B-lymphocytes with low affinity antibodies undergo apoptosis.

With the exception of T_{FH} cells which remain in the germinal centers of the lymph nodes and spleen, progeny of the activated B-lymphocytes and T4 effector lymphocytes leave the secondary lymphoid organs and migrate to tissues where they continue to respond to the invading antigen as long as it is present.

In the case of systemic infections or vaccinations where the antigens enter the bloodstream, plasma cells migrate to the bone marrow where antibodies can be produced for decades. After the antibodies are secreted by the plasma cells, they are found dissolved in the blood plasma and lymph. From here they can be delivered anywhere in the body via the circulatory system and the inflammatory response. In the case of infections of the mucous membranes, however, plasma cells only enter the mucous membranes where antibodies are only produced for a few months to a year or so.

During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes stop replicating and become circulating, long-lived memory cells. Memory cells are capable of what is called anamnestic response or "memory", that is, they "remember" the original antigen. If that same antigen again enters the body while the B-memory cells (and T4-memory cells) are still present, these memory cells will initiate a rapid, heightened secondary response against that antigen (Figure 12.3F.7). This is why the body sometimes develops a permanent immunity after an infectious disease and is also the principle behind immunization.

Activation of B-lymphocytes by T-independent antigens

T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector T4-lymphocytes. Bacterial LPS from the Gram-negative cell wall and capsular polysaccharides are examples of TI antigens. The resulting antibody molecules are generally of the IgM isotype and do not give rise to a memory response. There are two basic types of T-independent antigens: TI-1 and TI-2.

a. TI-1 antigens arepathogen-associated molecular patterns or PAMPS such as lipopolysaccharide (LPS) from the outer membrane of the gram-negative cell wall and bacterial nucleic acid. These antigens activate B-lymphocytes by binding to their specific pattern-recognition receptors , in this case toll-like receptors, rather than to B-cell receptors (Figure $12.3F.8$). Antibody molecules generated against TI-1 antigens are often called "natural antibodies" because they are always being made against bacteria present in the body.

For More Information: Pathogen-Associated Molecular Patterns from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

b. TI-2 antigens, such as capsular polysaccharides, are molecules with multiple, repeating subunits. These repeating subunits activate B-lymphocytes by simultaneously cross-linking a number of B-cell receptors (Figure $12.3F.9$).

For More Information: T4-Lymphocytes from Unit 6

For More Information: MHC Molecules from Unit 6

For a Summary of Key Surface Molecules and Cellular Interactions of Naive B-Lymphocytes, see Figure $12.3F.10$.

Concept Map for B-lymphocytes

Summary

1. B-lymphocytes are responsible for the production of antibody molecules during adaptive immunity.
2. Antibodies are critical in removing extracellular microorganisms and toxins.
3. B-lymphocytes refer to lymphocytes that are produced in the bone marrow and require bone marrow stromal cells and their cytokines for maturation.
4. During its development, each B-lymphocyte becomes genetically programmed to produce an antibody molecule with a unique 3-dimensional shape capable of binding a specific epitope of an antigen, and puts molecules of that antibody on its surface that function as B-cell receptors or BCRs.
5. Naive B-lymphocytes can be activated by both T-dependent antigens and T-independent antigens.
6. In order for naive B-lymphocytes to proliferate, differentiate, and mount an antibody response against T-dependent antigens, such as most proteins, these B-lymphocytes must interact with effector T4-lymphocytes called TFH cells.
7. The first signal for the activation of a naive B-lymphocyte occurs when BCRs on the surface of the B-lymphocyte bind epitopes of antigens having a corresponding shape.
8. Once bound to the BCR, the antigen is engulfed, placed in a phagosome, and degraded with lysosomes. During this process, protein antigens are broken down into a series of peptide epitopes, bind to MHC-II molecules, and are transported to the surface of the B-lymphocyte.
9. The T-cell receptors and CD4 molecules on TFH cells bind to the MHC-II molecules with bound peptide epitope on the B-lymphocyte which enables the TFH cells to produce cytokines that collectively enable the B-lymphocytes to proliferate, synthesize and secrete antibodies, differentiate into antibody-secreting plasma cells, and switch the class of antibodies being produced.
10. By way of a mutation process called affinity maturation, activated B-lymphocytes are able over time to “fine-tune" the shape of the antibody for better fit with the original epitope.
11. During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes stop replicating and become circulating, long-lived memory cells that will initiate a rapid, heightened secondary response against that antigen if it again enters the body.
12. T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector

T4-lymphocytes, but the resulting antibody molecules are generally of the IgM isotype only and do not give rise to a memory response.

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12.3G: Natural Killer Cells (NK Cells)

Briefly describe how NK cells bind to and kill infected cells and tumor cells through ADCC.

- Briefly describe how NK cells recognize and kill infected cells and tumor cells that suppress MHC-I production.

NK cells are another group of cytolytic lymphocytes that are distinct from B-lymphocytes and T-lymphocytes, and participate in both innate immunity and adaptive immunity. NK cells are lymphocytes that lack B-cell receptors and T-cell receptors. They are designed to kill certain mutant cells and virus-infected cells in one of two ways:

Antibody-dependent Cellular Cytotoxicity

NK cells kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC) as shown in Figure $12.3G.1$, Figure $12.3G.2$, and Figure $12.3G.3$. The Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody. The NK cell is then able to contact the cell and by inducing a programmed cell suicide called apoptosis.

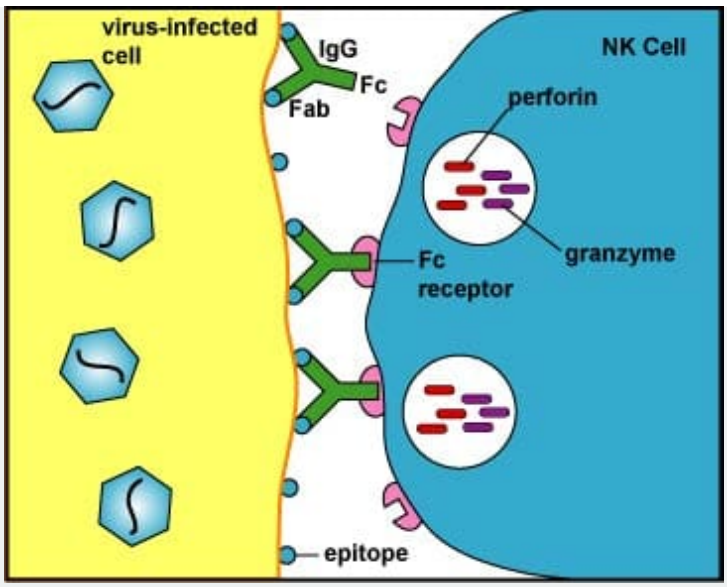


Figure $12.3G.3$

As a result, the infected cell breaks into membrane-bound fragments that are subsequently removed by phagocytes. If very large numbers of perforins are inserted into the plasma membrane of the infected cell, this can result in a weakening of the membrane and lead to cell lysis rather than apoptosis. An advantage to killing infected cells by apoptosis is that the cell's contents, including viable virus particles and mediators of inflammation, are not released as they are during cell lysis.

Innate Immunity

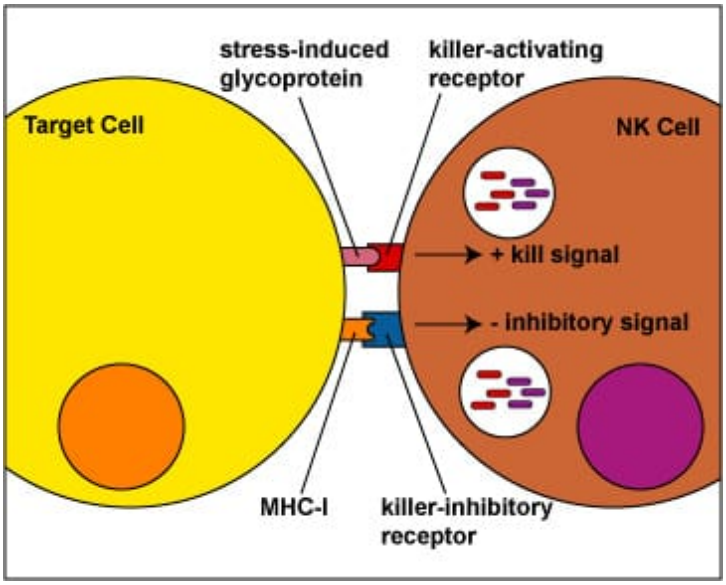


Figure $12.3G.6$). Perforins can also sometimes result in cell lysis.

Flash animation of a NK cell interacting with a normal body cell.
Flash animation of a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

Flash animation of apoptosis by NK cells

html5 version of animation for iPad showing a NK cell interacting with a normal body cell.

html5 version of animation for iPad showing a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

html5 version of animation for iPad showing apoptosis by NK cells.

In addition, NK cells produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses. For example, through cytokine production NK cells also suppress and/or activate macrophages, suppress and/or activate the antigen-presenting capabilities of dendritic cells, and suppress and/or activate T-lymphocyte responses.

Summary

1. Natural Killer (NK) cells are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses.
2. NK cells play a role in adaptive immune responses by way of antibody-dependent cellular cytotoxicity or ADCC where they bind to and kill cells to which antibody molecules have bound.
3. During ADCC, the Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody and the NK cell is then able to contact and kill the cell by inducing a programmed cell suicide called

apoptosis.

4. During innate immunity, NK cells use a dual receptor system in determining whether to kill or not kill human cells.
5. When body cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell.
6. The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.
7. The second receptor, called the killer-ihibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound.
8. NK cells kill their target cells by inducing apoptosis, a programmed cell suicide.

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12.4: The Lymphoid System

Learning Objectives

1. Compare and give examples of the following:
   a. primary lymphoid organs
   b. secondary lymphoid organs
2. Define the following:
   a. plasma
   b. tissue fluid
   c. lymph
   d. lymph vessels
   e. MALT
3. Briefly describe the importance of the lymphoid system in adaptive immune responses and how microbes and other antigens encounter naive B-lymphocytes and T-lymphocytes.

The body uses the lymphoid system to enable lymphocytes to encounter antigens and it is here that adaptive immune responses are initiated. The lymphoid system consists of primary lymphoid organs, secondary lymphoid organs, and lymphatic vessels.

The bone marrow and the thymus constitute the primary lymphoid organs. Both B-lymphocytes and T-lymphocytes are produced from stem cells in the bone marrow. B-lymphocytes mature in the bone marrow while T-lymphocytes migrate to the thymus and mature there. After maturation, both naive B-lymphocytes and naive T-lymphocytes circulate between the blood and the secondary lymphoid organs.

Lymphatic vessels are responsible for flow of lymph within the lymphoid system and are a part of the body's fluid recirculation system. The liquid portion of the blood, called plasma, constantly leaks out of capillaries to deliver oxygen and nutrients to cells of the surrounding tissue. Once in the tissue, the plasma is now called tissue fluid. While most of this tissue fluid re-enters capillaries and is returned directly to the bloodstream, some fluid enters lymph vessels as lymph. The lymph flows through regional lymph nodes and eventually enters the circulatory system at the heart to maintain the fluid volume of the circulation.

Secondary lymphoid organs

Adaptive immune responses require antigen-presenting cells, such as macrophages and dendritic cells, and ever changing populations of B-lymphocytes and T- lymphocytes. These cells gather to detect and present antigens in secondary lymphoid organs. The secondary lymphoid organs include highly organized lymphoid organs such as lymph nodes and the spleen, as well as less organized accumulations of lymphoid organs scattered strategically throughout the body.

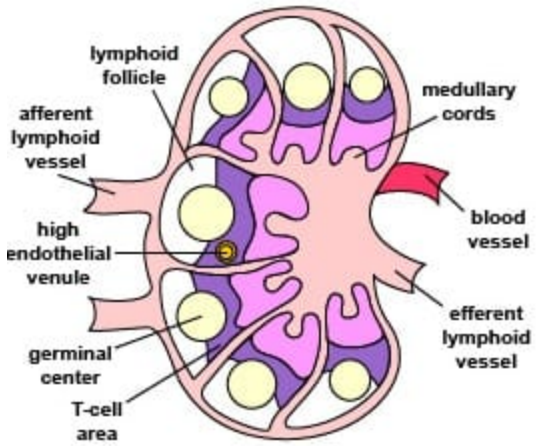


Figure 12.4.1: Structure of a Lymph Nodes. Antigens enter lymph nodes through afferent lymphoid vessels. Antigen-presenting dendritic cells enter the lymph node through afferent lymphatic vessels while naive B-lymphocytes, and naive T-lymphocytes enter through high endothelial venules. Non-activated and effector lymphocytes leave the lymph node through efferent lymphatic vessels. Naive B-lymphocytes become activated, proliferate, and differentiate into plasma cells in the germinal centers of lymphoid follicles while naive T-lymphocytes become activated, proliferate and differentiate into T-effector lymphocytes in the T-cell area.

Lymph nodes (Figure 12.4.1) contain many reticular fibers that support fixed macrophages and dendritic cells as well as ever changing populations of circulating B-lymphocytes and T-lymphocytes. When microorganisms and other antigens enter tissues, they are transported by tissue fluid into the lymph vessels. Lymph vessels, in turn, carry these antigens, now in the lymph, to regional lymph nodes. In addition, immature dendritic cells located under the surface epithelium of the skin and the surface epithelium of the mucous membranes of the respiratory tract, genitourinary tract, and the gastrointestinal tract capture antigens through pinocytosis and phagocytosis. The dendritic cells detach from their initial site, enter lymph vessels, and are carried to regional lymph nodes. Here the microbes and other antigens in the lymph encounter changing populations of B-lymphocytes, are filtered out and phagocytosed by the fixed macrophages and dendritic cells, and are presented to changing populations of T-lymphocytes (Figure 12.4.2). Approximately 25 billion different lymphocytes migrate through each lymph node every day.

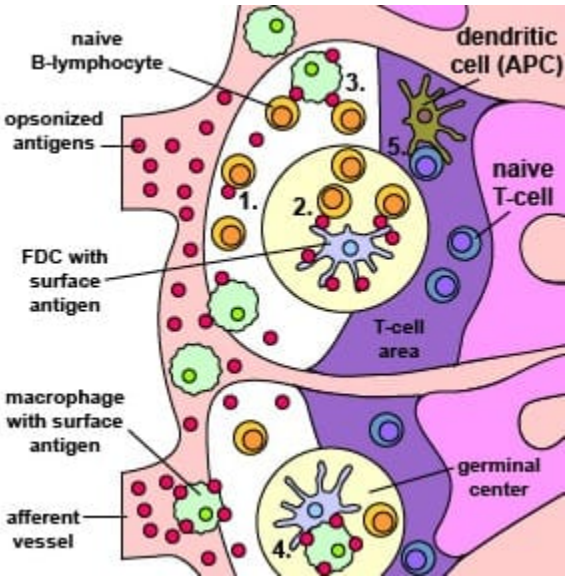


Figure 12.4.2: B-lymphocyte and T-Lymphocytes Recognizing Antigens in a Lymph Node. Opsonized antigens (those coated with C3b and Ced from the complement pathways) enter a lymph node through afferent lymphoid vessels. These opsonized antigens bind to and remain on the surface of specialized macrophages and follicular dendritic cells (FDCs). In addition, macrophages can transfer antigens to FDCs (see 4. above). Using their B-cell receptor (BCR), naive B-lymphocytes are able to recognize antigens directly (see 1. above), or more commonly, on the surface of FDCs (see 2. above), or on the surface of macrophages (see 3. above) in the germinal centers and lymphoid follicles of the lymph node. Meanwhile, naive T-lymphocytes are being activated by antigen-presenting dendritic cells in the T-cell areas of the lymph node (see 5. above). T4-effector cells and activated B-lymphcytes then interact with one another at the interface between the geminal centers and the T-cell areas.

Like the lymph nodes, the spleen contains many reticular fibers that support fixed macrophages and dendritic cells as well as ever changing populations of circulating B-lymphocytes and T-lymphocytes. When microorganisms and other antigens enter the blood, they are transported by the blood vessels to the spleen. Most of the spleen is referred to as red pulp. This area is involved in the disposal of old red blood cells. Scattered throughout the spleen are isolated areas called the white pulp (Figure 12.4.3). Here antigens in the blood encounter macrophages, dendritic cells, and ever-changing populations of B-lymphocytes and T-lymphocytes.

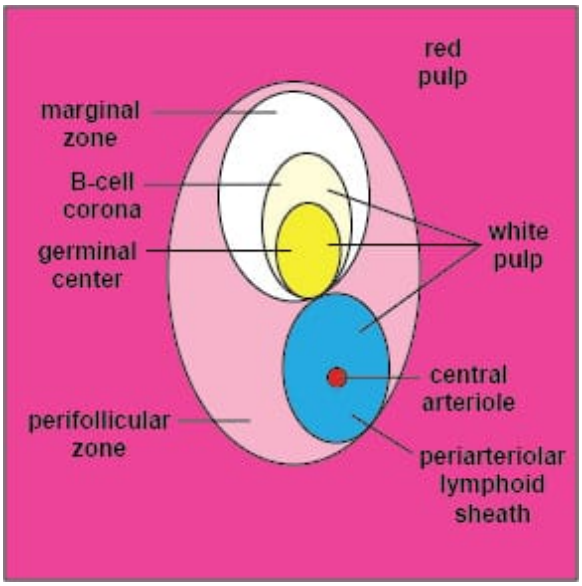


Figure 12.4.3: Section of a Spleen Showing Red Pulp and White Pulp. The red pulp makes up the majority of the spleen. This is where old red blood cells are destroyed. Scattered throughout the spleen are areas of white pulp where microbes, cells, and antigens encounter macrophages, dendritic cells, and changing populations of B-lymphocytes and T-lymphocytes. Soluble antigens, blood-borne microbes, and antigen-antibody complexes are filtered out of the blood and phagocytosed by immature dendritic cells and macrophages within the marginal zone. After maturation, dendritic cells migrate to the periphery of the periarteriolar lymphoid sheath, The T-cell area of the white pulp, and present antigens bound to MHC molecules to the TCRs of T-lymphocytes. Secondary follicles consisting of germinal centers surrounded by a B-cell corona are where B-lymphocytes encounter microbes and soluble antigens.

Mucosal surfaces within the body, the most common sites of microbial invasion, are protected by the mucosal immune system consisting of the mucosa-associated lymphoid tissue or MALT, an extensive diffuse system of small concentrations of lymphoid tissue found in various sites of the body such as the gastrointestinal tract, thyroid, breast, lung, salivary glands, eye, and skin. MALT is populated by loose clusters of T-lymphocytes, B-lymphocytes, plasma cells, activated T_H cells, and macrophages. MALT can be subdivided into:

- GALT (gut-associated lymphoid tissue, such as the Peyer's patches (Figure 12.4.4) in the lining of the small intestines, as well as the adenoids, tonsils, and appendix)
- BALT (bronchial-associated lymphoid tissue in the bronchi)
- SALT (skin-associated lymphoid tissue beneath the epidermis)
- NALT (nose-associated lymphoid tissue)
- LALT (larynx-associated lymphoid tissue)
- CALT (conjunctiva-associated lymphoid tissue in the eye)

As can be seen, no matter how microbes and other antigens enter the body, they will eventually encounter the lymphoid system to initiate adaptive immune responses.

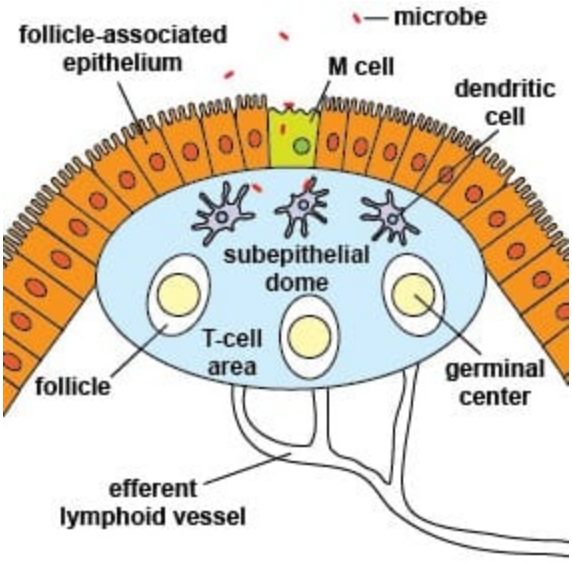


Figure 12.4.4: Diagram of a Peyer's Patch. Peyer's patches are part of the mucosa-associated lymphoid tissue (MALT) in the small intestines. Microbes and antigens enter through specialized epithelial cells called microfold (M) cells. Changing populations of naive B-lymphocytes and naive T-lymphocytes enter the Peyer's patch via blood vessels with B-lymphocytes entering the follicles and germinal centers and T-lymphocytes entering the T-cell area. Dendritic cells engulf and process antigens and present them by way of MHC molecules to the TCRs of naive T-lymphocytes.

Summary

1. The body uses the lymphoid system to enable lymphocytes to encounter antigens and it is here that adaptive immune responses are initiated.
2. The lymphoid system consists of primary lymphoid organs, secondary lymphoid organs, and lymphatic vessels.
3. The bone marrow and the thymus constitute the primary lymphoid organs.
4. While both B-lymphocytes and T-lymphocytes are produced from stem cells in the bone marrow, B-lymphocytes mature in the bone marrow and T-lymphocytes migrate to the thymus to mature.
5. After maturation, both naive B-lymphocytes and naive T-lymphocytes circulate between the blood and the secondary lymphoid organs.
6. Adaptive immune responses require antigen-presenting cells, such as macrophages and dendritic cells, and ever changing populations of B-lymphocytes and T- lymphocytes. These cells gather to detect and present antigens in secondary lymphoid organs.
7. The secondary lymphoid organs include highly organized lymphoid organs such as lymph nodes and the spleen, as well as less organized accumulations of lymphoid organs scattered strategically throughout the body.
8. Lymphatic vessels are responsible for flow of lymph within the lymphoid system and are a part of the body's fluid recirculation system. The lymph flows through regional lymph nodes and eventually enters the circulatory system at the heart to maintain the fluid volume of the circulation.

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12.5: An Overview of the Steps Involved in Adaptive Immune Responses

Learning Objectives

1. List the 5 general steps involved in the immune responses in their correct order.
2. State where antigens may encounter APCs, B-lymphocytes, and T-lymphocytes if they enter the following:
   a. the blood
   b. tissues
   c. the respiratory tract
   d. the gastrointestinal tract
   e. the genitourinary tract
3. Briefly describe how the receptor molecules on the surface of naive B-lymphocytes, T4-helper lymphocytes, and T8-lymphocytes eventually recognize or bind epitope, indicating the roles of BCR, TCR, CD4, CD8, MHC-I, and MHC-II molecules in lymphocyte activation.
4. State the overall function of T4-effector lymphocytes and the importance behind rapid proliferation of activated lymphocytes.
5. State what types of effector cells the proliferating B-lymphocytes and T8-lymphocytes differentiate into in order to destroy or neutralize the antigen.
6. Define cytokine.
7. State the function of memory cells.
8. State what is meant by immunologic tolerance.

Whether considering *humoral immunity* or *cell-mediated immunity*, there are several general steps involved in the immune responses.

Step 1. The antigen must encounter the B-lymphocytes, T-lymphocytes, and antigen-presenting cells (APCs) capable of carrying out an adaptive immune response.

Fundamental Statement for this Step:

> *1. Antigens encounter the APCs, B-lymphocytes, and T-lymphocytes in the secondary lymphoid organs of the lymphoid system.*

Antigens encounter the APCs, B-lymphocytes, and T-lymphocytes in the secondary lymphoid organs of the lymphoid system. Tissue fluid carries antigens to lymph nodes, blood carries antigens to the spleen, and immature dendritic cells under the skin and mucosal epithelium carry antigens to regional lymph nodes. Here they encounter ever changing populations of naive B-lymphocytes, T4-lymphocytes, and T8-lymphocytes as they circulate back and forth between the blood and the lymphatics.

a. Antigens that enter through the bloodstream, encounter the APCs, B-lymphocytes, and T-lymphocytes in the spleen ; see Figure 12.5.1.
b. Antigens that enter through the tissue, are picked up by tissue fluid, enter the lymph vessels, and are carried to the lymph nodes where they encounter APCs, B-lymphocytes, and T-lymphocytes; see Figure 12.5.2.
c. Antigens that enter the respiratory tract, encounter APCs, B-lymphocytes, and T-lymphocytes in the tonsils and the mucosa-associated lymphoid tissue (MALT), including the bronchial-associated lymphoid tissue (BALT), the nose-associated lymphoid tissue (NALT), and the larynx-associated lymphoid tissue (LALT).
d. Antigens that enter the intestinal tract, encounter APCs, B-lymphocytes, and T-lymphocytes in the Peyer's patches (see Figure 12.5.3) and other gut-associated lymphoid tissues (GALT).
e. Antigens that enter the genitourinary tract, encounter APCs, B-lymphocytes, and T-lymphocytes in the mucosa-associated lymphoid tissue (MALT) found there.

f. Finally, antigens that penetrate the skin, encounter APCs, B-lymphocytes, and T-lymphocytes of the skin-associated lymphoid tissue (SALT).

Step 2. Naive B-lymphocytes, T4-lymphocytes, and T8-lymphocytes must recognize epitopes of an antigen by means of antigen-specific receptor molecules on their surface and become activated. This is known as clonal selection.

Fundamental Statements for this Step:

1. Dendritic cells bind peptide epitopes to MHC-II molecules to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on naive T4-lymphocyte.
2. Dendritic cells bind peptide epitopes to MHC-I molecules to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD8 molecules on naive T8-lymphocytes.
3. These interactions are required to enable the T4-lymphocyte or T8-lymphocyte to become activated, proliferate, and differentiate into effector cells.
4. Naive T4-lymphocytes have T cell receptors (TCRs) that, in cooperation with CD4 molecules, bind to MHC-II molecules with attached epitope from an antigen found on the surface of an antigen-presenting dendritic cell.
5. Naive T8-lymphocytes have T cell receptors (TCRs) that, in cooperation with CD8 molecules, bind to MHC-I molecules with attached epitope from an antigen found on the surface of antigen-presenting dendritic cells.
6. Most proteins are T-dependent antigens. In order for naive B-lymphocytes to proliferate, differentiate and mount an antibody response against T-dependent antigens, these B-lymphocytes must interact with effector T4-lymphocytes.
7. Specialized macrophages and specialized dendritic cells called FDCs are located in the lymphoid tissues. Antigens and microbes are are found on the surface of these FDCs and macrophages which present them to complementary-shaped BCRs on naive B-lymphocytes**.**
8. A few antigens are called T-independent antigens. T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector T4-lymphocytes but the antibody response is much more limited than with T-dependent antigens.

a. The role of antigen-presenting dendritic cells

The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes.

- Dendritic cells bind peptide epitopes to MHC-II molecules (see Figure 12.5.4) to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on naive T4-lymphocyte.
- Dendritic cells bind peptide epitopes to MHC-I molecules (see Figure 12.5.5) to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD8 molecules on naive T8-lymphocytes.

These interactions are required to enable the T4-lymphocyte or T8-lymphocyte to become activated, proliferate, and differentiate into effector cells.

Flash animation of MHC-II molecules binding epitopes from exogenous antigens.

html5 version of animation for iPad showing MHC-II molecules binding epitopes from exogenous antigens.

Flash animation of MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells. They are located under the surface epithelium of the skin and the surface epithelium of the mucous membranes of the respiratory tract, genitourinary tract, and the

gastrointestinal tract. They are also found throughout the body's lymphoid tissues and in most solid organs.

Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by proinflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes (see Figure 12.5.6). By the time they enter the lymph nodes, they have matured and are now able to present antigen to the ever changing populations of naive T-lymphocytes located in the T-cell area of the lymph nodes (see Figure 12.5.7).

- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the University of Illinois College of Medicine.
- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

For More Information: Antigen-presenting cells from Unit 6

b. Naive T4-helper lymphocytes recognizing peptide epitopes

Naive T4-lymphocytes circulate in the blood. In response to chemokines produced by lymphoid tissues, they leave the vascular endothelium in regions called high endothelial venules and enter lymph nodes or other secondary lymphoid tissues, a process called diapedesis.

Naive T4-lymphocytes have T-cell receptors (TCRs) that, in cooperation with CD4 molecules, bind to MHC-II molecules with attached epitope from an antigen found on the surface of an antigen-presenting dendritic cells ; (see Figure 12.5.8). Each T4-lymphocyte is genetically programmed to make a unique TCR. The TCR recognizes the peptide while the CD4 molecule recognizes the MHC-II molecule.

Flash animation of a naive T4-lymphocyte recognizing epitopes on MHC-II via its TCR and CD4.

html5 version of animation for iPad showing a naive T4-lymphocyte recognizing epitopes on MHC-II via its TCR and CD4.

For More Information: MHC Molecules from Unit 6

For More Information: Antigen-presenting cells from Unit 6

For More Information: T4-Lymphocytes from Unit 6

c. Naive T8-lymphocytes recognizing peptide epitopes

Naive T8-lymphocytes circulate in the blood. In response to chemokines produced by lymphoid tissues, they leave the vascular endothelium in regions called high endothelial venules and enter lymph nodes or other secondary lymphoid tissues, a process called diapedesis.

Naive T8-lymphocytes have T-cell receptors (TCRs) that, in cooperation with CD8 molecules, bind to MHC-I molecules with attached epitope from an antigen found on the surface of antigen-presenting dendritic cells (see Figure 12.5.9). Each T8-lymphocyte is genetically programmed to make a unique TCR. The TCR recognizes the peptide while the CD8 molecule recognizes the MHC-I molecule.

Flash animation of a naive T8-lymphocyte recognizing epitopes on MHC-I via its TCR and CD8.

html5 version of animation for iPad showing a naive T8-lymphocyte recognizing epitopes on MHC-I via its TCR and CD8.

For More Information: MHC Molecules from Unit 6

For More Information: Antigen-presenting cells from Unit 6

For More Information: T8-Lymphocytes from Unit 6

d. Naive B-lymphocytes recognizing epitopes of antigens

Most proteins are T-dependent antigens. In order for naive B-lymphocytes to proliferate, differentiate and mount an antibody response against T-dependent antigens, these B-lymphocytes must interact with effector T4-lymphocytes. All classes or isotypes of antibody molecules can be made against T-dependent antigens and there is usually a memory response against such antigens.

Naive B-Lymphocytes encounter antigens in secondary lymphoid organs such as the lymph nodes and the spleen. Using a lymph node as an example, soluble antigens, such as microbial polysaccharides and proteins and toxins, as well as **microbes such as bacteria and viruses**, **enter the lymph node** through afferent lymphatic vessels. By this time, complement pathway activation has coated these soluble antigens or microbes with opsonins such as C3b, which in turn can be degraded to C3d.

Located within the lymphoid tissues are specialized macrophages and specialized dendritic cells called follicular dendritic cells (FDCs). These macrophages have poor endocytic ability and produce few lysosomes. The FDCs are nonphagocytic. Both cell types, however, have complement receptors called CR1 and CR2 that bind to the C3b and C3d, enabling the antigens and microbes to stick to the surface of the macrophages and FDCs. However,because of the poor endocytic ability of the macrophages and the lack of endocytosis by the FDCs, the antigens and microbes are not engulfed but rather remain on the surface of the cells. In addition, the macrophages can transfer their bound antigens or microbes to FDCs (see Figure 12.5.10). Here the antigens and microbes in the lymph node can bind to complementary-shaped BCRs on naive B-lymphocytes **directly, by way of macrophages, or via the FDCs** (see Figure 12.5.10).

Flash animation of the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.

Flash animation of an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

html5 version of animation for iPad showing the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.

html5 version of animation for iPad showing an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

For More Information: B-Lymphocytes from Unit 6

For More Information: Antigen-presenting cells from Unit 6

A few antigens are called T-independent antigens. T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector T4-lymphocytes. Bacterial lipopolysaccharide (LPS) from the Gram-negative cell wall and capsular polysaccharides are examples of TI antigens. The resulting antibody molecules are generally of the IgM isotype and do not give rise to a memory response. There are two basic types of T-independent antigens: TI-1 and TI-2.

1. TI-1 antigens are pathogen-associated molecular patterns or PAMPS such as lipopolysaccharide (LPS) from the outer membrane of the Gram-negative cell wall and bacterial nucleic acid. These antigens activate B-lymphocytes by binding to their specific pattern-recognition receptors, in this case toll-like receptors, rather than to B-cell receptors (see Figure 12.5.11). Antibody molecules generated against TI-1 antigens are often called "natural antibodies" because they are always being made against bacteria present in the body.

For More Information: Pathogen-Associated Molecular Patterns from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

2. TI-2 antigens, such as capsular polysaccharides, are molecules with multiple, repeating subunits. These repeating subunits activate B-lymphocytes by simultaneously cross-linking a number of B-cell receptors (see Figure 12.5.12).

Those naive B-lymphocytes not activated by epitopes of antigens exit the lymph node or other lymphoid tissue and eventually re-enter the bloodstream.

3. After the naive B-lymphocytes, T4-lymphocytes, and T8-lymphocytes bind their corresponding epitopes, they must proliferate into large clones of identical cells in order to mount a successful immune response against that antigen. This is known as clonal expansion.

Fundamental Statements for this Step:

1. With the exception of T-independent antigens, naive B-lymphocytes must be stimulated to proliferate by means of cytokines called interleukins produced primarily by effector T4- lymphocytes such as T_{FH} cells.
2. In the case of T4-lymphocytes and T8-lymphocytes, dendritic cells produces cytokines that contribute to proliferation of the activated T-lymphocytes. CD28-dependent co-stimulation of the T4-lymphocyte also stimulates it to synthesize the cytokine interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor. The binding of IL-2 to its high affinity receptor allows for cell proliferation and formation of a clone of thousands of identical T-lymphocytes after several days.

With the exception of T-independent antigens, the naive B-lymphocytes that were activated in step 2 must be stimulated to proliferate by means of cytokines called interleukins (such as IL-2, IL-4, IL-5, Il-6, and IL-10) produced primarily by effector T4- lymphocytes such as T_{FH} cells (see Figure 12.5.13).

For More Information: T4-Lymphocytes from Unit 6

Flash animation of an effectorT4-lymphocyte interacting with an activated B-lymphocyte.

html5 version of animation for iPad showing an effectorT4-lymphocyte interacting with an activated B-lymphocyte.

In the case of T4-lymphocytes and T8-lymphocytes, dendritic cells produces cytokines such as interleukin-6 (IL-6), IL-4, IL-12, and T-cell growth factor-beta (TGF-ß) that contribute to proliferation of the activated T-lymphocytes. CD28-dependent co-stimulation of the T4-lymphocyte also stimulates it to synthesize the cytokine interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor. The binding of IL-2 to its high affinity receptor allows for cell proliferation and formation of a clone of thousands of identical T-lymphocytes after several days.

It is thought that in most immune responses, only around 1/1000 to 1/10,000 lymphocytes will have a receptor capable of binding the initiating antigen. Thus, proliferation allows the production of clones of thousands of identical lymphocytes having specificity for the original antigen. This is essential to give enough cells to mount a successful immune response against that antigen.

GIF Animation showing proliferation of a B-lymphocyte.
GIF Animation showing proliferation of a T4-lymphocyte.
GIF Animation showing proliferation of a T8-lymphocyte.

4. The large clones of identical B-lymphocytes, T4-lymphocytes, and T8-lymphocytes now differentiate into effector cells capable of directing body defenses against the original antigen resulting in its destruction or neutralization.

Fundamental Statements for this Step:

1. Cytokines produced by dendritic cells and T4-effector lymphocytes enable the clones of B-lymphocytes and T-lymphocytes above to differentiate into effector cells.
2. In the case of humoral immunity, B-lymphocytes differentiate into effector cells called plasma cells. These cells synthesize and secrete vast quantities of antibodies capable of reacting with and eliminating or neutralizing the original antigen.
3. T4-lymphocytes differentiate into T4-effector lymphocytes. Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Examples include T_H1 cells, T_H2 cells, T_H17 cells, T_{reg} cells, and T_{FH} cells.
4. In the case of cell-mediated immunity, the T8-lymphocytes differentiate into cytotoxic T-lymphocytes (CTLs) capable of destroying body cells having the original epitope on their surface, such as viral infected cells, bacterial infected cells, and

tumor cells by inducing apoptosis.
5. Antibodies, cytokines, activated macrophages, and cytotoxic T-lymphocytes eventually destroy or remove the antigen.

Cytokines produced by dendritic cells and T4-effector lymphocytes enable the clones of B-lymphocytes and T-lymphocytes from step 3 above to differentiate into effector cells.

a. In the case of humoral immunity, B-lymphocytes differentiate into effector cells calledplasma cells. These cells synthesize and secrete vast quantities of antibodies capable of reacting with and eliminating or neutralizing the original antigen (see Figure 12.5.14).

GIF Animation showing proliferation of a B-lymphocyte
and its differentiation into an effector cell.

For More Information: B-Lymphocytes from Unit 6

b. T4-lymphocytes differentiate into T4-effector lymphocytes. Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Immune reactions are typically dominated by five primary types: T_H1 cells, T_H2 cells, T_H17 cells, T_{reg} cells, and T_{FH} cells.

1. CD4 T_H1 cells: Coordinate immunity against intracellular bacteria and promote opsonization. They:

- Produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis, Mycobacterium leprae, Leishmania donovani*, and *Pneumocystis jiroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness.
- They produce cytokines that promote the production of opsonizing antibodies that enhance phagocytosis (see Figure 12.5.15).
- Produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so the can be engulfed and killed by macrophages.
- Produce the cytokine interleukin-2 (IL-2) that induces T-lymphocyte proliferation.
- Produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.
- Produces the chemokine CXCL2 to attract macrophages to the infection site.
- Produce cytokines that block the production of T_H2 cells.

2. CD4 T_H2 cells: Coordinate immunity against helminths and microbes that colonize mucous membranes

- Produce the cytokine interleukin-4 (IL-4) that promotes the production of the antibody isotype IgE in response to helminths and allergens. IgE is able to stick eosinophils to helminths for extracellular killing of the helminth (see Figure 12.5.16); it also promotes many allergic reactions.
- Produce cytokines that attract and activate eosinophils and mast cells.
- Promote the production of antibodies that neutralize microbes (see Figure 12.5.17) and toxins (see Figure 12.5.18) preventing their attachment to host cells.
- Produce cytokines that function as B-lymphocyte growth factors such as IL-4, IL-5, IL-9. and IL-13 (see Figure 12.5.13).
- Produce interleukin-22 (IL-22) that promotes the removal of microbes in mucosal tissues.
- Produce cytokines that block the production of T_H1 cells.

3. CD4 T_H17 cells: Promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes

- Produce cytokines like interleukin-17 (IL-17) and interleukin-6 (IL-6) that trigger local epithelial cells and fibroblasts to produce chemokines that recruit neutrophils to remove extracellular pathogens.

4. CD4 T_{reg} cells: Suppress immune responses

- Produce inhibitory cytokines such as Interleukin-10 (IL-10) and TGF-ß that help to limit immune responses and prevent autoimmunity by suppressing T-lymphocyte activity.

- Promoting anamnestic response (immunologic memory) to resist repeat infections by the same microbe.
- Protecting beneficial normal flora in the intestines from being destroyed by the immune system.
- Aiding in sustaining pregnancy so that the immune system doesn't recognize a fetus as foreign and try to destroy it.
- Controlling established inflammation in tissues.

5. T_{FH} cells: Promote humoral immunity by stimulating antibody production and antibody isotype switching by B-lymphocytes

- T follicular helper cells (T_{FH} cells) are located in lymphoid follicles.
- T_{FH} cells are now thought to be the primary effector T-lymphocytes that stimulate antibody production and isotype switching by B-lymphocytes. They are able to produce cytokines that are characteristic of both T_H2 cells and T_H1 cells.
- T_{FH} cells producing (IFN-?) promote the production of opsonizing antibodies; those producing IL-4 promote the production of IgE.

c. In the case of cell-mediated immunity , the T8-lymphocytes differentiate into cytotoxic T-lymphocytes (CTLs) capable of destroying body cells having the original epitope on their surface, such as viral infected cells, bacterial infected cells, and tumor cells. They do this by inducing apoptosis, a programmed cell suicide (see Figure 12.5.19 and Figure 12.5.20). T-lymphocytes also secrete various cytokines that participate in various aspects of adoptive and innate immunity.

GIF Animation showing proliferation of a T8-lymphocyte and its differentiation into an effector cell.

Flash animation of a CTL triggering apoptosis by way of perforins and granzymes.

html5 version of animation for iPad showing a CTL triggering apoptosis by way of perforins and granzymes.

Flash animation of CTL-induced apoptosis of a virus-infected cell.

html5 version of animation for iPad showing CTL-induced apoptosis of a virus-infected cell.

For More Information: T8-Lymphocytes from Unit 6

For More Information: Cytotoxic T-Lymphocytes from Unit 6

Progeny of the original lymphocytes leave the secondary lymphoid organs and migrate to tissues where they continue to respond to the invading antigen.

Antibodies, cytokines, activated macrophages, and cytotoxic T-lymphocytes eventually destroy or remove the antigen. Antibodies and cytokines amplify defense functions and collaborate with cells of the innate immune system, such as phagocytes and NK cells, as well as with molecules of the innate immune system, such as those of the complement system and the acute phase response. Cytotoxic T-lymphocytes (CTLs) destroy body cells having the original epitope on their surface, e.g., viral infected cells, bacterial infected cells, and tumor cells. Cytokines also amplify innate immune defenses such as inflammation, fever, and the acute phase response.

5. Some of the B-lymphocytes, T4-lymphocytes, and T8-lymphocytes differentiate into long-lived, circulating memory cells.

Fundamental Statements for this Step:

1. During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes and T-lymphocytes stop replicating and become circulating, long-lived memory cells.
2. Memory cells are capable of what is called anamnestic response or "memory", that is, they "remember" the original antigen. If that same antigen again enters the body while the memory cells are still present, these memory cells will

initiate a rapid, heightened secondary response against that antigen.

During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes and T-lymphocytes stop replicating and become circulating, long-lived memory cells. Memory cells are capable of what is called *anamnestic response* or "memory", that is, they "remember" the original antigen. If that same antigen again enters the body while the memory cells are still present, these memory cells will initiate a rapid, heightened secondary response against that antigen (see Figure 12.5.14 and Figure 12.5.21).

This is why the body sometimes develops a permanent immunity after an infectious disease and is also the principle behind immunization.

Concept Map for The General Steps in Adaptive Immunity

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Immune Regulation

The immune responses are carefully regulated by a variety of mechanisms. They are turned on only in response to an antigen and are turned off once the antigen has been removed.

Fundamental Statements for this Process:

1. *The immune responses are carefully regulated by a variety of mechanisms. They are turned on only in response to an antigen and are turned off once the antigen has been removed.*
2. *The immune responses are also able to discriminate between self and non-self in order to prevent autoimmune tissue damage.*
3. *During the random gene-splicing reactions mentioned earlier, some lymphocytes are bound to produce receptors that fit the body's own proteins and polysaccharides. The body develops immunologic tolerance to these self antigens by triggering apoptosis in self-reactive lymphocytes.*
4. *Alternately, immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive. This process is called receptor editing.*
5. *Some autoreactive T-lymphocytes are able to slip through the system but a group of T4-effector lymphocytes called T_{reg} cells are able to suppress their action.*
6. *If there is a breakdown in this normal elimination or suppression of self-reacting cells, autoimmune diseases may develop.*

The immune responses are also able to discriminate between self and non-self in order to prevent autoimmune tissue damage. During the random gene-splicing reactions mentioned earlier, some lymphocytes are bound to produce receptors that fit the body's own proteins and polysaccharides. Through mechanisms that are not fully understood, the body develops immunologic tolerance to these self antigens. In other words, the immune system becomes tolerant of the body's own molecules.

During lymphocyte development, the body eliminates self-reactive lymphocytes. Self-reactive B-lymphocytes undergo negative selection. Since the bone marrow, where the B-lymphocytes are produced and mature, is normally free of foreign substances, any B-lymphocytes that bind substances there must be recognizing "self" and are eliminated by apoptosis, a programmed cell suicide. Apoptosis results in the activation of proteases within the target cell which then degrade the cell's structural proteins and DNA. Alternately, immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive. This process is called receptor editing.

This negative selection also occurs in secondary lymphoid organs whenever a T-dependent B-lymphocyte binds to an antigen but is then unable to react with its specific T-4 lymphocyte because the T4-lymphocyte does not recognize that antigen as foreign.

Self-reactive T-lymphocytes undergo both negative selection and positive selection. Positive selection occurs in the thymus and eliminates T-lymphocytes that cannot recognize MHC molecules. Because T4-lymphocytes and T8-lymphocytes can only recognize peptide epitopes bound to MHC molecules, any T-lymphocytes that cannot recognize MHC molecules fail this positive selection, do not develop any further, and are eventually eliminated. Then, each T-lymphocyte that passes positive selection

by being able to recognize a MHC molecule must undergo negative selection. Any T-lymphocytes recognizing "self" peptides bound to MHC molecules are eliminated by apoptosis. Like with B-lymphocytes, this negative selection also occurs in secondary lymphoid organs whenever a T-lymphocyte binds to a peptide on a MHC molecule but is then unable to react with its specific T-4 lymphocyte because the T4-lymphocyte does not recognize that peptide as foreign.

Some autoreactive T-lymphocytes are able to slip through the system but a group of T4-effector lymphocytes called T_{reg} cells are able to suppress their action. If there is a breakdown in this normal elimination or suppression of self-reacting cells, autoimmune diseases may develop.

We will now look at the various events discussed above in greater detail as they apply to both humoral immunity and cell-mediated immunity with special emphasis on infectious diseases. Keep in mind that some infectious agents live outside human cells (e.g., most bacteria), a few live inside the phagosomes and lysosomes of human cells through which they enter (e.g., *Mycobacterium tuberculosis, Mycobacterium leprae*), and others live in the fluid interior of human cells (e.g., viruses, Rickettsias, and Chlamydias). Through a combination of humoral immunity and cell-mediated immunity, all types of infectious agents, as well as many types of tumor cells, may be eliminated from the body.

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12.E: Introduction to Adaptive Immunity (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

12.1: An Overview of Innate and Adaptive Immunity

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe what is meant by the following:
    a. innate immunity
    b. adaptive (acquired) immunity
2. Define the following:
    a. antigen
    b. immunogen
    c. epitope
    d. humoral immunity
    e. cell-mediated immunity

12.2: Antigens and Epitopes

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

    _____ Asubstance that reacts with antibody molecules and antigen receptors on lymphocytes.

    _____ An antigen that is recognized by the body as non-self and stimulates an adaptive immune response.

    _____ The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes as well as with free antibody molecules.

    _____ An antibody molecule composed of 4 glycoprotein chains whose Fc portion is anchored to the membrane of certain lymphocytes; able to recognize epitopes on protein and polysaccharide antigens.

    _____ A molecule composed of 2 glycoprotein chains anchored to the membrane of certain lymphocytes; able to recognize peptide epitopes from protein antigens presented by the body's own cells by way of MHC molecules.

    ____ Antigens are proteins found within the cytosol of human cells such as viral proteins, proteins from intracellular bacteria, and tumor antigens.

    _____ An organism’s own antigens (self-antigens) that stimulate an autoimmune reaction.

    ____ Antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses.

    a. B-cell receptor
    b. T-cell receptor
    c. immunogen
    d. hapten
    e. epitope
    f. antigen

g. autoantigens
h. endogenous antigens
i. exogenous antigens.

2. Briefly describe how the body recognizes an antigen as foreign.
3. In terms of infectious diseases, describe 2 categories of microbial materials that may act as an antigen.
   a.
   b.
4. Describe 3 groups of noninfectious materials that may act as an antigen.
   a.
   b.
   c.

12.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses

12.3A: Major Histocompatibility Complex (MHC) Molecules

12.3B: Antigen-Presenting Cells (APCs)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of antigen-presenting dendritic cells presenting antigens to naive T4-lymphocytes:

   _____ Dendritic cells engulf _____ antigens.

   _____ Once engulfed by dendritic cells, protein antigens are degraded into peptides by organelles called _____.

   _____ Dendritic cells bind peptides to grooves in _____.

   _____ The dendritic cell then presents the MHC/peptide complex to the _____.

   _____ Dendritic cells produce co-stimulatory signals after pathogen-associated molecular patterns bind to _____.

   a. TCR of T4-lymphocytes
   b. TCR of T8-lymphocytes
   c. MHC-I molecules
   d. MHC-II molecules
   e. exogenous
   f. endogenous
   g. toll-like receptors
   h. lysosomes
   i. proteasomes
   j. cytosol

2. Match the following in terms of ntigen-presenting dendritic cells presenting antigens to naive T8-lymphocytes:

   _____ Dendritic cells engulf _____ antigens.

   _____ Once engulfed by dendritic cells, protein antigens are degraded into peptides by organelles called _____.

   _____ Some proteins escape from phagosomes and phagolysosomes into the _____.

   _____ Once in the cytosol, protein antigens are degraded into peptides by organelles called _____.

   _____ Dendritic cells then bind peptides to grooves in _____.

_____ The Dendritic cell then presents the MHC/peptide complex to the _____.

a. TCR of T4-lymphocytes
b. TCR of T8-lymphocytes
c. MHC-I molecules
d. MHC-II molecules
e. exogenous
f. endogenous
g. toll-like receptors
h. lysosomes
i. proteasomes
j. cytosol

3. Name the primary type of cell that functions as an antigen-presenting cell to naive T4-lymphocytes and naive T8-lymphocytes.
4. State the role of T4-effector cells in activating macrophages .
5. State the role of T4-effector cells in the proliferation and differentiation of activated B-lymphocytes.

12.3C: T4-Lymphocytes (T4-Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of activation and function of T4-lymphocytes:

_____ Epitopes of antigens are recognized by T4-lymphocytes by way of their _____.

_____ The TCR/CD4 molecules of T4-lymphocytes recognize _____ on antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B-lymphocytes.

a. peptides from exogenous antigens bound to MHC-II molecules
b. peptides from endogenous antigens bound to MHC-I molecules
c. MHC-I molecules
d. toll-like receptors
e. B-cell receptors
f. T-cell receptors
g. plasma cells
h. lysosomes
i. proteasomes

2. Matching

_____ Promote cell-mediated immunity against intracellular pathogens; enhance the killing ability of macrophages, promote diapedesis and chemotaxis of macrophages, and promote the production of opsonizing antibodies.

_____ Help to limit immune responses and prevent autoimmunity by suppressing T-lymphocyte activies, promote immune memory, help to sustain pregnancy, and control established inflammation.

_____ Promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes.

_____ Promote the production of the antibody isotype IgE in response to helminthsand allergens, attract and activate eosinophils and mast cells, promote the production of antibodies that neutralize microbesand toxins, and promote the removal of microbes in mucosal tissues.

A. CD4 T_H2 cells
B. CD4 T_H1 cells
C. CD4 T_{reg} cells
D. CD4 T_H17 cells
E. CD4 T_{FH} cells

12.3D: T8-Lymphocytes (T8-Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of activation and function of T8-lymphocytes:

   _____ Epitopes of antigens are recognized by T8-lymphocytes by way of their _____.

   _____ The TCR/CD8 molecules of naive T8-lymphocytes recognize _____ on antigen-presenting dendritic cells.

   _____ After activation, T8-lymphocytes proliferate and differentiate into _____

   a. peptides from exogenous antigens bound to MHC-II molecules
   b. peptides from endogenous antigens bound to MHC-I molecules
   c. MHC-I molecules
   d. toll-like receptors
   e. B-cell receptors
   f. T-cell receptors
   g. plasma cells
   h. cytotoxic T-lymphocytes (CTLs)
   i. natural killer cells (NK cells)
2. State the overall function of activated T8-lymphocytes in adaptive immunity.

12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Epitopes of glycolipid antigens are recognized by iNKT lymphocytes by way of their _____.
2. The TCR molecules of iNKT lymphocytes recognize _____ on antigen-presenting dendritic cells.
3. iNKT lymphocytes can also be activated by the cytokine _____ produced by activated dendritic cells.
4. iNKT cells promote both innate and adaptive immunity and may also regulate immune responses by way of the _____ they produce once activated.

12.3F: B-Lymphocytes (B-Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of activation of B-lymphocytes by T-dependent antigens:

   _____ Epitopes of antigens are recognized by B-lymphocytes by way of their _____.

   _____ Once engulfed by APCs, protein antigens are degraded into peptides by organelles called _____.

   _____ B-lymphocytes bind peptides to grooves in _____.

   _____ The B-lymphocyte then presents the MHC/peptide complex to the _____.

   _____ B-lymphocytes eventually differentiate into antibody-secreting cells called _____.

   a. TCR of T4-lymphocytes
   b. TCR of T8-lymphocytes
   c. MHC-I molecules
   d. MHC-II molecules
   e. B-cell receptors

f. CD4 molecules
g. plasma cells
h. lysosomes
i. proteasomes

2. State the overall function of B-lymphocytes in adaptive immunity.

12.3G: Natural Killer Cells (NK Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe how NK cells bind to and kill infected cells and tumor cells through ADCC.
2. Briefly describe how NK cells recognize and kill infected cells and tumor cells that suppress MHC-I production.

12.3A: Major Histocompatibility Complex (MHC) Molecules

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

_____ Produced by all nucleated cells in the body.

_____ Produced primarily by antigen-presenting cells such as macrophages, dendritic cells, and B-lymphocytes.

_____ Primarily bind peptides from exogenous antigens.

_____ Primarily bind peptides from endogenous antigens.

_____ Recognize peptides bound to MHC-II molecules.

_____ Recognize peptides bound to MHC-I molecules.

a. TCR of T4-lymphocytes
b. TCR of T8-lymphocytes
c. MHC-I molecules
d. MHC-II molecules

2. State the role of proteasomes in binding of peptides from endogenous antigens by MHC-I molecules.
3. State the role of lysosomes in binding of peptides from exogenous antigens by MHC-II molecules.
4. Multiple Choice

12.3B: Antigen-Presenting Cells (APCs)

12.3C: T4-Lymphocytes (T4-Cells)

12.3D: T8-Lymphocytes (T8-Cells)

12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

12.3F: B-Lymphocytes (B-Cells)

12.3G: Natural Killer Cells (NK Cells)

12.4: The Lymphoid System

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following with the BEST answer:

   _____ Contain antigen-presenting cells, such as macrophages and dendritic cells, and ever changing populations ofB-lymphocytes and T- lymphocytes. Examples include the tonsils, the appendix, Peyer's patches, MALT, SALT, lymph nodes, and the spleen.

   _____ Produce B-lymphocytes and T-lymphocytes. The bone marrow and the thymus.

   _____ The fluid surrounding cells in the body.

   _____ The liquid portion of the blood.

   _____ A diffuse system of small concentrations of lymphoid tissue found in various sites of the body such as the gastrointestinal tract, respiratory tract, eye, and skin. It is populated by loose clusters of T-lymphocytes, B-lymphocytes, plasma cells, activated T_H cells, and macrophages.

   _____ The liquid found in lymph vessels.

   _____ Expose antigens found in the lymph to dendritic cells, B-lymphocytes, and T-lymphocytes.

   _____ Expose antigens found in the blood to dendritic cells, B-lymphocytes, and T-lymphocytes.

   a. plasma
   b. lymph
   c. tissue fluid
   d. primary lymphoid organs
   e. secondary lymphoid organs
   f. the spleen
   g. lymph nodes
   h. MALT
2. Briefly describe the importance of the lymphoid system in adaptive immune responses.

12.5: An Overview of the Steps Involved in Adaptive Immune Responses

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write

them out. This will not test your understanding of this tutorial.

1. State where antigens may encounter APCs, B-lymphocytes, and T-lymphocytes if they enter the following:
   a. the blood
   b. tissues
   c. the respiratory tract
   d. the gastrointestinal tract
   e. the genitourinary tract
2. Match the following:

   _____ Use lysosomes to degrade exogenous antigens into peptides, bind them to MHC-II molecules, and present them to naive T4-lymphocytes.

   _____ Uses BCR to recognize epitopes of antigens; a few antigens are recognized by toll-like receptors.

   _____ Uses TCR and CD4 to recognize peptide epitopes from exogenous antigens bound to MHC-II molecules of antigen-presenting dendritic cells, macrophages, and B-lymphocytes.

   _____ Uses TCR and CD8 to recognize peptide epitopes from endogenous antigens bound to MHC-I molecules of cells.

   _____ Cells that allow for a heightened secondary response upon subsequent exposure to the same antigen.

   _____ Once activated itself, secretes cytokines that enable activated B-lymphocytes and T-lymphocytes to proliferate and differentiate.

   _____ Use proteasomes to degrade endogenous antigens into peptides, bind them to MHC-I molecules, and present them to naive T8-lymphocytes.

   _____ Differentiate into antibody secreting plasma cells.

   _____ Differentiate into cytotoxic T-lymphocytes (CTLs).

   a. T4-lymphocytes
   b. T8-lymphocytes
   c. dendritic cells
   d. B-lymphocytes
   e. memory cells
3. State the overall function of T4-effector lymphocytes and the importance behind rapid proliferation of activated lymphocytes.
4. The ability of the body to initiate and direct adaptive immune responses against antigenic molecules foreign to the body but not against antigenic molecules that are a normal component of the body is called _____.

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13.1: ANTIBODIES (IMMUNOGLOBULINS)

Humoral Immunity refers to the production of antibody molecules in response to an antigen. These antibody molecules circulate in the plasma of the blood and enter tissue and organs via the inflammatory response. Humoral immunity is most effective microbes or their toxins located in the extracellular spaces of the body. Antibodies or immunoglobulins are specific glycoprotein configurations produced by B-lymphocytes and plasma cells in response to a specific antigen and capable of reacting with that antigen. In this section we will look at the structure of antibodies, the 5 classes or isotypes of human antibodies, generation of antibody diversity, clonal selection and clonal expansion, and memory (anamnestic) response.



- Topic hierarchy

13.1B: Antibody Structure

13.1C: The 5 Classes (Isotypes) of Human Antibodies

13.1D: Generation of Antibody Diversity

13.1E: Clonal Selection and Clonal Expansion

13.1F: Anamnestic (Memory) Response

Template:HideTOC

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13.1B: Antibody Structure

Learning Objectives

1. Describe an antibody molecule.
2. Draw the "stick figure" structure of IgG, indicating the Fab portion (variable region) and the Fc portion (constant region).
3. State the functions of the Fab and the Fc portions of an antibody.
4. State what is meant by the biological activity of an antibody.
5. Compare the structure of IgM and secretory IgA with that of IgG.

In this section we will look at the structure of antibodies. There are five classes or isotypes of human antibodies :

a. immunoglobulin G (IgG),
b. immunoglobulin M (IgM),
c. immunoglobulin A (IgA),
d. immunoglobulin D (IgD), and
e. immunoglobulin E (IgE).

The simplest antibodies, such as IgG, IgD, and IgE, are "Y"-shaped macromolecules called monomers. A monomer is composed of four glycoprotein chains: two identical heavy chains and two identical light chains. The two heavy chains have a high molecular weight that varies with the class of antibody. The light chains come in two varieties: kappa or lambda and have a lower molecular weight than the heavy chains. The four glycoprotein chains are connected to one another by disulfide (S-S) bonds and non-covalent bonds (Figure $13.1B.1$).

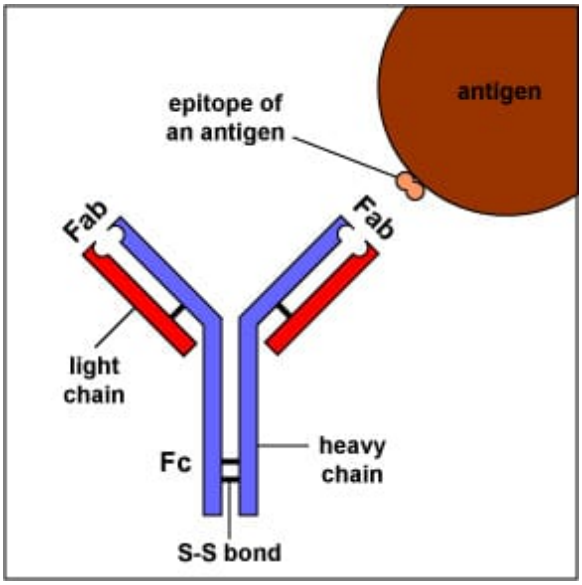


Figure $13.1B.1$: IgG.The Fab portion of the antibody has specificity for binding an epitope of an antigen. The Fc portion directs the biological activity of the antibody.

Additional S-S bonds fold the individual glycoprotein chains into a number of distinct globular domains (Figure $13.1B.2$). The area where the top of the "Y" joins the bottom is called the hinge. This area is flexible to enable the antibody to bind to pairs of epitopes various distances apart on an antigen.

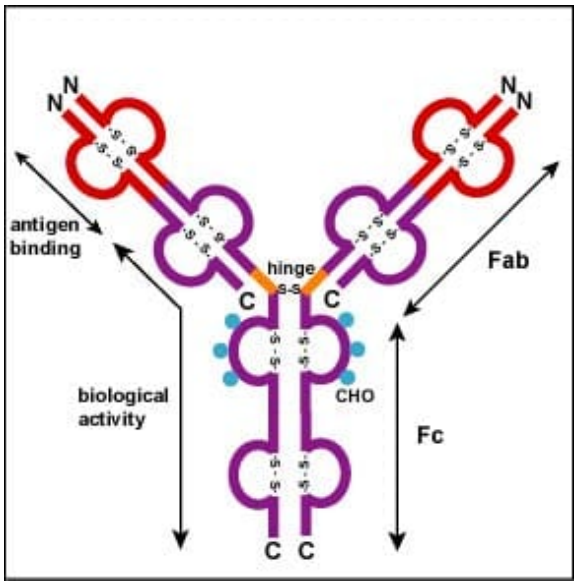


Figure 13.1B.2: Folding Domains of an Antibody. The Fab portion of the antibody, the first domain of the antibody shown in red has the complementarity-determining regions providing specificity for binding an epitope of an antigen. The Fc portion, shown in purple directs the biological activity of the antibody. (S-S = disulfide bond; N = amino terminal of glycoprotein; C = carboxy terminal of glycoprotein; CHO = carbohydrate.)

The two tips of the "Y" monomer are referred to as the antigen-binding fragments or Fab portions of the antibody (Figures 1-3). The first 110 amino acids or first domain of both the heavy and light chain of the Fab region of the antibody provide specificity for binding an epitope on an antigen. The amino acid sequence of this first domain of both the light chain and the heavy chain shows tremendous variation from antibody to antibody and constitutes the variable region (V region). This is because each B-lymphocyte, early in its development, becomes genetically programmed through a series of gene-splicing reactions to produce a Fab with a unique 3-dimensional shape capable of fitting some epitope with a corresponding shape.

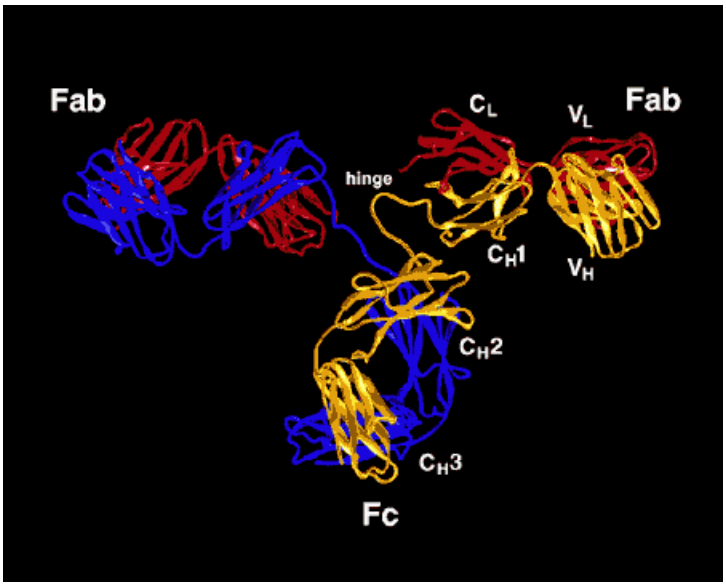


Figure 13.1B.3***:*** *Ribbon Drawing of the Antibody Molecule IgG2a, A ribbon drawing of the first intact antibody molecule ever crystallized (IgG2a). The Fab portion of the antibody has specificity for binding an epitope of an antigen. The Fc portion directs the biological activity of the antibody.*

The various genes the cell splices together determine the order of amino acids of the Fab portion of both the light and heavy chain; the amino acid sequence determines the final 3-dimensional shape (Figure 13.1B.4). Therefore, different antibody molecules produced by different B-lymphocytes will have different orders of amino acids at the tips of the Fab to give them unique shapes for binding epitope. The antigen-binding site is large enough to hold an epitope of about 5-7 amino acids or 3-4 sugar

residues. Epitopes bind to the Fab portion of the antibody by reversible, non-covalent bonds.

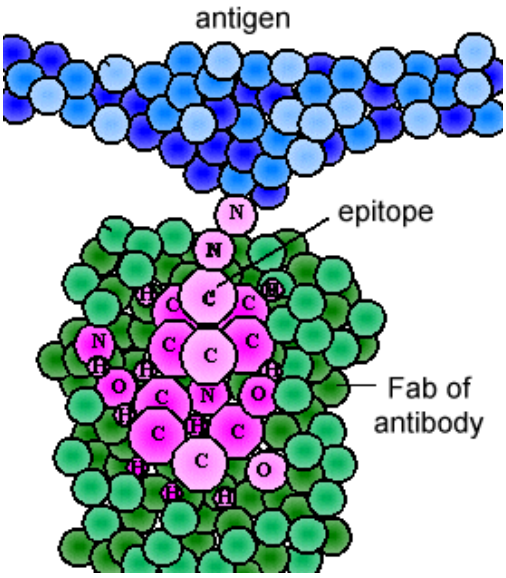


Figure $13.1B.4$: Epitope of an Antigen Binding to Fab of an Antibody

The bottom part of the "Y", the C terminal region of each glycoprotein chain, is called the Fc portion. The Fc portion, as well as one domain of both the heavy and light chain of the Fab region has a constant amino acid sequence and is referred to as the constant region (C region) of the antibody and defines the class and subclass of each antibody. The Fc portion is responsible for the biological activity of the antibody (Figures 1-3), however, the Fc portion only becomes biologically active after the Fab component has bound to its corresponding antigen. Depending on the class and subclass of antibody, biological activities of the Fc portion of antibodies include the ability to:

- Activate the classical complement pathway (IgG & IgM); see Figure $13.1B.5$.
- Activate the lectin complement pathway and the alternative complement pathway (IgA)
- Bind to receptors on phagocytes (IgG); see Figure $13.1B.6$.
- Bind to receptors on mast cells, basophils, and eosinophils (IgE); see Fig 7 and Figure $13.1B.8$.
- Bind to receptors on NK cells (IgG); see Figure $13.1B.9$.
- Determine the tissue distribution of the antibodies, that is, to what tissues types the antibody molecules are able to go.



Figure $13.1B.12$: Rotating GIF Animation of Humanized IgG

Individual "Y"-shaped antibody molecules are called monomers and can bind to two identical epitopes. Antibodies of the classes IgG, IgD, and IgE are monomers.

Two classes of antibodies are more complex. IgM (see Figure $13.1B.10$) is a pentamer, consisting of 5 "Y"-like molecules connected at their Fc portions by a "J" or joining chain. Secretory IgA (see Figure $13.1B.11$) is a dimer consisting of 2 "Y"-like molecules connected at their Fc portions by a "J" chain and stabilized to resist enzymatic digestion in body secretions by means of a secretory component.

Summary

1. There are 5 classes or isotypes of human antibodies or immunoglobulins: IgG, IgM, IgA, IgD, and IgE.
2. The simplest antibodies, such as IgG, IgD, and IgE, are "Y"-shaped macromolecules called monomers and are composed of four glycoprotein chains: two identical heavy chains and two identical light chains.
3. The two tips of the "Y" monomer are referred to as the antigen-binding fragments or Fab portions of the antibody and these portions provide specificity for binding an epitope on an antigen.
4. Early in its development, each B-lymphocyte becomes genetically programmed through a series of gene-splicing reactions to produce a Fab with a unique 3-dimensional shape capable of fitting some epitope with a corresponding shape.
5. The Fc portion only becomes biologically active after the Fab component has bound to its corresponding antigen. Biological activities include activating the complement pathways, and binding to receptors on phagocytes and other defense cells to promote adaptive immunity.
6. IgM is a pentamer, consisting of 5 monomers joined at their Fc portions.
7. IgA is a dimer, consisting of 2 monomers joined at their Fc portions.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe an antibody molecule. *(ans)*
2. Match the following:

    ____ The region of the antibody that provide specificity for binding an epitope on an antigen. *(ans)*

    _____ The region of the antibody that is responsible for the biological activity of the antibody. *(ans)*

    _____ Composed of four glycoprotein chains. There are two identical heavy chains having a high molecular weight and two identical light chains. *(ans)*

    _____ A pentamer, consisting of 5 "Y"-like molecules connected at their Fc portions by a "J" or joining chain. *(ans)*

    _____ A dimer consisting of 2 "Y"-like molecules connected at their Fc portions by a "J" chain and stabilized to resist enzymatic digestion. *(ans)*

    a. IgM
    b. secretory IgA
    c. IgG
    d. Fab
    e. Fc
3. Multiple Choice *(ans)*

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13.1C: The 5 Classes (Isotypes) of Human Antibodies

State which classes (isotypes) of human antibodies possess the following characteristics:

a. are monomers
b. is a pentamer
c. is a dimer
d. activates the classical complement pathway by its Fc portion
e. binds to macrophages and neutrophils by its Fc portion
f. binds to NK cells by its Fc portion
g. crosses the placenta
h. functions as a B-cell receptor
i. the first antibody produced during an adaptive immune response
j. binds to components of mucous by its Fc portion
k. found mainly in body secretions
l. binds to mast cells and basophils by its Fc portion and promotes inflammation, coughing, sneezing, vomiting, and allergic reactions
m. binds to eosinophils by its Fc portion and promotes the removal of parasitic worms and arthropods

Match the antibody isotype with its description.

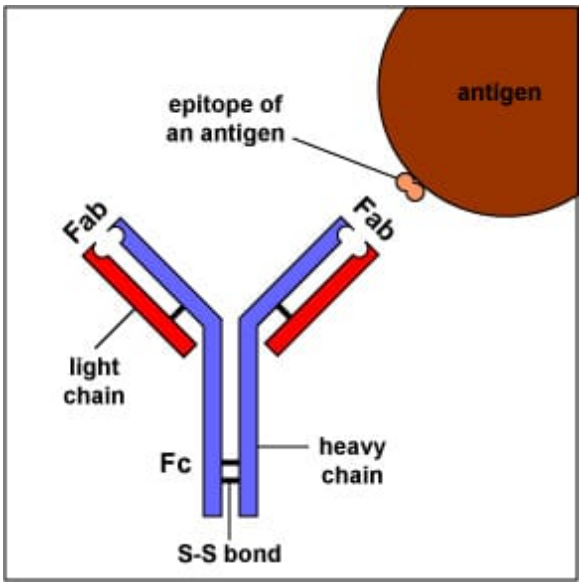


Figure 13.1C.13.3.3: Opsonization (Enhanced Attachment). The Fab portion of IgG binds to epitopes of an antigen. The Fc portion can now attach the antigen to Fc receptors on phagocytes for enhanced attachment. This is especially important against encapsulated microbes. C3b and C4b from the complement pathways can also attach antigens to phagocytes.

For More Information: Classical complement pathway from Unit 5

For More Information: Opsonization from Unit 6

For More Information: Antibody-dependent cellular cytotoxicity (ADCC) from Unit 6

IgM (Immunoglobulin M)

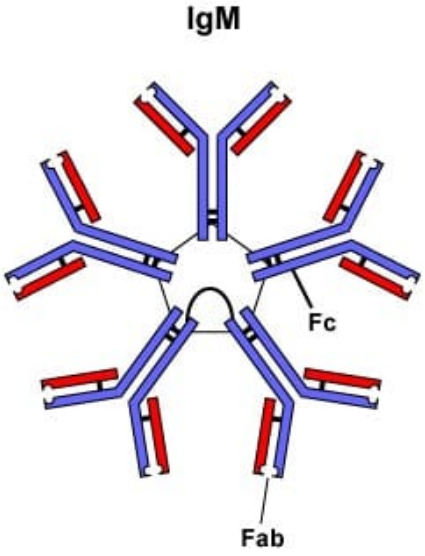


Figure 13.1C.13.3.6).

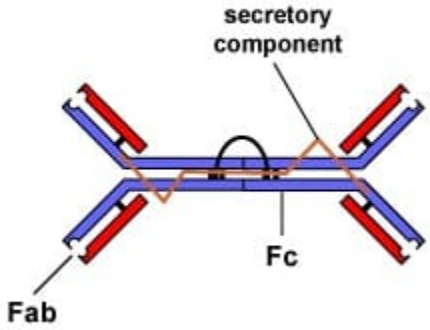


Figure 13.1C.13.3.6: Secretory IgA is a dimer and has 4 Fab sites. A secretory component helps protect it from digestion in body secretions.

The Fc portion of secretory IgA binds to components of mucous and contributes to the ability of mucous to trap microbes. The Fc portion of secretory IgA can bind to macrophages and neutrophils for enhanced attachment (opsonization). IgA can activate the lectin complement pathway and the alternative complement pathway.

IgD: (Immunoglobulin D)

IgD makes up approximately 0.2% of the serum antibodies. IgD is a monomer and has 2 epitope-binding sites and is found on the surface of B-lymphocytes (along with monomeric IgM) as a B-cell receptor where it may control of B-lymphocyte activation and suppression. IgD may play a role in eliminating B-lymphocytes generating self-reactive autoantibodies.

IgE (Immunoglobulin E)

IgE makes up about 0.002% of the serum antibodies with a half-life of 2 days. Most IgE is tightly bound to basophils and mast cells via its Fc region . IgE is a monomer and has 2 epitope-binding sites. IgE is made in response to parasitic worms (helminths) and arthropods. It is also often made in response to allergens(allergens are antigens causing allergic reactions). IgE may protect external mucosal surfaces by promoting inflammation, enabling IgG, complement proteins, and leukocytes to enter the tissues, as well as by triggering coughing, sneezing, and vomiting for mechanical removal of microbes and toxins. .

The Fc portion of IgE can bind to mast cells and basophils where it mediates many allergic reactions. Cross linking of cell-bound IgE by antigen triggers the release of vasodilators for an inflammatory response (Fig 7). The Fc portion of IgE made against

parasitic worms and arthropods can bind to eosinophils enabling opsonization (Figure $13.1C.8$). This is a major defense against parasitic worms and arthropods.

For More Information: IgE-mediated hypersensitivity (Type-I) from Unit 6

Each day an average adult produces approximately three grams of antibodies, about two-thirds of this IgA.

Summary

1. IgG makes up approximately 80% of the serum antibodies, is a monomer with 2 Fab sites. The Fc portion can activate the classical complement pathway, bind to macrophages and neutrophils to enable opsonization, bind to NK cells to promote ADCC, and can cross the placenta.
2. IgM makes up approximately 13% of the serum antibodies, is the first antibody produced during an immune response, is found mainly in the blood, and is a pentamer with 10 Fab sites. The Fc portion can activate the classical complement pathway. Monomeric forms of IgM are found on the surface of B-lymphocytes as B-cell receptors.
3. IgA makes up approximately 6% of the serum antibodies, is a dimer with 4 epitope-binding sites and is found mainly in body secretions as secretory IgA (sIgA) where it protects internal body surfaces exposed to the environment by blocking the attachment of bacteria and viruses to mucous membranes.
4. The Fc portion of secretory IgA binds to components of mucous and contributes to the ability of mucous to trap microbes, and can bind to macrophages and neutrophils to enable opsonization, and can activate the lectin complement pathway and the alternative complement pathway.
5. IgD makes up approximately 0.2% of the serum antibodies, is a monomer with 2 Fab sites, is found on the surface of B-lymphocytes as a B-cell receptor, and may play a role in eliminating B-lymphocytes generating self-reactive autoantibodies.
6. IgE makes up about 0.002% of the serum antibodies, is a monomer with 2 Fab sites, and is made in response to parasitic worms (helminths) and arthropods. It is also often made in response to allergens. The Fc portion of IgE can bind to mast cells and basophils (see Figure $13.1C.8$) where it mediates many allergic reactions, and the Fc portion of IgE made against parasitic worms can bind to eosinophils enabling opsonization. IgE may also protect external mucosal surfaces by promoting inflammation.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the class (isotype) of human antibody with its description.
2. Multiple Choice *(ans)*

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13.1D: Generation of Antibody Diversity

Define gene translocation and relate it to each B-lymphocyte being able to produce an antibody with a unique shaped Fab.

- Define the following:

  a. combinatorial diversity
  b. junctional diversity
  c. affinity maturation

In this section we will look at generation of antibody diversity through gene translocation. As mentioned earlier, the immune system of the body has no idea as to what antigens it may eventually encounter. Therefore, it has evolved a system that possesses the capability of responding to any conceivable antigen. The immune system can do this because both B-lymphocytes and T-lymphocytes have evolved a unique system of gene-splicing called gene translocation, a type of gene-shuffling process where various different genes along a chromosome are cut out of one location and joined with other genes along the chromosome.

To demonstrate this gene translocation process, we will look at how each B-lymphocyte becomes genetically programmed to produce an antibody functioning as a B-cell receptor(BCR) having a unique shaped Fab. As mentioned above, the Fab portion of an antibody is composed of 2 protein chains: a heavy and a light (see Figure $13.1D.1$).

The variable heavy chain portion of the Fab is coded for by a combination of 3 genes, called VH (variable heavy), DH (diversity heavy), and JH (joining heavy). The variable light chain portion of the Fab consists of either a kappa chain or a lambda chain coded for by a combination of 2 genes, VL (variable light) and JL (joining light). In the DNA of each B-lymphocyte there are multiple forms of each one of these variable determinant genes. Although the exact number of each gene isn't known and varies from person, there are approximately 38-46 VH genes; 23 DH genes; 6 JH genes; 34-38 kappa VL genes; 5 kappa JL genes; 29-33 lambda VL genes; and 4-5 lambda JL genes.

While a person inherits alleles for the various V(D)J genes from each parent, an individual B-lymphocyte will only express an inherited allele set from one parent. This increases a greater diversity of antibodies in that individual.

Through random gene translocation, any combination of the multiple forms of each gene can join together (see Figure $13.1D.2$) resulting in thousands of possible gene combinations. This is known as combinatorial diversity.

Gene translocation of the V(D)J genes is initiated when an enzyme called V(D)J recombinase recognizes recombination signal sequences located at the 3' end of V genes, the 5' end of J genes, and both ends of D genes. As a result, the chromosome forms a loop allowing different genes from different regions along the chromosome to align (see Figure $13.1D.3$). In the heavy chain any J-heavy gene and any D-heavy gene align and bind together as the genes are cut from one location and pasted into another. Subsequently, any one of the V-heavy genes is attached to this DJ segment. In the light chain, chromosomal looping enables any V-light gene to attach to any J-light gene.

Flash animation showing gene translocation and combinatorial diversity.

html5 version of animation for iPad showing gene translocation and combinatorial diversity.

During gene translocation, specialized enzymes in the B-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions. This change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called junctional diversity.

Furthermore, as B-lymphocytes proliferate, they undergo affinity maturation, a process that "fine tunes" the shape of the Fab epitope binding site. This is because the immunoglobulin V genes of B-lymphocytes have a mutation rate between 1000 to 10,000 times greater than other human genes in the body. This somatic hypermutation creates a great opportunity for selection

of variant B-lymphocytes with even better fitting antigen-binding sites that fit the epitope more precisely. The longer and more tightly the antigen binds to the B-cell receptor, the greater the chance that B-lymphocyte has of surviving and replicating. In other words, the "fit" of the antibody can be improved over time. Affinity maturation occurs in the germinal centers of the lymph nodes.

Most likely humans produce at least 10^{11} different shaped BCRs. Keep in mind that the 3-dimensional shape of a protein is ultimately determined by the sequence of its amino acids and the sequence of amino acids is determined by the order of nitrogenous bases in the genes coding for that protein. Between combinatorial diversity, junctional diversity, and affinity maturation, there are probably billions of possible gene combinations and rearrangements that can code for the Fab portions of an antibody. Chances are, then, each B-lymphocyte will carry out a unique series of gene translocations and be able to produce an antibody with a unique shaped epitope-binding site.

Because gene translocation is a random process, some immature B-lymphocytes do wind up making B-cell receptors that fit the body's own antigens. Immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive. Recognition of self antigen can reactivate genes that allow the B-lymphocyte to carry out new light chain V-J recombinations and enabling that cell to express a new B-cell receptor. This process is called receptor editing.

Alternately, self-reactive B-lymphocytes can also undergo negative selection. Since the bone marrow, where the B-lymphocytes are produced and mature, is normally free of foreign substances, any B-lymphocytes that bind substances there must be recognizing "self" and are eliminated by apoptosis, a programmed cell suicide. Apoptosis results in the activation of proteases within the target cell which then degrade the cell's structural proteins and DNA.

Summary

1. The adaptive immune responses have evolved a system that possesses the capability of responding to any conceivable antigen the body might eventually encounter through a process called gene translocation.
2. Gene translocation is a type of gene-shuffling process where various different genes along a chromosome are cut out of one location and joined with other genes along the chromosome to create a maximum number of different B-cell and T-cell receptors.
3. Each B-lymphocyte becomes genetically programmed to produce an antibody functioning as a B-cell receptor (BCR) having a unique shaped Fab.
4. The variable portion of both the heavy and light chain of the antibody is coded for by multiple genes and there are multiple forms of each one of these variable genes.
5. Through random gene translocations, any combination of the multiple forms of each gene can join together resulting in thousands of possible gene combinations. This is known as combinatorial diversity.
6. During gene translocation, specialized enzymes in the B-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions and this change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called junctional diversity.
7. As B-lymphocytes proliferate, they undergo affinity maturation, a process that "fine tunes" the shape of the Fab epitope binding site through a high rate of somatic hypermutation. This creates a great opportunity for selection of variant B-lymphocytes with even better fitting antigen-binding sites that fit the epitope more precisely.
8. Immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive through a process called receptor editing. Alternately, self-reactive B-lymphocytes can also undergo negative selection whereby any B-lymphocytes that bind substances recognized as "self" and are eliminated by apoptosis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define gene translocation. *(ans)*
2. Relate gene translocation to each B-lymphocyte being able to produce an antibody with a unique shaped Fab. (ans)
3. Define the following:
   a. combinatorial diversity *(ans)*
   b. affinity maturation *(ans)*

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13.1E: Clonal Selection and Clonal Expansion

Learning Objectives

- Briefly describe the process of clonal selection and clonal expansion.

As mentioned above, during early differentiation of naive B-lymphocytes in the bone marrow, each B-lymphocyte becomes genetically programmed to make an antibody with a unique antigen-binding site (Fab) through a series of gene translocations, and molecules of that antibody are put on its surface to function as the B-cell receptor (Figure $13.1E.1$).

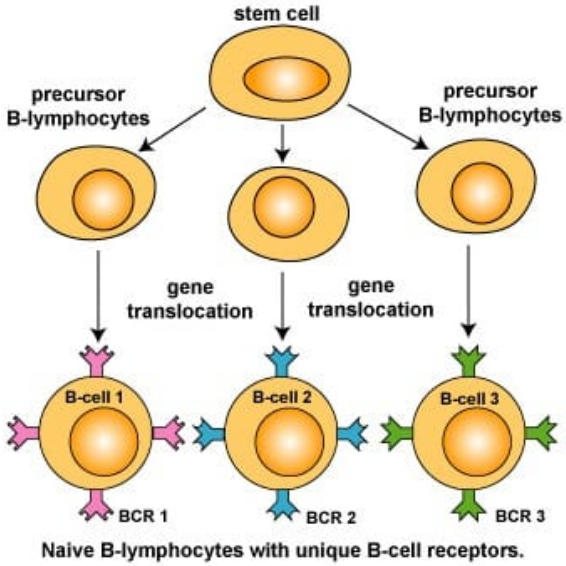


Figure $13.1E.1$: Clonal Selection, Step-1. During its development, each B-lymphocyte becomes genetically programmed, through a process called gene translocation, to make a unique B-cell receptor. Molecules of that B-cell receptor are placed on its surface where it can react with epitopes of an antigen.

When an antigen encounters the immune system, its epitopes eventually will react only with B-lymphocytes with B-cell receptors on their surface that more or less fit and this activates those B-lymphocytes. This process is known as *clonal selection* (Figure $13.1E.2$).

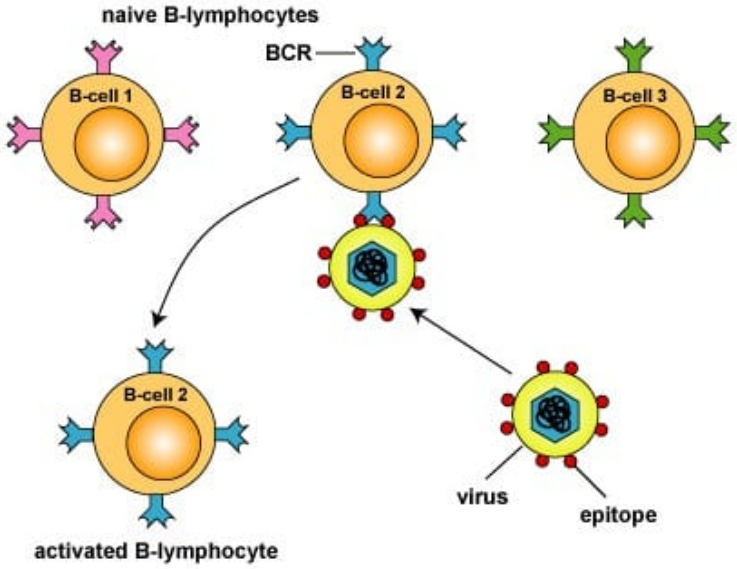


Figure $13.1E.2$: Clonal Selection, Step-2. A B-lymphocyte with an appropriately fitting B-cell receptor can now react with epitopes of an antigen having a corresponding shape. This activates the B-lymphocyte.

Cytokines produced by effector T4-helper lymphocytes enable those activated B-lymphocytes to rapidly proliferate to produce large clones of thousands of identical B-lymphocytes. In this way, even though only a few B-lymphocytes in the body may have an antibody molecule able to fit a particular epitope, eventually many thousands of cells are produced with the right specificity. This is referred to as *clonal expansion* (Figure $13.1E.3$).

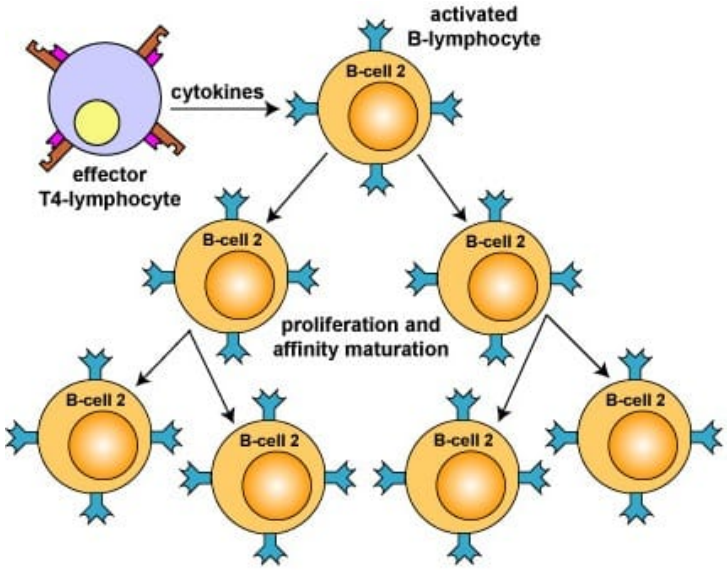


Figure $13.1E.3$: Clonal Expansion. Cytokines from an effector T4-lymphocyte now enable the activated B-lymphocyte to proliferate into a large clone of identical B-lymphocytes. During this time, "fine-tuning" of the B-cell receptor occurs through affinity maturation.

Furthermore, as the B-lymphocytes proliferate, they undergo affinity maturation as a result of somatic hypermutations. This allows the B-lymphocytes to "fine-tune" the shape of the antibody for better fit with the original epitope. B-lymphocytes having better fitting B-cell receptor on their surface bind epitope longer and more tightly allowing these cells to selectively replicate. Eventually these variant B-lymphocytes differentiate intoplasma cells that synthesize and secrete vast quantities of antibodies that have Fab sites which fit the original epitope very precisely (Figure $13.1E.4$). It generally takes 4-5 days for a naive B-lymphocyte that has been activated to complete clonal expansion and differentiate into effector B-lymphocytes.

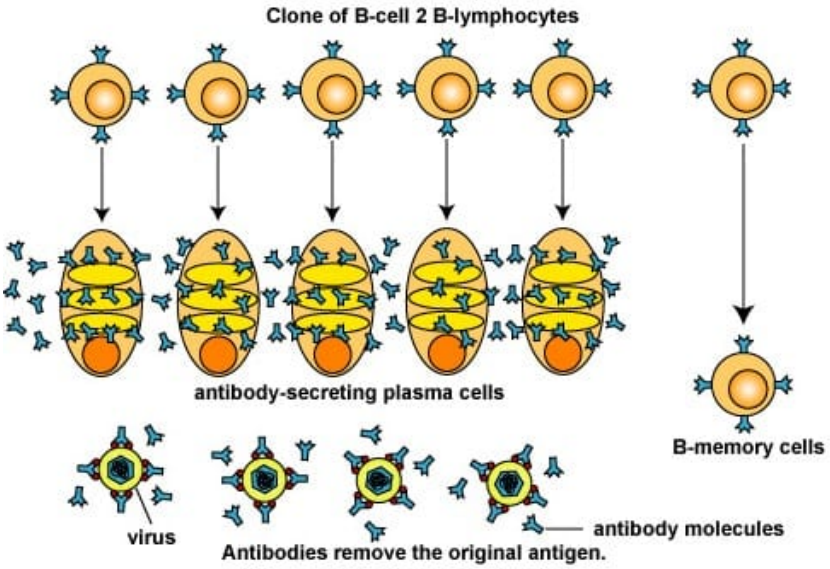
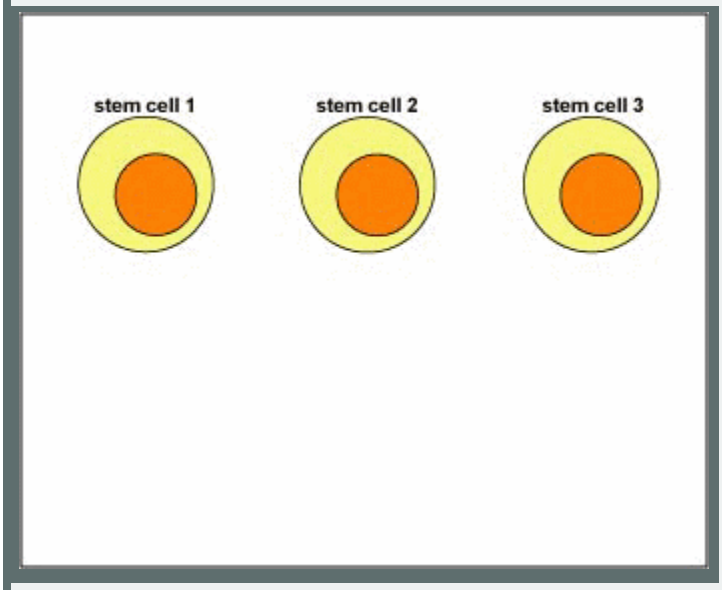


Figure $13.1E.4$: Differentiation of B-lymphocytes into Plasma Cells and B-Memory Cells. The B-lymphocytes now differentiate into antibody-secreting B-lymphocytes and plasma cells that secrete large quantities of antibodies that "fit" the original epitope. Some B-lymphocytes differentiate into B-memory cells capable of anamnestic response.

A single activated B-lymphocyte can, within seven days, give rise to approximately 4000 antibody-secreting cells. Over 2000 antibody molecules can be produced per plasma cell per second for typically up to four to five days. The B-memory cells that eventually form also have these high affinity antibodies on their surface.

Animation Overview: Clonal Selection and Clonal Expansion



During its development, each B-lymphocyte becomes genetically programmed, through a process called gene translocation, to make a unique antibody molecule that will function as a B-cell receptor. Molecules of that antibody are then placed on the cell's surface where it can react with epitopes of an antigen. A B-lymphocyte with an appropriately fitting B-cell receptor can now react with epitopes of an antigen having a corresponding shape. This activates the B-lymphocyte. Cytokines from an activated T4-lymphocyte now enable the activated B-lymphocyte to proliferate into a large clone of identical B-lymphocytes. During this time, "fine-tuning" of the B-cell receptor

occurs as a result of affinity maturation. The B-lymphocytes now differentiate into antibody-secreting B-lymphocytes and plasma cells that secrete large quantities of antibodies "fitting" the original epitope. Some B-lymphocytes differentiate into B-memory cells capable of anamnestic response.

As with naive B-lymphocytes, during its development, each naive T4-lymphocyte becomes genetically programmed by gene-splicing reactions similar to those in B-lymphocytes, to produce a TCR with a unique specificity. Identical molecules of that TCR are placed on its surface where they are able to bind an epitope/MHC-II complex on an antigen-presenting dendritic cell with a corresponding shape (Figure $13.1E.5$). This is clonal selection of the T4-lymphocytes that are required for the body's response to T-dependent antigens.

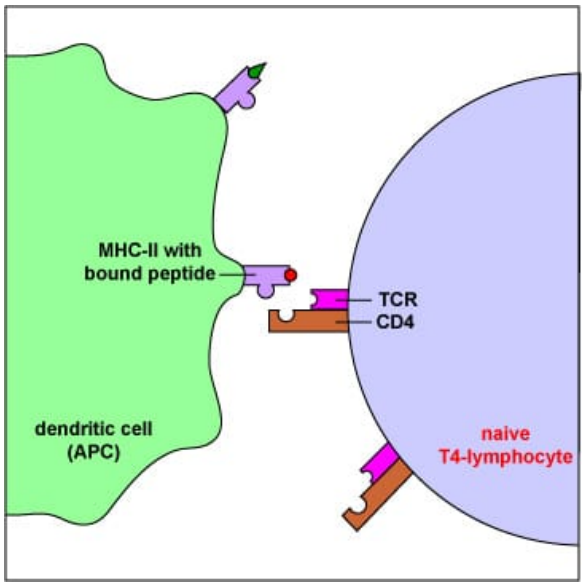


Figure $13.1E.5$: A Naive T4-Lymphocyte Recognizing Epitope/MHC-II on an Antigen-Presenting Dendritic Cell. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting dendriticcells through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the dendritic cell. Naive T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

In response to cytokines, these activated T4-lymphocytes now rapidly proliferate and differentiate into effector T4-lymphocytes. This is clonal expansion of the T4-lymphocytes. Before an antigen enters the body, the number of naive T4-lymphocytes specific for any particular antigen is between 1 in 10^5 to 10^6 lymphocytes. After antigen exposure, the number of T4-lymphocytes specific for that antigen may increase to 1 in 100 to 1000 lymphocytes.

Summary

1. Each naïve B-cell becomes genetically programmed to make an antibody with a unique antigen-binding site (Fab) through a series of gene translocations, and molecules of that antibody are put on its surface to function as the B-cell receptor.
2. When an antigen encounters the immune system, its epitopes eventually will react only with B-lymphocytes with B-cell receptors on their surface that more or less fit and this activates those B-lymphocytes. This process is known as clonal selection.
3. Cytokines produced by activated T4-helper lymphocytes enable those activated B-lymphocytes to rapidly proliferate to produce large clones of thousands of identical B-lymphocytes.
4. In this way, even though only a few B-lymphocytes in the body may have an antibody molecule able to fit a particular epitope, eventually eventually many thousands of cells are produced with the right specificity. This is referred to as clonal expansion.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write

them out. This will not test your understanding of this tutorial.

1. Briefly describe the process of clonal selection and clonal expansion. *(ans)*
2. Multiple Choice *(ans)*

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13: HUMORAL IMMUNITY

Humoral Immunity refers to the production of antibody molecules in response to an antigen. These antibody molecules circulate in the plasma of the blood and enter tissue and organs via the inflammatory response. Humoral immunity is most effective microbes or their toxins located in the extracellular spaces of the body. Antibodies or immunoglobulins are specific glycoprotein configurations produced by B-lymphocytes and plasma cells in response to a specific antigen and capable of reacting with that antigen.

13.1: Antibodies (Immunoglobulins)

13.1B: Antibody Structure

13.1C: The 5 Classes (Isotypes) of Human Antibodies

13.1D: Generation of Antibody Diversity

13.1E: Clonal Selection and Clonal Expansion

13.1F: Anamnestic (Memory) Response

13.2: Ways That Antibodies Help to Defend the Body

13.2A: Opsonization

13.2B: Cytolysis by the Membrane Attack Complex (MAC)

13.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells

13.2D: Neutralization of Exotoxins

13.2E: Neutralization of Viruses

13.2F: Preventing Bacterial Adherence

13.2G: Agglutination of Microorganisms

13.2H: Immobilization of Bacteria and Protozoans

13.2I: Promoting an Inflammatory Response

13.3: Naturally and Artificially Acquired Active and Passive Immunity

13.3A: Naturally Acquired Immunity

13.3B: Artificially Acquired Immunity

13.E: Humoral Immunity (Exercises)

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13.1F: Anamnestic (Memory) Response

Learning Objectives

1. In terms of humoral immunity, statewhat is meant by anamnestic response and discuss its role in immune defense.
2. Briefly describe why there is a heightened secondary response during anamestic response.

As a result of B-lymphocytes recognizing T-dependent antigens (proteins) during humoral immunity, numerous circulating B-memory cells and T4-memory cells develop (Figure $13.1F.1$), which possess anamnestic response or memory. (During cell-mediated immunity, T8-memory cells also develop.) A subsequent exposure to that same antigen results in:

- A more rapid production of antibodies;
- Produced in greater amounts; and
- Produced for a longer period of time.

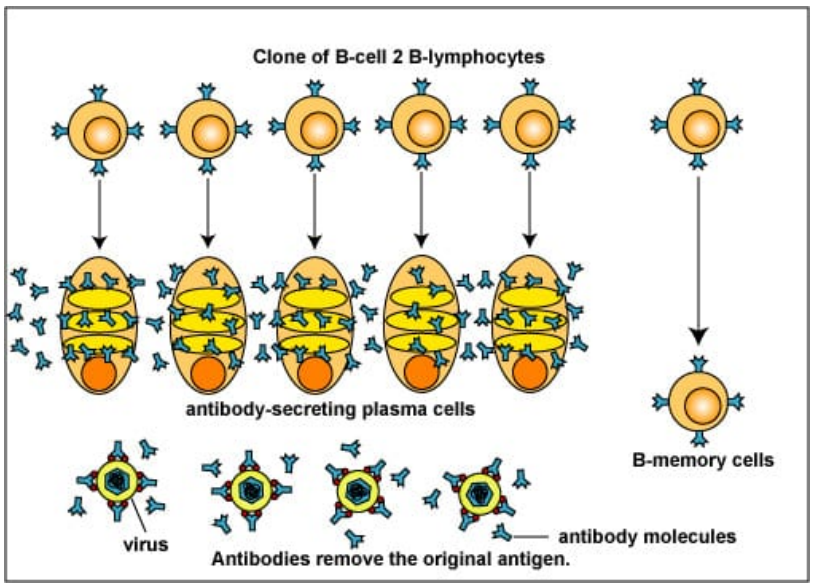


Figure $13.1F.1$**:** Differentiation of B-lymphocytes into Plasma Cells and B-Memory Cells. The B-lymphocytes now differentiate into plasma cells that secrete large quantities of antibodies that fit the original epitope. Some B-lymphocytes differentiate into B-memory cells capable of anamnestic response.

The primary response to a new antigen generally peaks at 5-10 days. IgM is made first later to be replaced by IgG. Because of the numerous circulating B-memory cells and T4-memory cells from the primary response, however, the secondary anamnestic response peaks in only 1-3 days (Figure $13.1F.2$). There is an increase in the amount of IgG made and under certain conditions, IgA or IgE may be made.

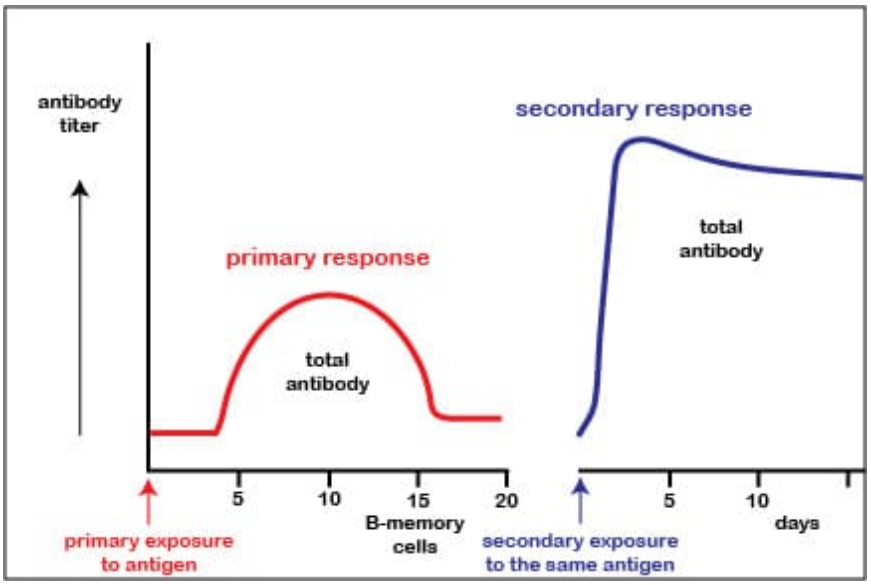


Figure $13.1F.2$**:** Anamnestic Response. After the primary exposure to an antigen, there is an inductive period of generally several days to a week when no measurable antibodies are detected in the serum. This is the period when the antigen is being exposed to immunocompetent cells, being processed by APCs, clonal selection and clonal expansion are taking place, and B-lymphocytes are differentiating into plasma cells and B-memory cells. Because of the memory cells, however, a second exposure to the same antigen results in more antibodies being made faster for a longer period of time, as shown in the secondary response.

Because of clonal expansion and affinity maturation , there is now a pool of B-memory cells having the "fine-tuned" B-cell receptors on their surface. The pool of B-memory cells migrate to lymph nodes, to mucosal tissue, and circulate in the blood waiting to encounter the original antigen if it again enters the body. B-memory cells have a long life and also replicate and produce antibodies periodically when they are exposed to persisting epitope remaining on the surface of follicular dendritic cells in the lymphoid organs. In addition to the B-memory cells, a pool of circulating T4-effector memory cells (CD4 T_{EM} cells), as well T4 tissue resident memory cells (CD4 T_{RM} cells) located in the mucosa enable an accelerated helper function.

This memory response applies to T-dependent antigens . In the case of the T-independent antigens, there is usually no anamnestic response.

In the case of systemic infections and most vaccinations, many of the plasma cells migrate to the bone marrow where they may continue to secrete antibodies for months or years after the antigen has been eliminated. Plasma cells produced in the mucous membranes generally remain in the mucous membranes and secrete antibodies for only around a year.

Memory is better in preventing systemic infections than preventing mucosal infections because infections limited to the mucous membranes generally do not provide enough time for the development of effector cells such as plasma cells, effector T4-lymphocytes , and cytotoxic T-lymphocytes from the activated memory cells.

Summary

1. As a result of B-lymphocytes recognizing T-dependent antigens (proteins) during humoral immunity, numerous circulating B-memory cells and T4-memory cells develop which possess anamnestic response or memory.
2. A subsequent exposure to that same antigen results in a more rapid production of antibodies that are produced in greater amounts for a longer period of time.
3. The primary response to a new antigen generally peaks at 5 - 10 days.
4. Because of the numerous circulating B-memory cells and T4-memory cells from the primary response, the secondary anamnestic response peaks in only 1 - 3 days.
5. In the case of systemic infections and most vaccinations, many of the plasma cells migrate to the bone marrow where they may continue to secrete antibodies for months or years after the antigen has been eliminated.
6. Plasma cells produced in the mucous membranes generally remain in the mucous membranes and secrete antibodies for only around a year. Therefore, anamnestic response is better at preventing systemic infections than preventing mucosal infections.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. In terms of humoral immunity, discusswhat is meant by anamnestic response. *(ans)*
2. Briefly describe why there is a heightened secondary response during anamestic response. *(ans)*

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13.2: WAYS THAT ANTIBODIES HELP TO DEFEND THE BODY

The antibodies produced during humoral immunity ultimately defend the body through a variety of different means.

- Topic hierarchy

13.2A: Opsonization

13.2B: Cytolysis by the Membrane Attack Complex (MAC)

13.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells

13.2D: Neutralization of Exotoxins

13.2E: Neutralization of Viruses

13.2F: Preventing Bacterial Adherence

13.2G: Agglutination of Microorganisms

13.2H: Immobilization of Bacteria and Protozoans

13.2I: Promoting an Inflammatory Response

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13.2A: Opsonization

Learning Objectives

- Discuss how antibodies defend the body by way of opsonization. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
- Briefly describe two different ways bacteria may resist opsonization.

Opsonization, or enhanced attachment, refers to the antibody molecules IgG and IgE, the complement proteins C3b and C4b, and other opsonins attaching antigens to phagocytes. This results in a much more efficient phagocytosis.

Opsonization with IgG, IgA, C3b, and C4b

The process starts with antibodies of the isotype IgG, IgA, or IgM being made against a surface antigen of the organism or cell to be phagocytosed. The Fab portions of the antibody react with epitopes of the antigen. The Fc portion of IgG (but not IgM) can then bind to receptors on neutrophils and macrophages thus sticking the antigen to the phagocyte (Figure $13.2A.1$). The Fc portion of secretory IgA can also bind to macrophages and neutrophils for opsonization.

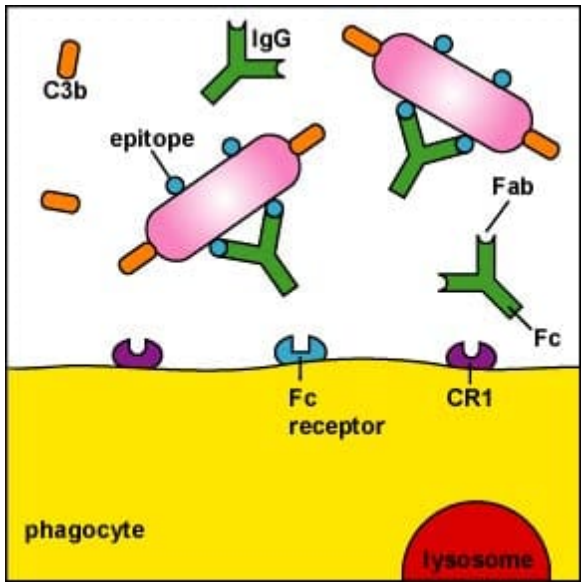


Figure $13.2A.1$: Opsonization (Enhanced Attachment). The Fab portion of IgG binds to epitopes of an antigen. The Fc portion can now attach the antigen to Fc receptors on phagocytes for enhanced attachment. This is especially important against encapsulated microbes. C3b and C4b from the complement pathways can also attach antigens to phagocytes.

The Fc portion of secretory IgA can also bind to macrophages and neutrophils for opsonization.

Alternately, IgG, IgA, and IgM can activate the complement pathways (Figure $13.2A.2$) and C3b or C4b can stick the antigen to phagocytes (Figure $13.2A.1$). Like IgG, C3b, and to a lesser extent C4b, can function as opsonins, that is, they can attach antigens to phagocytes.One portion of the C3b binds to proteins and polysaccharides on microbial surfaces; another portion attaches to CR1 receptors on phagocytes, B-lymphocytes, and dendritic cells for enhanced phagocytosis (Figure $13.2A.3$). (Remember that C3b and C4b are also produced during the alternative complement pathway and the lectin pathway as was discussed in Unit 5.) Activation of the complement pathway also promotes inflammation to bring phagocytes and defense chemicals from the bloodstream to the infection site as discussed later under this topic.

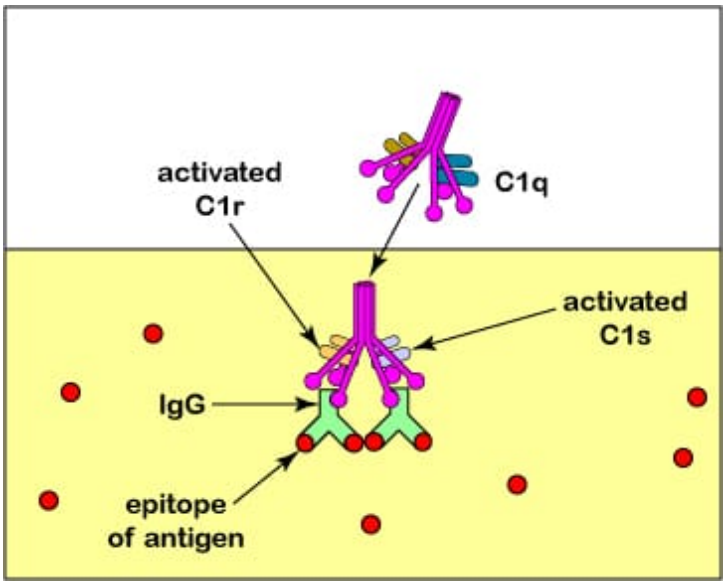


Figure 13.2A.2: Activation of C1 during the Classical Complement Pathway. The Fab of 2 molecules of IgG or 1 molecule of IgM bind to epitopes on an antigen. C1, consisting of C1q, C1r, and C1s then binds to the Fc portion of the antibodies. The binding of C1q to the antibody molecules activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b and complement protein C2 into C2a and C2b.

Actually, C3b molecule can bind to pretty much any protein or polysaccharide. Human cells, however, produce Factor H that binds to C3b and allows Factor I to inactivate the C3b. On the other hand, substances such as LPS on bacterial cells facilitate the binding of Factor B to C3b and this protects the C3b from inactivation by Factor I. In this way, C3b does not interact with our own cells but is able to interact with microbial cells.

Attachment then promotes destruction of the antigen. Microorganisms are placed in phagosomes (Figure 13.2A.4) where they are ultimately digested by lysosomes (Figure 13.2A.5). If the antigen is a cell too large to be ingested - such as virus-infected host cells, transplant cells, and cancer cells - the phagocyte empties the contents of its lysosomes directly on the cell for extracellular killing (Figure 13.2A.6 and Figure 13.2A.7).

Opsonization is especially important against microorganisms with antiphagocytic structures such as capsules since opsonizing antibodies made against the capsule are able to stick capsules to phagocytes (Figure 13.2A.8). In vaccines against pneumococccal pneumonia and *Haemophilus influenzae* type b, it is capsular polysaccharide that is given as the antigen in order to stimulate the body to make opsonizing antibodies against the encapsulated bacterium.

Opsonization with IgE and the promotion of inflammation

The antibody isotype IgE is made against parasitic worms (helminths) and arthropods. The Fab portions of IgE bind to epitopes on the helminth or arthropod while the Fc portion binds to receptors on eosinophils enabling opsonization. In other words, IgE sticks phagocytic eosinophils to helminths and arthropods for the extracellular killing of that organism (Figure 13.2A.9).

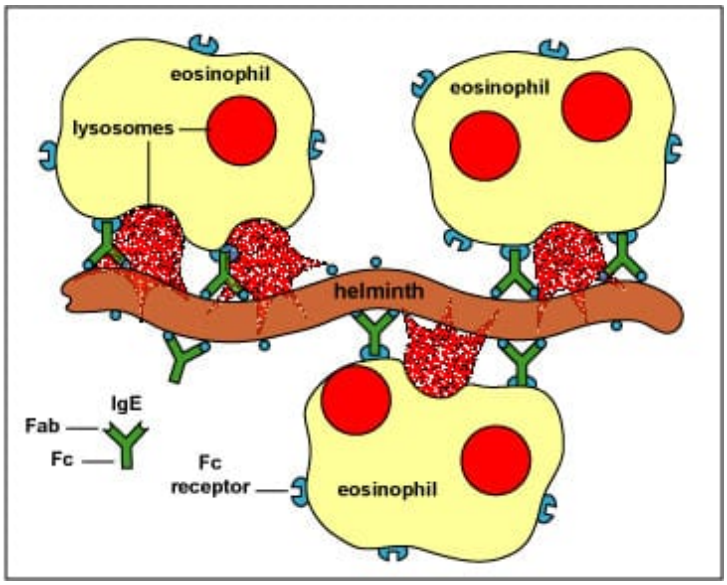


Figure 13.2A.9: Opsonization of a Helminth by IgE and Eosinophils. A major function of the cytokines produced by T_H2 cells is to enable B-lymphocytes to activate eosinophils and produce increased amounts of a class of antibodies called IgE against helminths (parasitic worms) and arthropods. IgE act as an opsonizing antibody to stick phagocytic eosinophils to helminths for extracellular killing of the helminths. The Fab portion of IgE reacts with epitopes on the helminth while the Fc portion binds to Fc receptors of activated eosinophils. The lysosomal proteases of eosinophils are able to destroy the tough integument of helminths. IgE also promotes inflammation to recruit phagocytes.

The Fc portion of IgE also binds to receptors on mast cells and basophils to trigger the release of *inflammatory mediators* (Figure 13.2A.10). The inflammatory response then enables phagocytes and defense chemicals to leave the bloodstream and go to the infected site as will be discussed later under this topic.

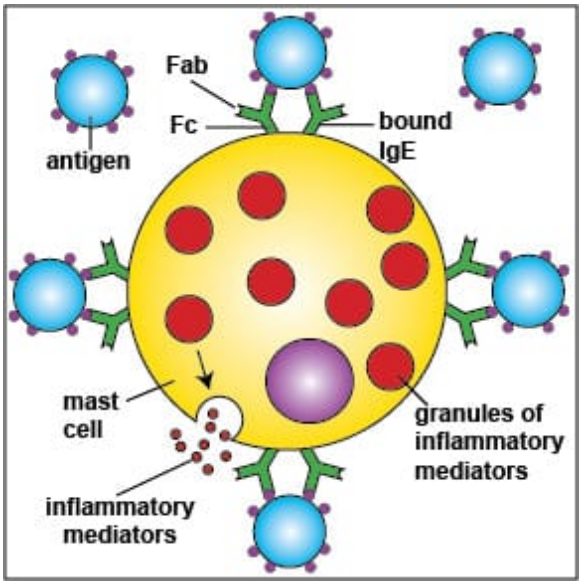


Figure 13.2A.10: IgE Binding to Mast Cells and Basophils and Promoting an Inflammatory Response. The Fc portion of IgE is able to bind to receptors on mast cells and basophils. The cross-binding of antigens to the Fab portion of IgE triggers the release of inflammatory mediators. The resulting inflammatory response subsequently delivers defense cells and defense molecules from the bloodstream to the infection site.

Exercise: Think-Pair-Share Questions

Compare and contrast how IgG, IgM, and IgE promote opsonization..

Because of a particular immunodeficiency disorder, a person is unable to produce C3 convertase. Which of the above antibody isotypes could still participate in opsonization? Briefly explain why.

How Bacteria Resist Attachment to Phagocytes

As we learned previously, some bacteria by means of the activities described below are able to resist phagocytic attachment :

- An outer membrane molecule of *Neisseria gonorrhoeae* called Protein II and the M-protein of *Streptococcus pyogenes* allow these bacteria to be more resistant to phagocytic engulfment. The M-protein of *S. pyogenes*, for example, binds factor H of the complement pathway and this leads to the degradation of the opsonin C3b by factor I and the formation of C3 convertase.
- Some capsules simply cover the C3b that does bind to the bacterial surface and prevent the C3b receptor on phagocytes from making contact with the C3b (Figure $13.2A.11$). This is seen with the capsule of *Streptococcus pneumoniae*.
- Capsules can also resist unenhanced attachment by preventing the glycoprotein receptors on phagocytes from recognizing the bacterial cell wall components and mannose-containing carbohydrates.
- *S. pneumonia* activates the classical complement pathway, but resists C3b opsonization, and complement causes further inflammation in the lungs.
- *Neisseria meningitidis* has a capsule composed of sialic acid *while Streptococcus pyogenes* (group A beta streptococci) has a capsule made of hyaluronic acid. Both of these polysaccharides closely resemble carbohydrates found in human tissue polysaccharides and because they are not recognized as foreign by the lymphocytes that carry out the immune responses, antibodies are not made against these capsules.
- Some bacteria are able to coat themselves with host proteins such as fibronectin, lactoferrin, or transferrin. This prevents antibody molecules from binding to epitopes on the bacterial surface.
- *Staphylococcus aureus* produces protein A while *Streptococcus pyogenes* produces protein G. Both of these proteins bind to the Fc portion of antibodies, the portion that normally binds to receptors on phagocytes (Figure $13.2A.12$). In this way the bacteria become coated with antibodies in a way that does not result in opsonization (Figure $13.2A.13$).
- *Streptococcus pyogenes* produces Mac proteins that are able to bind to the receptors on phagocytes to which IgG and C3b normally attach (Figure $13.2A.14$.and Figure $13.2A.15$). This blocks opsonization.
- Pathogenic *Yersinia*, such as the one that causes plague, contact phagocytes and, by means of a type III secretion system, deliver proteins which depolymerize the actin microfilaments needed for phagocytic engulfment into the phagocytes. Another *Yersinia* protein degrades C3b and C5a.

Summary

Opsonization, or enhanced attachment, refers to the antibody molecules IgG and IgE, the complement proteins C3b and C4b, and other opsonins attaching antigens to phagocytes. The Fab portions of the antibody IgG react with epitopes of the antigen. The Fc portion of IgG can then bind to neutrophils and macrophages thus sticking the antigen to the phagocyte. The Fc portion of secretory IgA can also bind to macrophages and neutrophils for opsonization. IgG and IgM can activate the classical complement pathway and C3b or C4b can stick the antigen to phagocytes. IgE is made against parasitic worms (helminths) and arthropods. The Fab portions of IgE bind to epitopes on the helminth or arthropod while the Fc portion binds to receptors on eosinophils enabling opsonization.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of opsonization. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. We know *Streptococcus pneumoniae* is encapsulated and capsules resist phagocytosis. Yet the body is eventually able to phagocytose this organism. Describe how. *(ans)*
3. *Staphylococcus aureus* produces an exotoxin called Protein A. Protein A is able to react with the Fc portion of IgG. In terms of humoral immunity, discuss how Protein A may help the *Staphylococcus* resist phagocytosis. *(ans)*
4. The M-protein of *Streptococcus pyogenes* binds factor H of the complement pathway and allows these bacteria to be more resistant to phagocytic engulfment. Explain how. *(ans)*
5. Multiple Choice *(ans)*

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13.2B: Cytolysis by the Membrane Attack Complex (MAC)

Learning Objectives

1. Discuss how antibodies defend the body by way of MAC cytolysis. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
2. State specifically how MAC cytolysis protects against the following:
   a. Gram-negative bacteria
   b. human cells recognized as nonself
   c. enveloped viruses
3. Describe one way Gram-negative bacteria may resist cytolysis.

The process starts with the antibody isotypes IgG or IgM being made against epitopes on membranes. The Fab portion of IgG or IgM reacts with the epitopes on the membrane and the Fc portion of the antibody then activates the classical complement pathway. $C5b6789_n$ (the membrane attack complex or MAC) then puts holes in the membrane. (Remember that MAC is also produced during the alternative complement pathway and the lectin pathway as was discussed in Unit 5.)

a. In the case of bacteria, MAC can put holes in the outer membrane and possibly the cytoplasmic membrane of the Gram-negative cell wall (Figure $13.2B.1$ left) causing lysis (Figure $13.2B.1$ right).

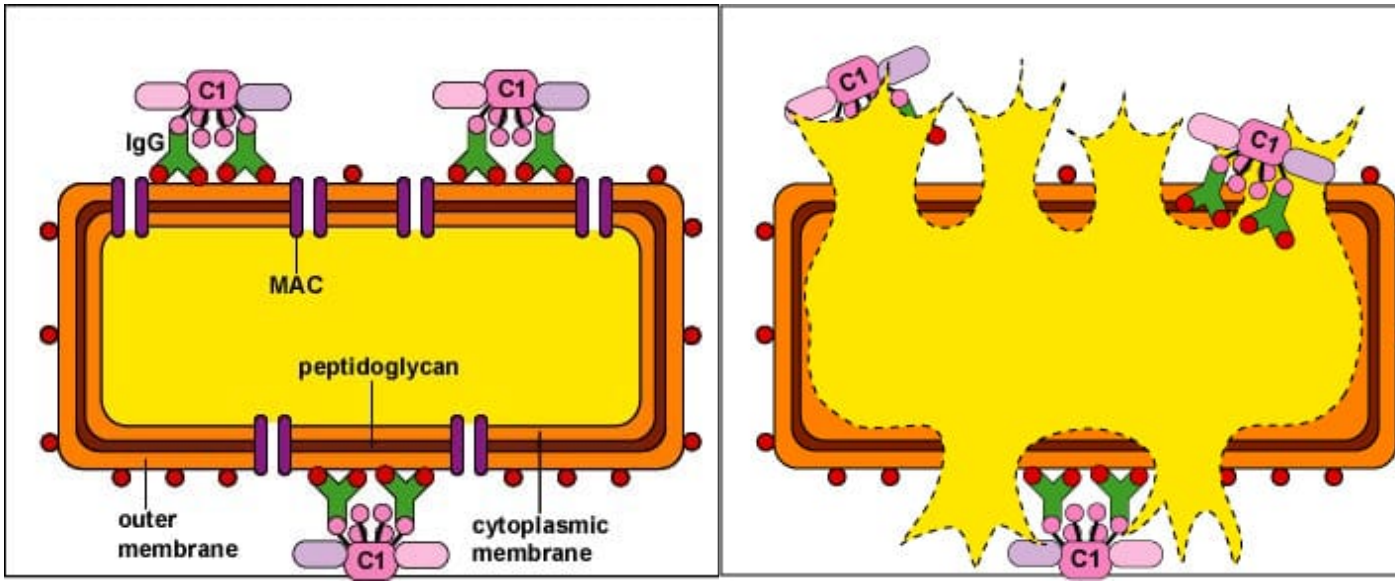


Figure $13.2B.1$: (left) Cytolysis of Gram-Negative Bacteria, Step 1. The Fab portion of IgG or IgM binds to epitopes on the outer membrane of the gram-negative cell wall. This activates the complement pathway enabling the membrane attack complex (MAC) to insert through the outer membrane and cytoplasmic membrane causing the bacterium to lyse. (right)Lysis of the gram-negative bacterium.

b. With enveloped viruses, the MAC can damage the viral envelope (Figure \(\PageIndex{12}\).3.2).

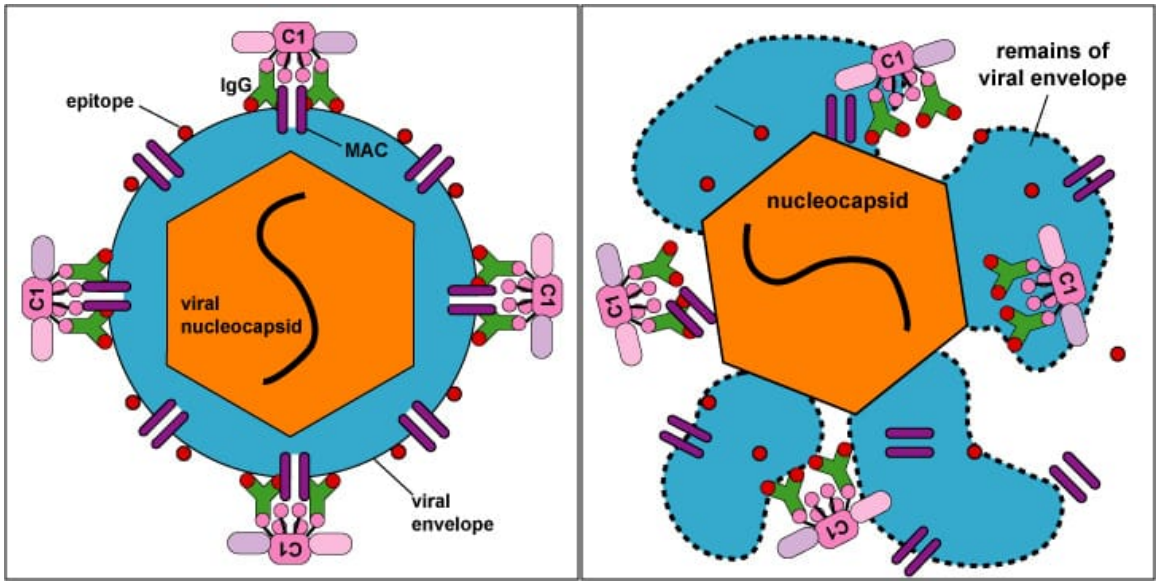


Figure $13.2B.2$: (left) MAC Damage to the Viral Envelope, Step 1: MAC (membrane attack complex) from the activated complement pathways is able to damage the envelope of enveloped viruses causing viral inactivation. (right) Step 2: Without its envelope, the virus is unable to infect new host cells.

c. In the case of human cells recognized as nonself- virus-infected cells, transplanted cells, transfused cells, cancer cells - the MAC causes direct cell lysis (see Figure $13.2B.5$ and Figure $13.2B.6$).

Concept Map for Ways in which Antibodies Protect the Body

However, as learned in Unit 3, some bacteria by means of the activities described below are more resistant to MAC lysis.

- The LPS of the cell wall is the principle target for complement in Gram-negative bacteria by activating the alternative complement pathway and serving as a binding site for C3b as well as the site for formation of MAC. Some Gram-negative bacteria attach sialic acid to the LPS O antigen (see Figure $13.2B.7$) and this prevents the formation of the complement enzyme C3 convertase that is needed for the eventual formation of all the beneficial complement proteins such as C3b, C5a, and MAC. Blood-invasive strains of *Neisseria gonorrhoeae* , as well as *Bordetella pertussis* and *Hemophilus influenzae* are examples of Gram-negative bacteria that are able to alter their LPS in this manner.
- Some Gram-negative bacteria, such as *Salmonella* , lengthen the LPS O antigen side chain (see Figure $13.2B.7$) and this prevents the formation of MAC. *Neisseria meningitidis* and Group B Streptococcus , on the other hand, produces capsular polysaccharides composed of sialic acid and as mentioned above, sialic acid prevents MAC lysis.
- An outer membrane molecule of *Neisseria gonorrhoeae* called Protein II binds factor H of the complement pathway and this leads to the degradation of the opsonin C3b by factor I and the formation of C3 convertase. Without C3 convertase, no MAC is produced.

Summary

The Fab portion of IgG or IgM reacts with the epitopes on the membrane and the Fc portion of the antibody then activates the classical complement pathway. C5b6789n (the membrane attack complex or MAC) then puts holes in the membrane. In the case of bacteria, MAC can put holes in the outer membrane and possibly the cytoplasmic membrane of the Gram-negative cell wall causing lysis. In the case of enveloped viruses, MAC can damage the viral envelope. In the case of human cells recognized as nonself - virus-infected cells, transplanted cells, transfused cells, cancer cells- the MAC causes direct cell lysis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of MAC cytolysis. (Include what classes or isotypes of immunoglobulins

are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*

2. Some Gram-negative bacteria attach sialic acid to the LPS O antigen of their outer membrane. Briefly describe how this may protect that Gram-negative bacterium from MAC cytolysis. *(ans)*
3. How does MAC affect viruses? *(ans)*
4. Multiple Choice *(ans)*

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13.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells

Learning Objectives

1. **Discuss** how antibodies defend the body by way of **ADCC by Natural Killer cells**. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Natural killer (NK) cells are capable of antibody-dependent cellular cytotoxicity or ADCC. NK cells have receptors on their surface for the Fc portion of certain subclasses of IgG. When the antibody IgG is made against epitopes on "foreign" membrane-bound cells, such as virus-infected cells and cancer cells, the Fab portions of the antibodies react with the "foreign" cell. The NK cells then bind to the Fc portion of the antibody (Figure $13.2C.1$).

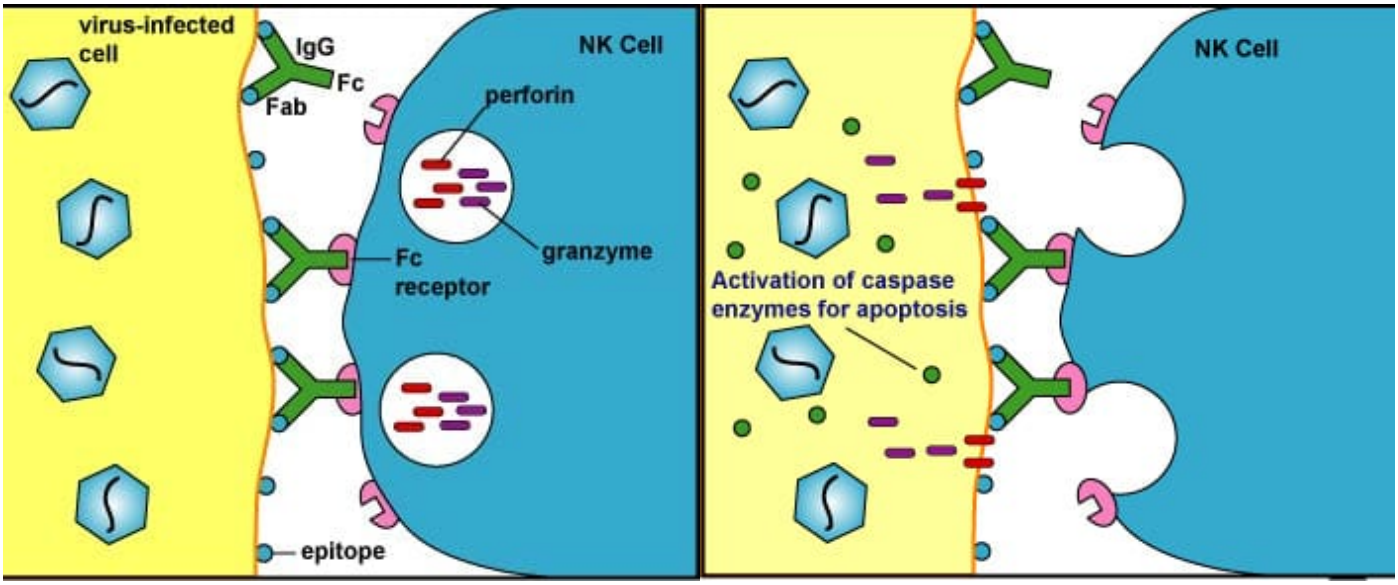


Figure $13.2C.1$: Destruction of Virus-Infected Cells by NK Cells through Antibody-Dependent Cellular Cytotoxicity (ADCC), (left) Step 1: The Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody. (right) Step 2: The NK cell is then able to contact the cell and release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis.

The NK cell then **releases pore-forming proteins called perforins, proteolytic enzymes called granzymes**, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to **apoptosis** of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation (Figure $13.2C.13.5.1$; right panel and Figure $13.2C.2$). As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis. (When NK cells are carrying out ADCC, they are sometimes also referred to as killer cells.)

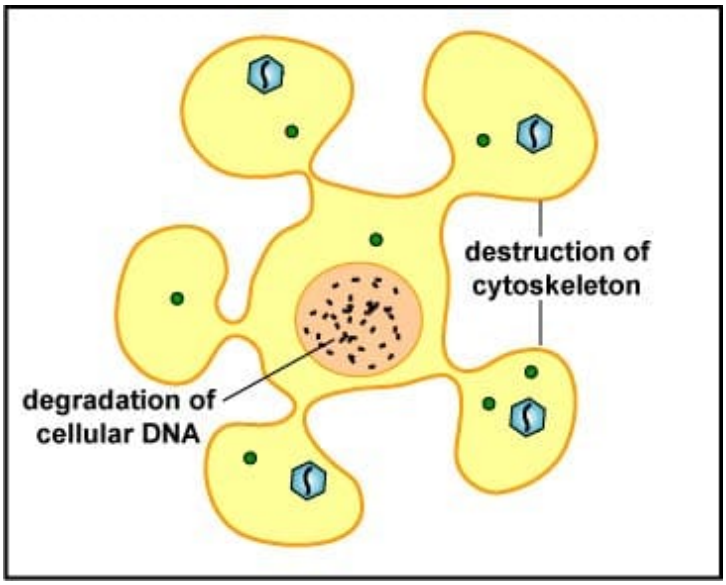


Figure 13.2C.2: NK cells release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis, a programmed suicide of the infected cell. Apoptosis occurs when certain granzymes activate a group of protease enzymes called caspases that destroy the protein structural scaffolding of the cell, degrade the cell's nucleoprotein, and activate enzymes that degrade the cell's DNA. As a result, the infected cell breaks into membrane-bound fragments that are subsequently removed by phagocytes. If very large numbers of perforins are inserted into the plasma membrane of the infected cell, this can result in a weakening of the membrane and lead to cell lysis rather than apoptosis. An advantage to killing infected cells by apoptosis is that the cell's contents, including viable virus particles and mediators of inflammation, are not released as they are during cell lysis.

Summary

NK cells are capable of antibody-dependent cellular cytotoxicity or ADCC. When IgG is made against epitopes on "foreign" membrane-bound cells, such as virus-infected cells and cancer cells, the Fab portions of the antibodies react with epitopes on the "foreign" cell and then NK cells bind to the Fc portion of the antibody. The NK cell then releases pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell and the cell breaks into fragments that are subsequently removed by phagocytes.

Questions

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. **Discuss** how antibodies defend the body by way of **ADCC by NK cells**. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
2. Antibody-dependent cellular cytotoxicity (ADCC) is a result of:
   a. Antibodies sticking infected cells and cancer cells to phagocytes.
   b. Antibodies sticking infected cells and cancer cells to cytotoxic T-lymphocytes (CTLs).
   c. Antibodies sticking infected cells and cancer cells to NK cells.
   d. MAC lysing the membranes of infected cells and cancer cells.
3. During ADCC, the Fab portion of the antibody _____while the Fc portion _____.
   a. binds to epitopes of an antigen; activates the complement pathway.
   b. activates the complement pathway; binds to epitopes of an antigen.
   c. binds to epitopes of an antigen; binds to cytotoxic T-lymphocytes.
   d. binds to epitopes of an antigen; binds to NK cells.
4. NK cells kill the cells they bind to by:
   a. Triggering apoptosis.
   b. Dumping the contents of their lysosomes on the cell.
   c. Producing cytolytic exotoxins that lyse the cell.

d. Inducing extracellular killing by eosinophils.

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13.2D: Neutralization of Exotoxins

Learning Objectives

- Discuss how antibodies defend the body by way of neutralizing exotoxins. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
- Describe how the ability of bacteria to sense their own population density, communicate with each other by way of secreted factors (cell-to-cell signaling), and behave as a population rather than as individual bacteria most likely plays an important role in pathogenicity for many bacteria.

For an exotoxin to cause harm it must first bind to receptors on a susceptible host cell. Antitoxin antibodies are made against microbial exotoxins. The Fab portion binds to the exotoxin molecules before they can interact with host target cells and thus neutralizes the toxin (Figure $13.2D.1$). IgG neutralizes toxins in tissues while IgA neutralizes toxins at mucosal surfaces within the body.

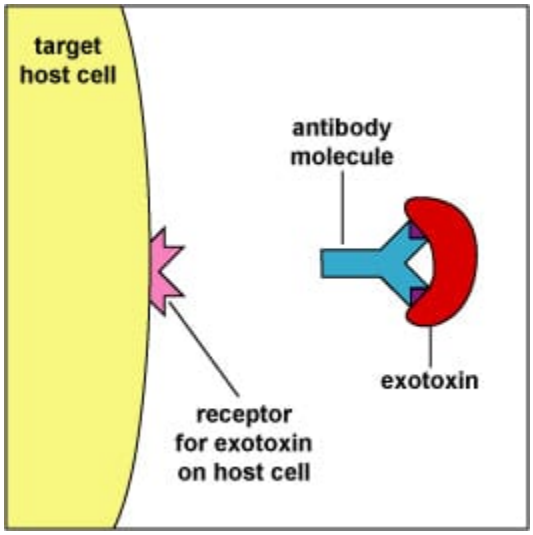


Figure $13.2D.1$: Neutralization of Exotoxins. The Fab portion of the antibodies made against epitopes of the binding site of an exotoxin blocks the exotoxin from binding to the exotoxin receptor on the host cell membrane. As a result, the toxin can not enter the cell and cause harm.

However, as learned in Unit 2, many Gram-negative and Gram-positive are able to sense their own population density, communicate with each other by way of secreted factors, and behave as a population rather than as individual bacteria. This is referred to as quorum sensing and most likely plays an important role in pathogenicity for many bacteria.

- For example, *Pseudomonas aeruginosa* causes severe nosocomial infections, chronic infections in people with cystic fibrosis, and potentially fatal infections in those who are immunocompromised. Its virulence depends on the secretion of a variety of harmful exotoxins and enzymes. If there was an isolated production of these virulence toxins and enzymes by a small number of *Pseudomonas*, the body's immune responses would most likely be able effectively neutralize these harmful agents with antibodies. However, through a coordination of the expression of the genes coding for these toxins and enzymes by the entire population of bacteria, *P. aeruginosa* appears to only secrete these extracellular virulence factors when the density of bacteria is large enough that they can be produced at high enough levels to overcome body defenses.

Summary

For an exotoxin to cause harm it must first bind to receptors on a susceptible host cell. Antitoxin antibodies are made against microbial exotoxins. The Fab portion binds to the exotoxin molecules before they can interact with host target cells and thus neutralizes the toxin.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of neutralizing exotoxins. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. Describe how the ability of *Pseudomonas aeruginosa* to sense its own population density, communicate with other *Pseudomonas* by way of secreted factors (cell-to-cell signaling), and behave as a population rather than as individual bacteria most likely plays an important role in pathogenicity of this organism. *(ans)*
3. Multiple Choice *(ans)*

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13.2E: Neutralization of Viruses

Discuss how antibodies defend the body by way of neutralizing viruses. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

- Briefly describe 2 different ways viruses may resist neutralizing antibodies.

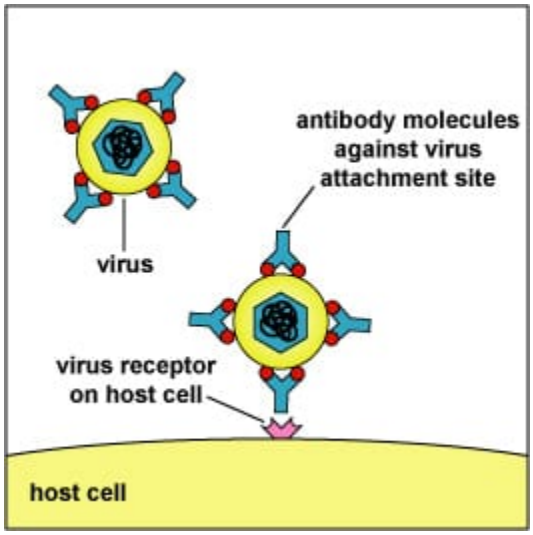


Figure $13.2E.1$: Neutralization of Viruses. The Fab portion of the antibodies made against epitopes of the virus attachment site blocks the virus from adsorbing to the receptor site on the host cell membrane. As a result, the virus can not penetrate and replicate.

However, as learned in Unit 4, some viruses by means of the activities described below are able to overcome this antibody defense.

- The influenza viruses undergo what is called antigenic drift and antigenic shift. With antigenic drift, mutations cause a gradual change in the hemagglutinin antigen that adsorbs to receptors on host cells. Antigenic shift is caused by a human influenza virus acquiring a new genome segment from an influenza virus capable of infecting other animals such as a ducks or swine. This new genome segment causes a major change in the hemagglutinin antigen. Antibodies made against the original human influenza virus can no longer bind to the new strain of virus or stick the virus to phagocytes.
- Likewise HIV, because of its high rate of mutation and its intracellular recombination with other strains of HIV, as mentioned earlier in this unit, produces altered gp120 to which antibodies made against the earlier strains of HIV can no longer bind.
- The hepatitis C virus (HCV) frequently, through mutation, produces viral variants ("escape mutants") to resist antibodies.

A child is fully immunized against measles, mumps, and rubella with the MMR vaccine. The child is subsequently exposed to measles but doesn't get the disease. Explain why the virus was unable to replicate and cause disease symptoms.

Summary

In order for viruses to infect a cell and replicate, they must first adsorb to receptors on the host cell's plasma membrane. Antibodies are made against viral capsids or envelope glycoproteins where the Fab portion binds to and covers the viral attachment molecules. This prevents viral adsorption to host cells. Neutralizing antibodies are especially important in preventing viral reinfection.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of neutralizing viruses. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. Describe one way a virus can resist virus-neutralizing antibodies and give an example. *(ans)*
3. Multiple Choice *(ans)*

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13.2F: Preventing Bacterial Adherence

Learning Objectives

1. Discuss how antibodies defend the body by way of preventing bacterial adherence to host cells. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
2. Briefly describe 2 different ways bacteria may resist antibodies that block bacterial adherence to host cells.

One of the body's innate defenses is the ability to physically remove bacteria from the body through such means as the constant shedding of surface epithelial cells from the skin and mucous membranes, the removal of bacteria by such means as coughing, sneezing, vomiting, and diarrhea, and bacterial removal by bodily fluids such as saliva, blood, mucous, and urine. Bacteria may resist this physical removal producing pili, cell wall adhesin proteins, and/or biofilm-producing capsules.

Antibodies are made against pili, capsules, and cell wall adhesins. The binding of the Fab portion of the antibody to the adhesive tip of the pili, the cell wall adhesins, or the capsular molecules prevents the bacteria from adhering to and colonizing host cells (see Figure $13.2F.1$ and Figure $13.2F.2$.) IgG blocks adherence of bacteria in tissues while IgA blocks adherence of bacteria at mucosal surfaces within the body.

The body is able to make antibody molecules against the adhesive tips of Escherichia coli pili and yet E. coli is still the most common cause of urinary tract infections. State what might account for this.

However, as learned in Unit 3, some bacteria by means of the activities described below are able to overcome this antibody defense.

- Some bacteria can produce immunoglobulin proteases which can degrade the protective IgA found in mucus. Examples include bacteria that colonize the mucous membranes such as *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Helicobacter pylori*, *Shigella flexneri* and enteropathogenic *Escherichia coli*.
- Another way certain bacteria can evade antibodies is by changing the adhesive tips of their pili as seen with *Neisseria gonorrhoeae* (see Figure $13.2F.3$). Bacteria can also vary other surface proteins so that antibodies already made will no longer "fit."

Summary

Bacteria resist physical removal by means of pili, cell wall adhesin proteins, and/or biofilm-producing capsules. The binding of the Fab portion of the antibody to the adhesive tip of the pili, the cell wall adhesins, or the capsular molecules prevents the bacteria from adhering to and colonizing host cells.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of preventing bacterial adherence to host cells. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. Describe how immunoglobulin proteases may protect bacteria from antibodies that block bacterial adhence to host cells. *(ans)*
3. Multiple Choice *(ans)*

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13.2G: Agglutination of Microorganisms

Learning Objectives

1. Discuss the how antibodies defend the body by agglutinating microorganisms. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role - if any - of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Agglutination is mainly a function of antibodies with multiple reactive Fab sites such as IgM and IgA. The Fab portion of the antibodies links microorganisms together (causes them to agglutinate) so they can be phagocytosed more effectively (see Figure $13.2G.1$).

Summary

Agglutination is mainly a function of antibodies with multiple reactive Fab sites such as IgM and IgA. The Fab portion of the antibodies links microorganisms together (causes them to agglutinate) so they can be phagocytosed more effectively.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by agglutinating microorganisms. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. State why IgM and IgA are good at causing agglutination of microorganisms. *(ans)*

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13.2H: Immobilization of Bacteria and Protozoans

Learning Objectives

1. Discuss how antibodies defend the body by immobilizing bacteria and protozoans. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Flagella and cilia are organelles of locomotion and enable motile microorganisms to move towards or away from environmental molecules through a process called taxis. The mucosal surfaces of the bladder and the intestines constantly flush bacteria away in order to prevent colonization.Motile bacteria that can swim chemotactically toward mucosal surfaces may have a better chance to make contact with the mucous membranes, attach, and colonize.

Antibodies are made against the flagella of motile bacteria or the flagella or cilia of motile protozoans. The Fab portions of the antibodies bind to these locomotor organelles and arrest the organism's movement blocking its ability to spread.

Summary

1. Flagella and cilia are organelles of locomotion and enable motile microorganisms to move towards or away from environmental molecules through a process called taxis.
2. Antibodies are made against the flagella of motile bacteria or the flagella or cilia of motile protozoans.
3. The Fab portions of the antibodies bind to these locomotor organelles and arrest the organism's movement blocking its ability to spread.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discusshow antibodies defend the body by immobilizing bacteria and protozoans. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*

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13.2I: Promoting an Inflammatory Response

Learning Objectives

1. Describe two different ways antibodies defend the body by promoting an inflammatory response and state the importance of inflammation. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Antigen-antibody reactions can also promote an inflammatory response:

a. IgG and IgM can activate the classical complement pathway (see Figure $13.2I.1$).

As learned under innate immunity in Unit 5, the classical complement pathway is primarily activated when a complement protein complex called C1 interacts with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen via their Fab portion . C1 is also able to directly bind to the surfaces of some pathogens.

The C1 complex is composed of three complement proteins called C1q, C1r, and C1s.

- The C1q is the portion of the C1 complex that binds to the antibodies or the microbe.
- The binding of C1q activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b and C2 into C2a and C2b and begin the classical complement pathway.

The beneficial results of the activated complement proteins include :

1. Triggering inflammation : C5a>C3a>C4a.

2. Chemotactically attracting phagocytes to the infection site: C5a;

3. Promoting the attachment of antigens to phagocytes via enhanced attachment or opsonization : C3b>C4b (discussed earlier under opsonization);

4. Causing the lysis of Gram-negative bacteria, viral envelopes, and human cells displaying foreign epitopes (discussed earlier under MAC cytolysis).

b. IgA can activate the lectin complement pathway and the alternative complement pathway and C5a, C3a, and C4a can trigger inflammation.

c. IgE can bind to mast cells and basophils and trigger the release of inflammatory mediators.

The Fc portion of IgE can bind to receptors on mast cells and basophils . Cross linking of the cell-bound IgE by antigen triggers the release of vasodilators and other inflammatory mediators for an inflammatory response (see Fig 2).

As learned under inflammation in Unit 5, most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site.

The inflammatory response produces vasodilators that increase capillary permeability. As a result of this increased permeability:

a. Plasma flows out of the blood into the tissue.

Beneficial molecules in the plasma include:

1. Clotting factors. Tissue damage activates the coagulation cascade causing fibrin clots to form to localize the infection, stop the bleeding, and chemotactically attract phagocytes.

2. Antibodies . These help remove or block the action of microbes through a variety of methods described in this section.
3. Proteins of the complement pathways . These, in turn: 1) stimulate more inflammation (C5a, C3a, and C4a), 2) stick microorganisms to phagocytes (C3b and C4b), 3) chemotactically attract phagocytes (C5a), and 4) lyse membrane-bound cells displaying foreign antigens (membrane attack complex or MAC).
4. Nutrients. These feed the cells of the inflamed tissue.
5. Lysozyme, cathelicidins, phospholipase A_2, and human defensins . Lysozyme degrades peptidoglycan. Cathelicidins are cleaved into two peptides that are directly toxic to microbes and can neutralize LPS from the gram-negative bacterial cell wall. Phospholipase A_2 hydrolyzes the phospholipids in the bacterial cytoplasmic membrane. Human defensins put pores in the cytoplasmic membranes of many bacteria. Defensins also activate cells involved in the inflammatory response.
6. Transferrin . Transferrin deprives microbes of needed iron.

b. Leukocytes enter the tissue through a process called diapedesis or extravasation.

Benefits of diapedesis include:

1. Increased phagocytosis. Phagocytes such as neutrophils, monocytes that differentiate into macrophages when they enter the tissue, and eosinophils are phagocytic leukocytes.
2. More vasodilation. Basophils, eosinophils, neutrophils, and platelets enter the tissue and release or stimulate the production of vasoactive agents that promote inflammation.
3. Cytotoxic T-lymphocytes (CTLs) , effector T4-cells , and NK cells enter the tissue to kill cells such as infected cells and cancer cells that are displaying foreign antigens on their surface (discussed in Unit 6).

Summary

1. IgG and IgM can activate the classical complement pathway and C5a, C3a, and C4a can trigger inflammation.
2. IgA can activate the lectin complement pathway and the alternative complement pathway and C5a, C3a, and C4a can trigger inflammation.
3. IgE can bind to mast cells and basophils and trigger the release of inflammatory mediators.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe one way antibodies defend the body by promoting an inflammatory response and state the importance of inflammation. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*

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13.3: NATURALLY AND ARTIFICIALLY ACQUIRED ACTIVE AND PASSIVE IMMUNITY

Immunity may be passive or active. During **passive immunity**, antibodies made in another person or animal enter the body and the immunity is short-lived and Active Immunity: In the case of **active immunity**, antigens enter the body and the body responds by making its own antibodies and B-memory cells. In this case, immunity is longer lived although duration depends on the persistence of the antigen and the memory cells in the body. Both passive and active immunity can be either naturally or artificially acquired.

13.3A: Naturally Acquired Immunity

13.3B: Artificially Acquired Immunity

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13.3A: Naturally Acquired Immunity

Learning Objectives

1. Give an example of naturally acquired active immunity.
2. Give two examples of naturally acquired passive immunity and state why this is important to newborns and infants.

Active Naturally Acquired Immunity

Active naturally acquired immunity refers to the natural exposure to an infectious agent or other antigen by the body. The body responds by making its own antibodies.

Passive Naturally Acquired Immunity

There are two examples of passive naturally acquired immunity: (1) The placental transfer of IgG from mother to fetus during pregnancy. These antibodies generally last 4 to 6 months following birth. The immune responses reach full strength at about age 5. (2) The IgA and IgG found in human colostrum and milk of babies who are nursed. In addition to the IgA and IgG, human milk also contains:

- Oligosaccharides and mucins that adhere to bacteria and viruses to interfere with their attachment to host cells;
- Lactoferrin to bind iron and make it unavailable to most bacteria;
- B_{12} binding protein to deprive bacteria of needed vitamin B_{12};
- Bifidus factor that promotes the growth of *Lactobacillus bifidus*, normal flora in the gastrointestinal tract of infants that crowds out harmful bacteria;
- Fibronectin that increases the antimicrobial activity of macrophages and helps repair tissue damage from infection in the gastrointestinal tract;
- Gamma-interferon, a cytokine that enhances the activity of certain immune cells;
- Hormones and growth factors that stimulate the baby's gastrointestinal tract to mature faster and be less susceptible to infection;
- Lysozyme to break down peptidoglycan in bacterial cell walls.

Benefits of Breast Feeding

According to the Centers for Disease Control and Prevention (CDC), breast-fed infants have a lower incidence of gastrointestinal infections, ear infections, atopic dermatitis, respiratory infections, urinary tract infections, meningitis, type 2 diabetes, and sudden infant death syndrome. Benefits to the mother include a decreased risk of breast cancer, ovarian cancer, and type 2 diabetes, as well stopping post-birth bleeding and temporarily suppressing ovulation. It may also be associated with a reduced risk of pediatric overweight.

Summary

Active naturally acquired immunity refers to the natural exposure to an infectious agent or other antigen by the body. The body responds by making its own antibodies. There are two examples of passive naturally acquired immunity: The placental transfer of IgG from mother to fetus during pregnancy that generally lasts 4 to 6 months after birth; and The IgA and IgG found in human colostrum and milk of babies who are nursed.

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13.3B: Artificially Acquired Immunity

Define and give at least one example of each of the following types of immunity:

a. artificially acquired active immunity
b. artificially acquired passive immunity

- List 3 different forms of antigen that may be used for artificially acquired active immunity and state 2 common examples of each.
- State what DTaP stands for and what specifically is being injected with the DTaP vaccine.
- Briefly compare active immunization with passive immunization in terms of tetanus prophylaxis.
- Define adjuvant.
- In artificially acquired immunity, active immunization is preferred over passive immunization. Explain why.
- Describe what is meant by herd immunity (community immunity).

Active Artificially Acquired Immunity

Active artificially acquired immunity refers to any immunization with an antigen. By giving a safe form of the antigen artificially, the body will produce its own antibodies and, more importantly, develop circulating, long-lived B-memory cells with high affinity B-cell receptors on their surface. If at a later date the body is again exposed to that same antigen, the memory cells will cause immediate and rapid production of the appropriate antibodies for protection. With artificially acquired active immunity, one is immunized with one or more of the following:

Attenuated microbes

Attenuated microbes are living, non-virulent strains of a microbe. Viruses are attenuated by growing them in non-human cells until they mutate and adapt to the non-human host. In the process, they lose virulence for humans. Viruses can also be attenuated using recombinant DNA techniques to either mutate or delete virulence genes in the viral genome.

Attenuated viral vaccines tend to be immunologically quite effective since the viruses can multiply slowly in the body, thus increasing the amount and persistence of the antigen for a greater antibody response. In addition, attenuated viruses enter the cytosol of cells and peptides from viral antigens can be presented by MHC-I molecules to activate naive T8-lymphocytes and stimulate the production of cytotoxic T-lymphocytes (CTLs). Living attenuated microbes can, however, sometimes be potentially dangerous to highly immunosuppressed individuals in whom they may cause opportunistic infections.

Examples of vaccines that contain attenuated microbes include:

- The MMR vaccine containing attenuated measles, mumps, and rubella viruses;
- The MMRV vaccine containing attenuated measles, mumps, rubella viruses and varicella zoster (chickenpox) viruses;
- The TOPV or trivalent oral polio vaccine containing attenuated poliomyelitis viruses types 1, 2, and 3;
- The yellow fever vaccine containing attenuated yellow fever viruses;
- The Var or varicella zoster virus vaccine containing attenuated varicella zoster viruses.

The body responds by producing antibodies that block viral adsorption to host cells.

Flash animation showing neutralization of a virus.

html5 version of animation for iPad showing neutralization of a virus.

Killed organisms, fragmented microorganisms, or antigens produced by recombinant DNA technology

Examples of vaccines containing killed or inactivated microbes include:

- The IPV or inactivated poliomyelitis vaccine containing inactivated poliomyelitis viruses types 1, 2, and 3;
- The rabies vaccines containing whole, killed rabies viruses;
- The influenza vaccines consist of inactivated influenza viruses, either whole or broken down;
- The hepatitis A vaccine containing inactivated hepatitis A virus;
- RV1, an attenuated strain of a human rotavirus. Rotaviruses are the most common cause of gastroenteritis in children.

Examples of vaccines containing fragments of microorganisms include the immunizations for:

- Meningococcal meningitis; contains capsular polysaccharide from 4 strains of *Neisseria meningitidis*;
- Pneumococcal pneumonia; PCV13 containing capsular material from the 13 most serious strains of *Streptococcus pneumoniae* in children conjugated to diphtheria toxoid protein; PCV 23 containing capsular material from the 23 most serious strains of *S. pneumoniae* in adults conjugated to diphtheria toxoid protein;
- *Hemophilus influenzae* type b containing capsular polysaccharide from *H. influenzae* type B conjugated to protein (either diphtheria toxoid or an outer membrane protein from *Neisseria meningitidis*).

These vaccines contain polysaccharide capsular material from the bacteria, usually conjugated to protein for greater immunogenicity. The body responds by producing opsonizing antibodies against the capsule.

Flash animation showing phagocytosis of an encapsulated bacterium through opsonization.

html5 version of animation for iPad showing phagocytosis of an encapsulated bacterium through opsonization.

While the B-cell receptors of B-lymphocytes can recognize epitopes on polysaccharides, T4-lymphocytes can only recognize peptide epitopes bound to MHC-II molecules. The protein conjugate added to the polysaccharide in the vaccine is degraded into peptides and bound to MHC-II molecules by APCs. They then present the peptide to the TCRs on T4-lymphocytes for their activation. In this way the cytokines produced by the activated T4-lymphocytes become available for use by the B-lymphocytes sensitized to the polysaccharide component of the vaccine.

c. Examples of vaccines produced by recombinant DNA technology include:

- The hepatitis B vaccine, the first human vaccine produced by recombinant DNA technology, contains hepatitis B virus surface antigen (HBsAG);
- The acellular pertussis part of the diphtheria, tetanus, and acellular pertussis vaccine (DTaP) containing diphtheria toxoid, tetanus toxoid, and antigens from the whooping cough bacterium *Bordetella pertussis* (Acellular pertussis vaccines contain inactivated pertussis toxin (PT) and may contain one or more other bacterial components (e.g., filamentous hemagglutinin [FHA], an outer-membrane protein; pertactin [Pn], and fimbriae [Fim] types 2 and 3);
- The vaccine against Lyme disease;
- Gardasil, a vaccine against human papilloma virus (HPV) types 6, 11 that cause about 90% of genital warts, and types 16, and 18 responsible for around 70% of cervical cancer in the US; and Cervarix, a vaccine against HPV types 16 and 18. Both contain recombinant L1 capsid protein from the different strains of HPV;
- RV5, an oral vaccine against human rotavirus gastroenteritis. Capsid proteins from human rotaviruses have been expressed on the surface of harmless non-human rotavirus strains.

Toxoid

A toxoid is an exotoxin treated so as to be non-poisonous but still immunogenic. Examples of vaccines containing toxoids include the diphtheria and tetanus components of the DTaP and Td vaccines. The body responds by making antibodies capable of neutralizing the exotoxin. The antigen may be adsorbed to an adjuvant, a substance such as aluminum hydroxide or aluminum phosphate that is not immunogenic but enhances the immunogenicity of antigens.

Flash animation showing neutralization of an exotoxin.

html5 version of animation for iPad showing neutralization of an exotoxin.

Routine immunization practices protect more than just the individuals receiving the vaccine. When a critical portion of a community becomes immunized against a particular infectious disease, most members of the community - including those who were not immunized - are protected against that disease because there is little opportunity for an outbreak. This is known as herd immunity or community immunity.

Passive Artificially Acquired Immunity

Passive artificially acquired immunity refers to the injection of antibody-containing serum, or immune globulin (IG), from another person or animal. Since the body is not making its own antibodies and memory cells are not produced, passive artificially acquired immunity is short lived and offers only mediate, short term protection. Also, the injection of serum during passive immunization carries a greater risk of allergic reactions than the injection of antigens during active immunization. These allergic reactions are referred to as serum sickness and will be discussed later under hypersensitivities.

Examples include:

- The use of pooled adult human immune globulin (IG) to prevent hepatitis A and measles and to prevent infections in people with certain immunodeficiency diseases;
- Human HBIG to prevent hepatitis B in those not actively immunized with the HepB vaccine;
- Human TIG to prevent tetanus in those not actively immunized with the DTP, DTaP, or Td vaccines;
- RhoGAM to prevent Rh hemolytic disease of newborns;
- VZIG to prevent varicella;
- CMV-IGIV to prevent cytomegalovirus infections in highly immunosuppressed individuals;
- RIG to prevent rabies, given concurrently with active immunization with the rabies vaccine;
- The antisera used for botulism; and
- IVIG (intravenous immune globulin), now being used to reduce infections in people with certain immunosuppressive diseases such as primary immunodeficiency syndrome and chronic lymphocytic leukemia as well as to treat certain autoimmune diseases such as immune thrombocytopenia purpura (ITP) and Kawasaki disease.

Tetanus provides a nice example of how active immunization (DTaP) and passive immunization (TIG) may be used in preventing a disease (Table $13.3B.13$.3B.1:).

Table $13.3B.13$.3B.1: Tetanus prophylaxis in Routine Wound Management

History of tetanus toxoid doses	Clean, minor wound		All other wounds (1)	
	Td (2)	TIG (3)	Td	TIG
Unknown or < 3	Yes	No	Yes	Yes
Three or more	No (4)	No	No (5)	No

(1) Such as, but not limited to, wounds contaminated with dirt, feces, soil, saliva, etc.: puncture wounds, avulsions, and wounds resulting from missles, crushing, burns, and frostbite.
(2) Tetanus toxoid, diphtheria toxoid (active immunization).
(3) Tetanus Immune Globulin (passive immunization).
(4) Yes, if more than 10 years since last dose.
(5) Yes, if more than 5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

There is also some early evidence that immunization may be of value in the treatment of some infections as well as in their prevention, possibly by supercharging the immune system of those already infected. Vaccine therapies in various stages of testing include those against diseases such as herpes, leprosy, tuberculosis, and hepatitis B.

A patient with a deep puncture wound who has never received a DTaP vaccination is given both Td and TIG. Another patient with an identical wound and who had 4 DTaP vaccinations as a child and a Td booster 3 years ago is given nothing. Discuss the reasoning behind this.

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13.E: Humoral Immunity (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

13.1: Antibodies (Immunoglobulins)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define antibody.
2. In terms of infectious disease, state what humoral immunity is most effective against.

13.1A: An Overview

13.1B: Antibody Structure

13.1C: The 5 Classes (Isotypes) of Human Antibodies

13.1D: Generation of Antibody Diversity

13.1E: Clonal Selection and Clonal Expansion

13.1F: Anamnestic (Memory) Response

13.2: Ways That Antibodies Help to Defend the Body

- List 9 ways that antibodies help to defend the body.

13.2A: Opsonization

13.2B: Cytolysis by the Membrane Attack Complex (MAC)

13.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells

13.2D: Neutralization of Exotoxins

13.2E: Neutralization of Viruses

13.2F: Preventing Bacterial Adherence

13.2G: Agglutination of Microorganisms

13.2H: Immobilization of Bacteria and Protozoans

13.2I: Promoting an Inflammatory Response

13.3: Naturally and Artificially Acquired Active and Passive Immunity

1. Define the following:
   a. active immunity
   b. passive immunity

2. Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

   1.Matching

   _____ Antibodies made in another person or animal enter the body and the immunity is short-lived.

   _____ Antigens enter the body and the body responds by making its own antibodies and B-memory cells.

   A. active immunity
   B. passive immunity

13.3A: Naturally Acquired Immunity

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Give an example of naturally acquired active immunity.
2. Give two examples of naturally acquired passive immunity.
   A.
   B.
3. State why naturally acquired passive immunity is important to newborns and infants.

13.3B: Artificially Acquired Immunity

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define and give an example of artifically acquired passive immunity.
2. Define and give an example of artifically acquired active immunity.
3. List 3 different forms of antigen that may be used for artificially acquired active immunity and state 2 common examples of each.
   A.
   B.
   C.
4. A patient with a deep puncture wound who has never received a DTP vaccinationis given both Td and TIG. Another patient with an identical wound and who had 4 DTP vaccinationsas a child and a Td booster 3 years ago is given nothing. Discuss the reasoning behind this. (hint: see Fig. 1)

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14.1: Cell-Mediated Immunity - An Overview

Learning Objectives

1. Briefly compare humoral immunity with cell-mediated immunity.
2. Define cell-mediated immunity and state what it is most effective against.
3. State three different ways by which cell-mediated immunity protects the body.
4. Define gene translocation and relate it to each T-lymphocyte being able to produce T-cell receptor with a unique shape.
5. Define the following:
    a. combinatorial diversity
    b. junctional diversity
6. In terms of cell-mediated immunity, state what is meant by anamnestic response and discuss its role in immune defense.
7. Briefly describe why there is a heightened secondary response during anamestic response.

Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen . Cellular immunity protects the body by:

1. Activating antigen-specific cytotoxic T-lymphocytes (CTLs) that are able to destroy body cells displaying epitopes of foreign antigen on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens;
2. Activating macrophages and NK cells, enabling them to destroy intracellular pathogens; and
3. Stimulating cells to secrete a variety of cytokines that influence the function of other cells involved in adaptive immune responses and innate immune responses.

Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in destroying virus-infected cells, intracellular bacteria, and cancers. It also plays a major role in delayed transplant rejection.

Generation of T-cell receptor (TCR) diversity through gene translocation

As mentioned earlier, the immune system of the body has no idea as to what antigens it may eventually encounter. Therefore, it has evolved a system that possesses the capability of responding to any conceivable antigen. The immune system can do this because both B-lymphocytes and T-lymphocytes have evolved a unique system of gene-splicing called gene translocation, a type of gene-shuffling process where various different genes along a chromosome move and join with other genes from the chromosome. To demonstrate this gene translocation process, we will look at how each T-lymphocyte becomes genetically programmed to produce a T-cell receptor (TCR) having a unique shape to fit a specific epitope.

In a manner similar to B-lymphocytes, T-lymphocytes are able to cut out and splice together different combinations of genes along their chromosomes. Through random gene translocation, any combination of the multiple forms of each gene can join together. This is known as *combinatorial diversity*. The T-cell receptors or TCRs (Figure 14.1.1) of most T-lymphocytes involved in adaptive immunity consist of an alpha (a) and a beta (ß) chain. There are 70-80 different V_a genes and 61 different J_a genes that code for the variable portion of the a chain of the TCR. Likewise, there are 52 $V_ß$ genes, 1 $D_{ß1}$ gene, 1 $D_{ß2}$ gene, and 6-7 $J_ß$ genes that can recombine to form the variable portion of the TCR.

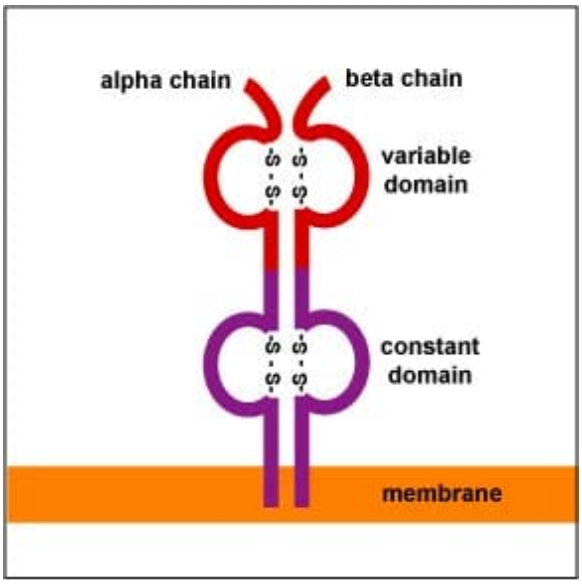


Figure 14.1.1:The T-Cell Receptor. Most T-cell receptors are composed of two polypeptide chains, an alpha (α) chain and a beta (β) chain. The variable domains of the α and β chains (red) provide specificity for binding a peptide bound to a MHC molecule. The terminus of the constant domains (purple) anchors the receptor to the cytoplasmic membrane of the T-lymphocyte. (S-S = disulfide bond)

During gene translocation, specialized enzymes in the T-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions. This change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called *junctional diversity*. Unlike the BCR, somatic hypermutation does not occur during the production of the TCRs. As a result of combinatorial diversity and junctional diversity, each T-lymphocyte is able to produce a unique shaped T-cell receptor (TCR) capable of reacting with complementary-shaped peptide bound to a MHC molecule.

Anamnestic Response (Memory)

As a result of T-lymphocytes recognizing epitopes of protein antigens during cell-mediated immunity, numerous circulating **T8-memory cells** and **T4-memory cells** develop which possess anamnestic response or memory. These T-memory cells persist for the remainder of a person's life. Effector memory T-cells (T_{EM} cells) circulate in the blood whereas tissue resident memory T-cells (T_{RM} cells) are found within the epithelium of the skin and mucous membranes. CD8 T_{RM} cells are typically activated by viral antigens and subsequently produce inflammatory cytokines that trigger an innate immune response for nonspecific antiviral activity. CD4 T_{RM} cells are found in clusters surrounding macrophages in the mucosa. Unlike T_{EM} cells, T_{RM} cells do not circulate in the blood and are not replenished from the blood. They remain in peripheral tissues.

A subsequent exposure to that same antigen results in:

- A more rapid and longer production of cytotoxic T-lymphocytes (CTLs);
- A more rapid and longer production of T4-effector lymphocytes; and
- Triggering of nonspecific innate immune responses.

Clonal Selection and Clonal Expansion

As mentioned above, during early differentiation of naive T-lymphocytes in the thymus marrow, each T4-lymphocyte and each T8-lymphocyte becomes genetically programmed to make a T-cell receptor or TCR with a unique shape through a series of gene translocations, and molecules of that TCR are put on its surface of that T-lymphocyte to function as its epitope receptor. When an antigen encounters the immune system, epitopes from protein antigens bound to MHC-I or MHC-II molecules eventually will react with a naive T4- and T8-lymphocyte with TCRs and CD4 or CD8 molecules on its surface that more or less fit and this activates that T-lymphocyte. This process is known as *clonal selection*.

Cytokines produced by effector T4-helper lymphocytes enable the now activated T4- and T8-lymphocyte to rapidly proliferate to produce large clones of thousands of identical T4- and T8-lymphocytes. In this way, even though only a few T-lymphocytes in the body may have TCR molecule able to fit a particular epitope, eventually many thousands of cells are produced with the right

specificity. This is referred to as clonal expansion. These cells then differentiate into effector T4-lymphocytes and cytotoxic T-lymphocytes or CTLs.

Cellular immunity is also the mechanism behind delayed hypersensitivity (discussed later in this unit). Delayed hypersensitivity is generally used to refer to the harmful effects of cell-mediated immunity (tissue and transplant rejections, contact dermatitis, positive skin tests like the PPD test for tuberculosis, granuloma formation during tuberculosis and deep mycoses, and destruction of virus-infected cells).

Summary

1. Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.
2. Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in destroying virus-infected cells, intracellular bacteria, and cancers.
3. In a manner similar to B-lymphocytes, T-lymphocytes are able to randomly cut out and splice together different combinations of genes along their chromosomes through a process called gene translocation. This is known as combinatorial diversity and results in each T-lymphocyte generating a unique T-cell receptor (TCR).
4. During gene translocation, specialized enzymes in the T-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions. This change in the nucleotide base sequence generates even greater diversity in the shape of the TCR. This is called junctional diversity.
5. As a result of combinatorial diversity and junctional diversity, each T-lymphocyte is able to produce a unique shaped T-cell receptor (TCR) capable of reacting with complementary-shaped peptide bound to a MHC molecule.
6. As a result of T-lymphocytes recognizing epitopes of protein antigens during cell-mediated immunity, numerous circulating T8-memory cells and T4-memory cells) develop which possess anamnestic response or memory.
7. A subsequent exposure to that same antigen results in a more rapid and longer production of cytotoxic T-lymphocytes (CTLs), and a more rapid and longer production of T4-effector lymphocytes.
8. When an antigen encounters the immune system, epitopes from protein antigens bound to MHC-I or MHC-II molecules eventually will react with a naive T4- and T8-lymphocyte with TCRs and CD4 or CD8 molecules on its surface that more or less fit and this activates that T-lymphocyte. This process is known as clonal selection.
9. Cytokines produced by effector T4-helper lymphocytes enable the now activated T4- and T8-lymphocyte to rapidly proliferate to produce large clones of thousands of identical T4- and T8-lymphocytes. This is referred to as clonal expansion.

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14.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes

Learning Objectives

1. In terms of the role of cytotoxic T-lymphocytes (CTLs) in body defense:
   a. State from what cells cytotoxic T-lymphocytes are derived.
   b. Describe how they can react with and destroy virus-infected cells, cells containing intracellular bacteria, and cancer cells without harming normal cells. (Indicate the role of following: TCR, CD4, MHC-I, and peptides from endogenous antigens.)
   c. State the mechanism by which cytotoxic T-lymphocytes kill the cells to which they bind. (Indicate the role of the following: perforins, granzymes, caspases, and macrophages in the process.)
2. Briefly describe two ways certain viruses may evade cell-mediated immunity.

Marking an Infected Cell or a Tumor Cell for Destruction by Cytotoxic T-Lymphocytes

One of the body's major defenses against viruses, intracellular bacteria, and cancers is the destruction of infected cells and tumor cells by cytotoxic T-lymphocytes (CTLs). These CTLs are effector cells derived from naive T8-lymphocytes during cell-mediated immunity. Both T8-lymphocytes and CTLs produce T-cell receptors or TCRs and CD8 molecules that are anchored to their surface.

a. The TCRs and CD8 molecules on the surface of naive T8-lymphocytes are designed to recognize peptide epitopes bound to MHC-I molecules on antigen-presenting cells or APCs .
b. The TCRs and CD8 molecules on the surface of cytotoxic T-lymphocytes (CTLs) are designed to recognize peptide epitopes bound to MHC-I molecules on infected cells and tumor cells.

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes . Other endogenous antigens such as proteins released into the cytosol from the phagosomes of antigen-presenting cells, such as macrophages and dendritic cells as well, as a variety of the human cell's own proteins (self-proteins) are also degraded by proteasomes. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides, typically 8-11 amino acids long (Figure 14.2.1).

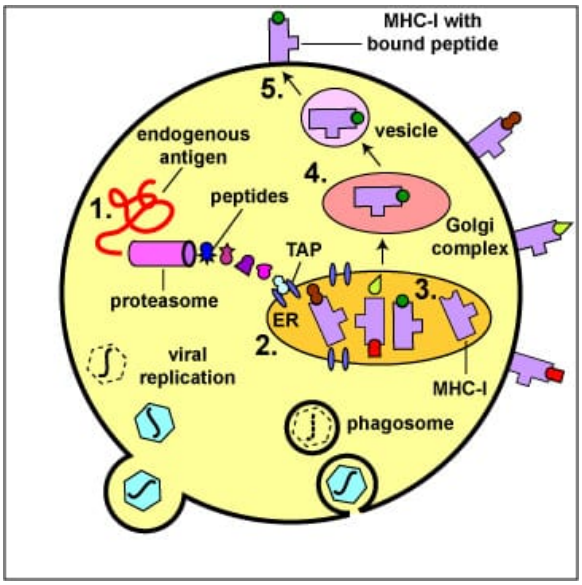
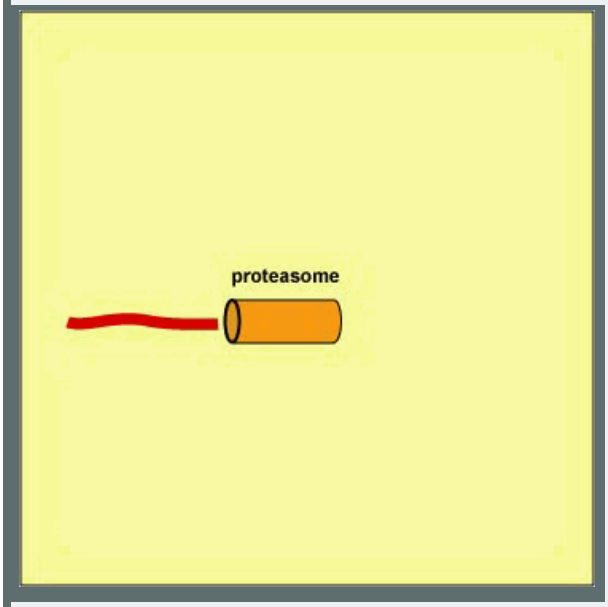


Figure 14.2.1: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Molecules. Endogenous antigens are those located within the cytosol of cells of the body. Examples include: a. viral proteins produced during viral replication, b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication, c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells d. tumor antigens produced by cancer cells, e. and self peptides from human cell proteins. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind. 1. Endogenous antigens, such as viral proteins, pass through proteasomes where they are degraded into a series of peptides. 2. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP. 3. The peptides then bind to the grooves of newly synthesized MHC-I molecules. 4. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex. 5. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.

of a proteasome degrading proteins into peptides



During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins, as well proteins released from phagosomes of phagocytes and various human cell or self-proteins, are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. As endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides, typically 8-11 amino acids long.

A transporter protein called TAP located in the membrane of the cell's endoplasmic reticulum then transports these peptide epitopes into the endoplasmic reticulum where they bind to the grooves of various newly made MHC-I molecules. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles. The exocytic vesicles carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they become anchored to its surface (Figure 14.2.2). A single cell may have up to 250,000 molecules of MHC-I with bound epitope on its surface.

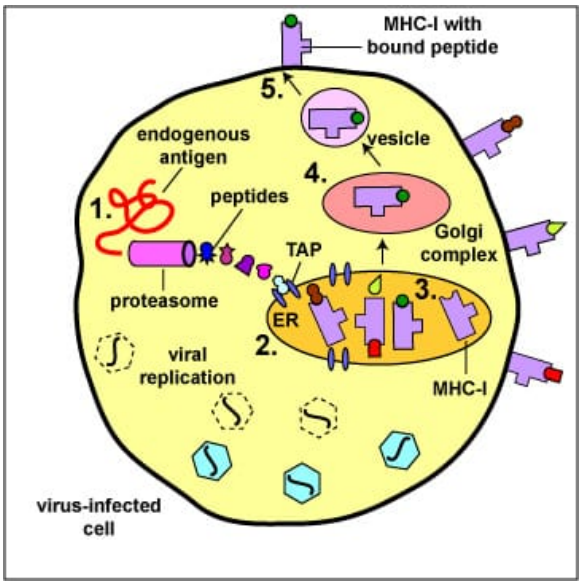


Figure 14.2.2: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Moleculesby a Virus-Infected Cell. *The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind: (1) During viral replication within the host cell, endogenous antigens, such as viral proteins, pass through proteasomes where they are degraded into a series of peptides. (2) The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP. (3) The peptides then bind to the grooves of newly synthesized MHC-I molecules. (4) The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex. (5) The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.*

During cell-mediated immunity, MHC-I molecule with bound peptide on the surface of infected cells and tumor cells can be recognized by a complementary-shaped TCR/CD8 on the surface of a cytotoxic T-lymphocyte (CTL) to initiate destruction of the cell containing the endogenous antigen (Figure 14.2.3).

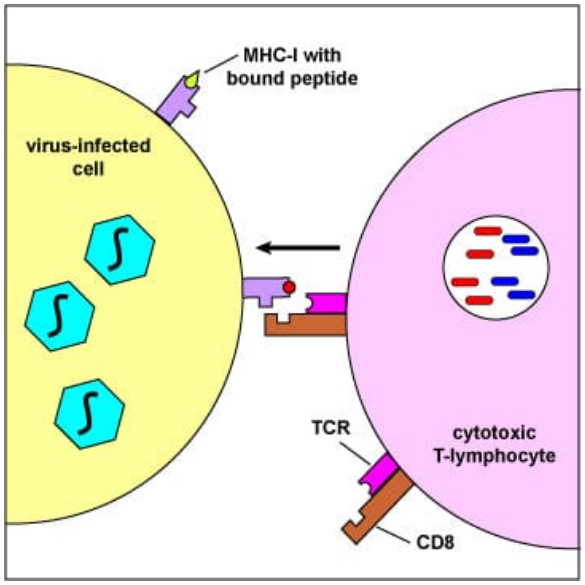


Figure 14.2.3: A Cytotoxic T-lymphocyte Recognizing a Virus-Infected Cell. Endogenous antigens are those being produced within cells of the body. Examples include proteins from replicating viruses, proteins from intracellular bacteria, and tumor antigens. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

Endogenous antigens

Endogenous antigens are those located within the cytosol of cells of the body. Examples include:

a. viral proteins produced during viral replication,
b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication,
c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells
d. tumor antigens produced by cancer cells,
e. and self peptides from human cell proteins.

The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

1. Endogenous antigens, such as viral proteins, pass through proteasomes where they are degraded into a series of peptides.
2. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP.
3. The peptides then bind to the grooves of newly synthesized MHC-I molecules.
4. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex.
5. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.

Cytotoxic T-Lymphocyte (CTL) Destruction of Body Cells Displaying Epitopes of Foreign Antigen on their Surface

The cytotoxic T-lymphocytes (CTLs) produced during cell-mediated immunity are designed to remove body cells displaying "foreign" epitope, such as virus-infected cells, cells containing intracellular bacteria, and cancer cells with mutant surface proteins. The CTLs are able to kill these cells by inducing a programmed cell death known as apoptosis. Using virus-infected cells as an example, the CTLs circulate throughout the body where they encounter virus-infected cells and induce apoptosis. This involves involves a complex of intracellular cytotoxic granules containing:

1. Pore-forming proteins called perforins
2. Proteolytic enzymes called granzymes and
3. Granulysin

When the TCR and CD8 of the CTL binds to the MHC-I/epitope on the surface of the virus-infected cell or tumor cell (Figure 14.2.4), this sends a signal through a CD3 molecule which triggers the release of the cytotoxic perforins/granzymes/granulysin granules from the CTL.

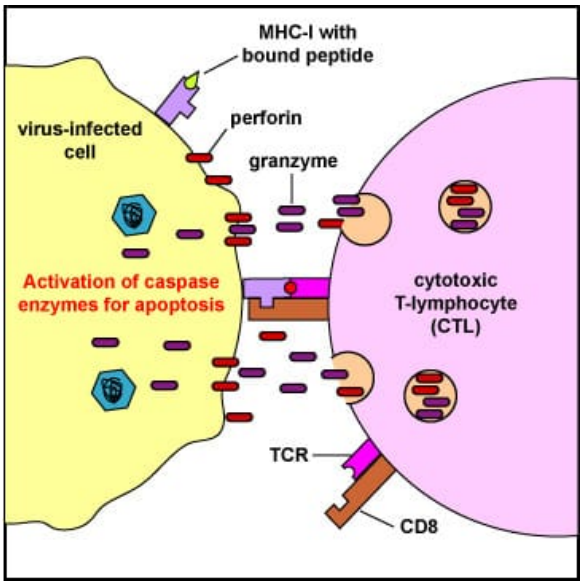


Figure 14.2.4: Cytotoxic T-lymphocyte (CTL)-Induced Apoptosis of a Virus-Infected Cell. Binding of the CTL to the infected cell triggers the CTL to release pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the caspase enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes.

The exact mechanism of entry of the granzymes into the infected cell or tumor cell is still debated. It is, however, dependent on perforins. Possibilities include:

1. The perforins/granzymes/granulysin complex may be taken into the target cell by receptor-mediated endocytosis. The perforin molecules may then act on the endosomal membrane allowing granzymes to enter the cytosol.
2. The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol (Figure 14.2.5).

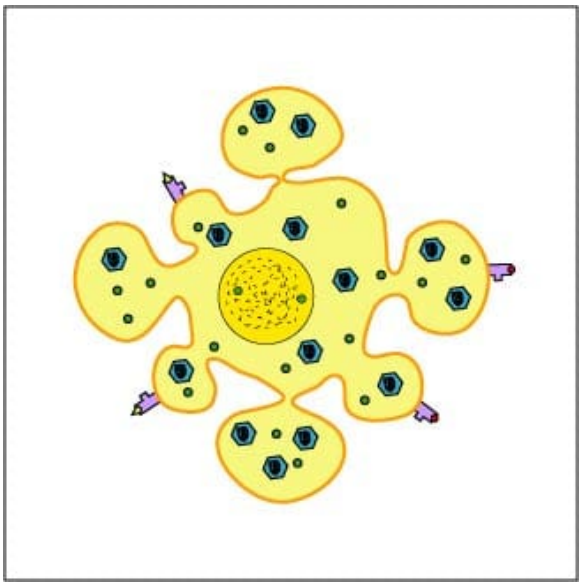


Figure 14.2.5: CTL-Induced Apoptosis of a Virus-Infected Cell. Binding of the CTL to the infected cell triggers the CTL to release pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the perforin pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. This prevents the release of any mature viruses that might occur if the infected cell was lysed.

Killing of the infected cell or tumor cell by apoptosis involves a variety of mechanisms:

1. Certain granzymes can activate the caspase enzymes that lead to apoptosis of the infected cell. The caspases are proteases that destroy the protein structural scaffolding of the cell - the cytoskeleton - and nucleases that degrade both the target cell's nucleoprotein and any microbial DNA within the cell (Figure 14.2.5).
2. Granzymes cleave a variety of other cellular substrates that contribute to cell death.
3. The perforin molecules may also polymerize and form pores in the membrane of the infected cell, similar to those produced by MAC. This can increase the permeability of the infected cell and contribute to cell death. If enough perforin pores form, the cell might not be able to exclude ions and water and may undergo cytolysis.
4. Granulysin has antimicrobial actions and can also induce apoptosis.
    - Electron micrograph of a CTL binding to a tumor cell.
    - Electron micrograph showing a killed tumor cell.

- CTLs can also trigger apoptosis through FasL/Fas interactions. Activated lymphocytes express both death receptors called Fas and Fas ligand or FasL (Figure 14.2.6) on their surface. This FasL/Fas interaction triggers an intracellular transduction that activates the caspase enzymes that lead to apoptosis. In this way, CTLs can kill other lymphocytes and terminate lymphocyte proliferation after the immune responses have eradicated an infection.

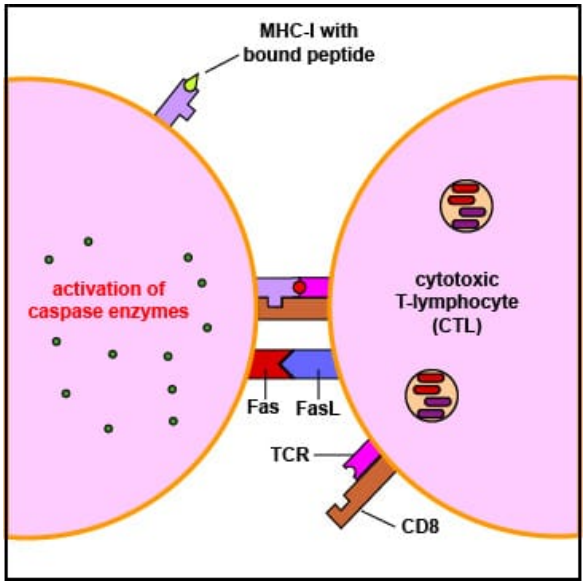


Figure 14.2.6: A Cytotoxic T-Lymphocyte (CTL) Inducing Apoptosis by Fas/FasL Interaction. A cytotoxic T-lymphocyte (CTL), by way of its TCR and CD8, can bind to MHC-I/epitope on a virus-infected and cause apoptosis by way of perforins and granzymes. In addition, a Fas ligand (FasL) on the CTL can bind to a Fas molecule on the surface of many cell types and activate the enzymes that lead to apoptosis. Most likely this mechanism is used to remove effector lymphocytes once they are no longer needed after an adaptive immune response.

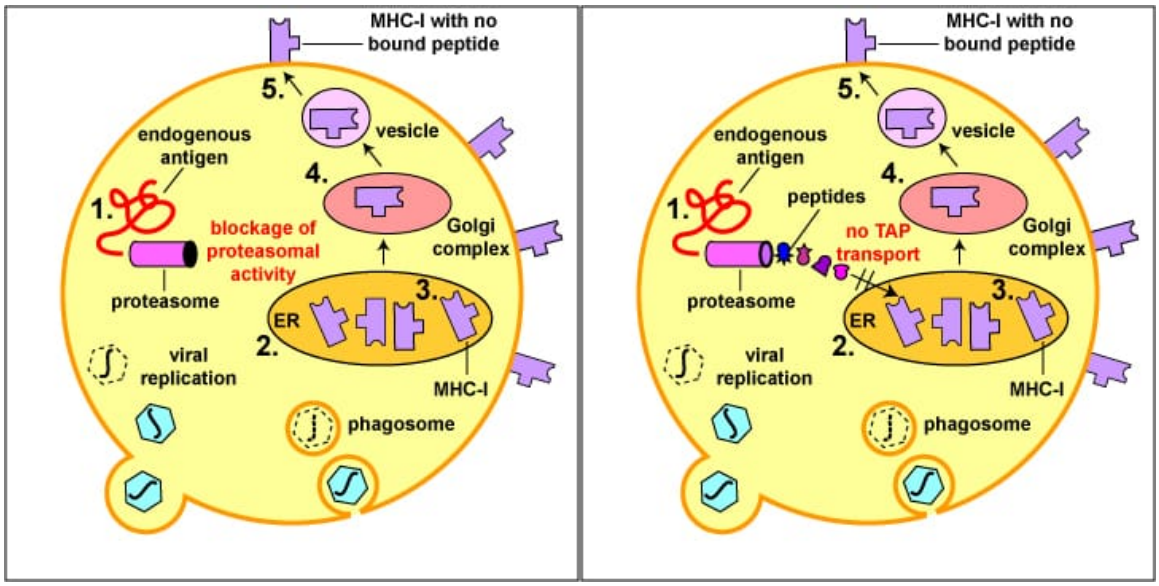
Death by apoptosis does not result in the release of cellular contents such as inflammatory mediators or viruses as occurs during immune-induced cell lysis. Instead, the cell breaks into membrane-bound apoptoptic fragments that are subsequently removed by macrophages. This reduces inflammation and also prevents the release of viruses that have assembled within the infected cell and their spread into uninfected cells. Since the CTLs are not destroyed in these reactions, they can function over and over again to destroy more virus-infected cells.

Exercise: Think-Pair-Share Questions

1. Some viruses inhibit proteasomal activity in the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.
2. Some viruses suppress the production of MHC-I molecules in the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.
3. Some viruses block the TAP transport of peptides into the endoplasmic reticulum of the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.
4. Some viruses block apoptosis of the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.

As with humoral immunity, certain microbes are able to evade to some degree cell-mediated immunity:

- Epstein-Barr virus (EBV) and cytomegalovirus (CMV) inhibit proteasomal activity so that viral proteins are not degraded into viral peptides. (see Figure 14.2.7A)
- Herpes simplex viruses (HSV) can block the TAP transport of peptides into the endoplasmic reticulum (see Figure 14.2.7B).
- Numerous viruses, such as the cytomegalovirus (CMV) and adenoviruses can block the formation of MHC-I molecules by the infected cell. As a result, no viral peptide is displayed on the infected cell and the CTLs are no longer able to recognize that the cell is infected and kill it (see Figure 14.2.7C).
- Epstein-Barr virus (EBV) down regulates several host proteins involved in attaching viral epitopes to MHC-I molecules and displaying them on the host cell's surface (see Figure 14.2.7D).
- Adenoviruses and Epstein-Barr Viruses (EBV) code for proteins that blocks apoptosis, the programmed cell suicide mechanism triggered by various defense mechanisms in order to destroy virus-infected cells.



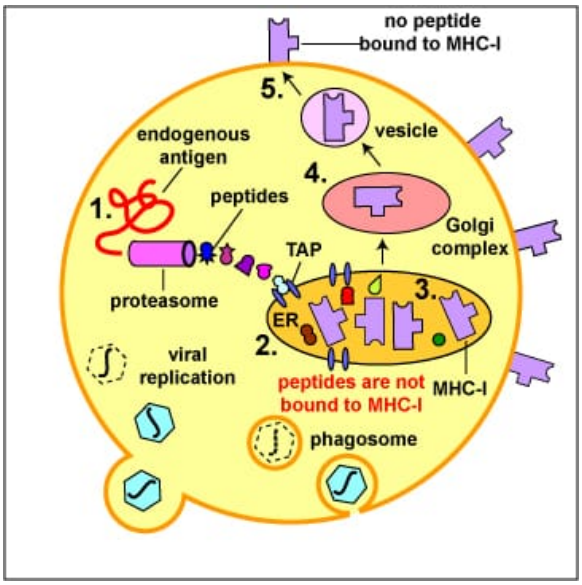


Figure 14.2.7: (top left) Inhibition of Proteasome Activity. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) inhibit proteosomal activity so that viral proteins are not degraded into viral peptides. (top right) Blockage of TAP Transport of Peptides into the Endoplasmic Reticulum. Herpes simplex viruses (HSV) can block the TAP transport of peptides into the endoplasmic reticulum. (bottom left) Suppression of the Synthesis of MHC-I Molecules. Numerous viruses, such as the cytomegalovirus (CMV) and adenoviruses can block the formation of MHC-I molecules by the infected cell. As a result, no viral peptide is displayed on the infected cell and the CTLs are no longer able to recognize that the cell is infected and kill it. (bottom right) Blockage of the Binding of Peptide Epitopes from Viruses to MHC-I Molecules. Epstein-Barr virus (EBV) down regulates several host proteins involved in attaching viral epitopes to MHC-I molecules and displaying them on the surface of the host cell. As a result, no viral peptide is displayed on the infected cell and the CTLs are no longer able to recognize that the cell is infected and kill it.

Summary

1. Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.
2. Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells.
3. One of the body's major defenses against viruses, intracellular bacteria, and cancers is the destruction of infected cells and tumor cells by cytotoxic T-lymphocytes or CTLs, effector cells derived from naïve T8-lymphocytes during cell-mediated immunity.
4. The TCRs and CD8 molecules on the surface of naive T8-lymphocytes are designed to recognize peptide epitopes bound to MHC-I molecules on antigen-presenting cells (APCs).
5. During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins (endogenous antigens) in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes.
6. These peptide epitopes bind to MHC-I molecules being synthesized in the endoplasmic reticulum which are eventually transported to the cytoplasmic membrane of that cell.
7. During cell-mediated immunity, MHC-I molecule with bound peptide on the surface of infected cells and tumor cells can be recognized by a complementary-shaped TCR/CD8 on the surface of a cytotoxic T-lymphocyte (CTL) to initiate destruction of the cell containing the endogenous antigens.
8. When the TCR and CD8 of the CTL binds to the MHC-I/epitope on the surface of the virus-infected cell or tumor cell, this triggers the release of cytotoxic perforins/granzymes/ granulysin granules from the CTL that lead to apoptosis, a programmed cell suicide of that cell.
9. Cell death by apoptosis does not result in the release of cellular contents such as inflammatory mediators or viruses as occurs during immune-induced cell lysis.
10. During apoptosis, the cell breaks into membrane-bound apoptotic fragments that are subsequently removed by macrophages.

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14.3: Activating Macrophages and NK Cells

Learning Objectives

1. Describe how T_H1 effector cells are able to interact with and activate macrophages.
2. Describe how NK cells are able to recognize and destroy infected cells and cancer cells lacking MHC-I molecules.

After interacting with APCs, some naive T4-lymphocytes differentiate into a subset of effector cells called T_H1 cells. T_H1 cells function primarily to promote phagocytosis of microbes and the killing of intracellular microbes.

Activation of Macrophages

Effector T4-lymphocytes called T_H1 cells coordinate immunity against intracellular bacteria and promote opsonization by macrophages. They produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis, Mycobacterium leprae, Leishmania donovani*, and *Pneumocystis jiroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness (Figure 14.3.1).

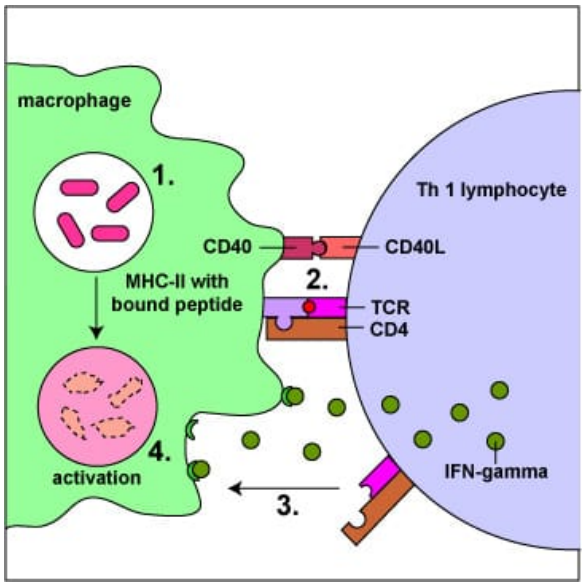


Figure 14.3.1: Activation of a Macrophage by a T_H1 Lymphocyte. (1) Engulfed bacteria inside a phagosome or a phagolysosome. (2) An activated T_H1 lymphocyte binds to a peptide/MHC-II complex on a macrophage by way of its TCR and CD4 molecule. Co-stimulatory molecules such as CD40L on the T_H1 cell then bind toCD40 on a macrophage. (3) This triggers the T_H1 lymphocyte to secrete the cytokine interferon-gamma (IFN-Î³) that binds to IFN-Î³ receptors receptors on the macrophage. (4) The IFN-Î³ activates the macrophage enabling it to produce more hydrolytic lysosomal enzymes, nitric oxide, and toxic oxygen radicals that destroy the microorganisms within the phagosomes and phagolysosomes.

They produce cytokines that promote the production of increases the production of opsonizing and complement activating IgG that enhances phagocytosis (Figure 14.3.1).

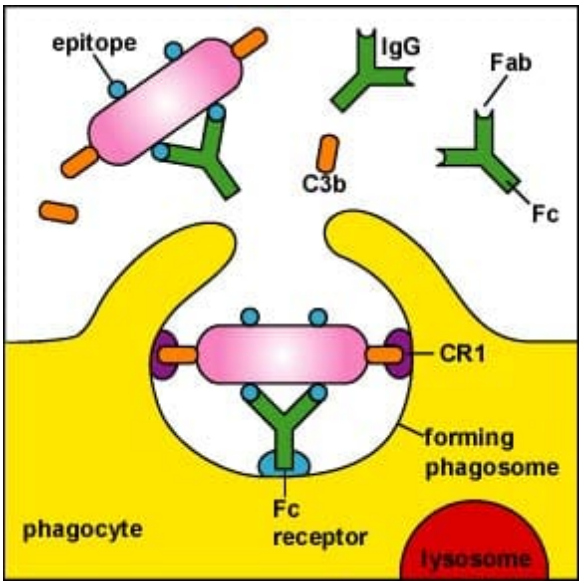


Figure 14.3.2: Opsonization (Enhanced Attachment). The Fab portion of the antibody IgG binds to epitopes of an antigen such as this bacterium. The Fc portion of IgG then binds to Fc receptors on phagocytes for opsonization or enhanced attachment. Once attached to the phagocyte the microbe can be engulfed more efficiently and placed in a phagosome. Complement pathway proteins such as C3b and C4b can also function as opsonins.

- They produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so they can be engulfed and killed by macrophages.
- They produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.
- They produce the chemokine CXCL2 to attract macrophages to the infection site.

Activated natural killer T-lymphocytes (NKT cells) also produce large amounts of IFN-gamma to activate macrophages.

Activation of macrophages Increases their production of toxic oxygen radicals, nitric oxide, and hydrolytic lysosomal enzymes enabling the killing of microbes within their phagolysosomes. It also causes the macrophages to secrete cytokines such as TNF-a, IL-1, and IL-12. TNF-a and IL-1 promote inflammation to recruit phagocytic leukocytes. lL-12 enables naive T4-lymphocytes to differentiate into T_H1 cells. Moreover activation increases the production of B7 co-stimulator molecules and MHC-1 molecules by macrophages for increased T-lymphocyte activation.

Activation of NK Cells

Cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) produced by T_H1 lymphocytes activate NK cells. NK cells are another group of cytolytic lymphocytes, distinct from B-lymphocytes and T-lymphocytes, that participate in both innate immunity and adaptive immunity. NK cells are lymphocytes that lack B-cell receptors and T-cell receptors. They are designed to kill certain mutant cells and virus-infected cells in one of two ways:

1. NK cells kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC) as shown in Figure 14.3.3 , Figure 14.3.4, and Figure 14.3.5 . The Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody. The NK cell is then able to contact the cell and by inducing a programmed cell suicide called **apoptosis**.

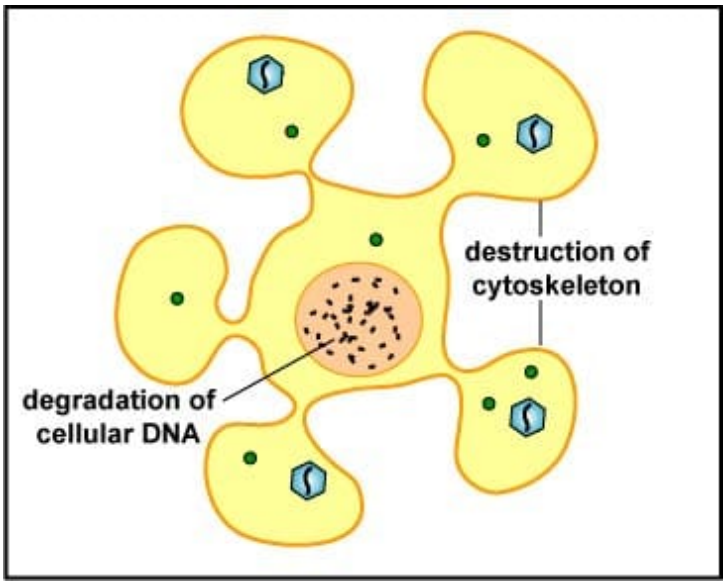


Figure 14.3.5: Destruction of Virus-Infected Cells by NK Cells through Antibody-Dependent Cellular Cytotoxicity (ADCC), Step-3. NK cells release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis, a programmed suicide of the infected cell. Apoptosis occurs when certain granzymes activate a group of protease enzymes called caspases that destroy the protein structural scaffolding of the cell, degrade the cell's nucleoprotein, and activate enzymes that degrade the cell's DNA. As a result, the infected cell breaks into membrane-bound fragments that are subsequently removed by phagocytes. If very large numbers of perforins are inserted into the plasma membrane of the infected cell, this can result in a weakening of the membrane and lead to cell lysis rather than apoptosis. An advantage to killing infected cells by apoptosis is that the cell's contents, including viable virus particles and mediators of inflammation, are not released as they are during cell lysis.

2. NK cells to use a duel receptor system in determining whether to kill or not kill human cells. When cells are either under stress, are turning into tumors, or are infected, various molecules such as MICA and MICB are produced and are put on the surface of that cell. The first receptor, called the **killer-activating receptor**, can bind to various molecules such as MICA and MICB that are produced and are put on the surface of that cell, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal. This second receptor, called the **killer-ihibitory receptor**, recognizes MHC-I molecules that are also usually present on all nucleated human cells. If MHC-I molecules are expressed on the cell, the killer-inhibitory receptor sends a negative signal that overrides the kill signal and prevents the NK cell from killing that cell (Figure 14.3.6).

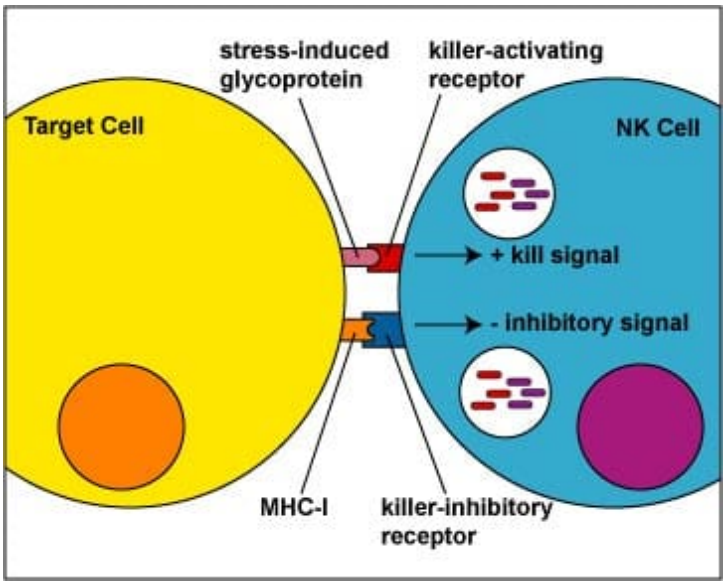


Figure 14.3.6: NK Cell Interacting with a Normal Body Cell. NK cells appear to use a duel receptor system in determining whether to kill or not kill human cells. NK cells appear to use a duel receptor system in determining whether to kill or not kill human cells. When cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell. The first NK cell receptor, called the killer-activating receptor, recognizes these stress-induced molecules. This interaction sends a positive signal which enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal. This second receptor, called the killer-inhibitory receptor, recognizes MHC-I molecules that are also usually present on all nucleated human cells. If MHC-I molecules are expressed on the cell, the killer-inhibitory receptor sends a negative signal that overrides the kill signal and prevents the NK cell from killing that cell.

Viruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound (Figure 14.3.7).

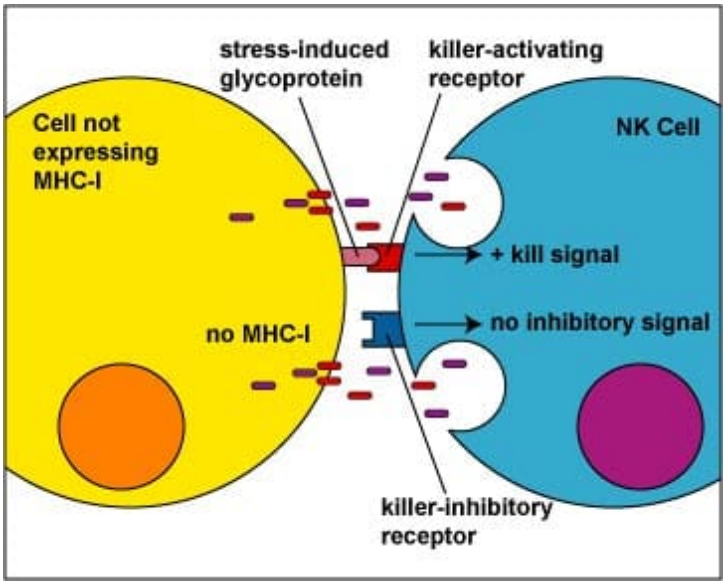


Figure 14.3.7: NK Cell Interacting with a Virus-Infected Cell or a Mutant Cell Not Expressing MHC-I Molecules. When cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell. In addition, v iruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell releases pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis.

The NK cell releases pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by macrophages (Figure 14.3.5). Perforins can also sometimes result in cell lysis. The distinction between causing apoptosis versus causing cell lysis is important because lysing a virus-infected cell would only release the virions, whereas apoptosis leads to destruction of the virus inside.

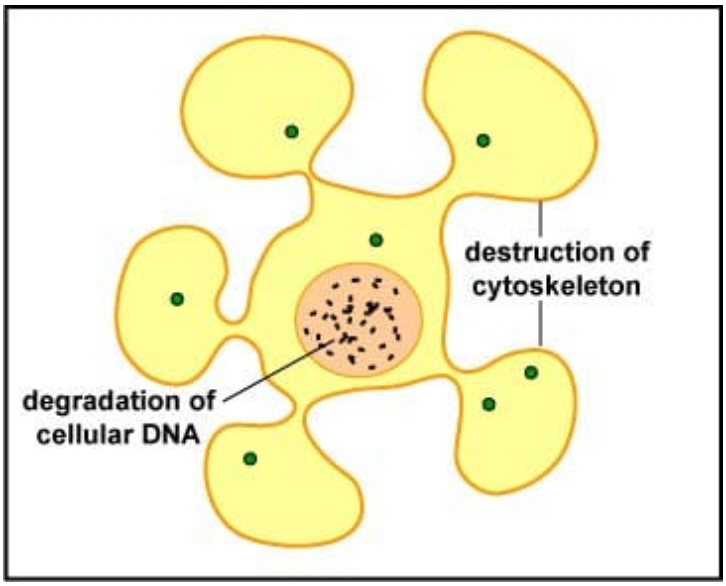


Figure 14.3.8: Apoptosis by NK Cells. Viruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound. The NK cell releases pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis.

NK cells also produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses. For example, through cytokine production NK cells also suppress and/or activate macrophages, suppress and/or activate the antigen-presenting capabilities of dendritic cells, and suppress and/or activate T-lymphocyte responses.

As with humoral immunity, certain microbes are able to evade to some degree NK cells:

- The cytomegalovirus (CMV) can also trigger its host cell to produce altered MHC-I molecules that are unable to bind viral epitopes, and, therefore, are not recognized by CTLs. However, NK cells are also unable to kill this infected cell because it is still displaying "MHC-I molecules" on its surface.
- CMV also produces microRNAs (miRNAs), small non-coding RNA molecules that down-regulates the production of stress-induced proteins that the killer-activating receptor of NK cells first recognizes. The miRNAs do this by binding to the host cell's mRNA coding for stress-induced proteins (Figure 14.3.14.3.9). Without this binding there is no kill signal by the NK cell.
- Cytomegalovirus (CMV) and herpes simplex type 1 virus (HSV-1) produce microRNAs (miRNAs), small non-coding RNA molecules that block protein involved in apoptosis, a programmed cell suicide. The miRNAs do this by binding to the host cell's mRNA coding for apoptosis-inducing proteins (Figure 14.3.9).

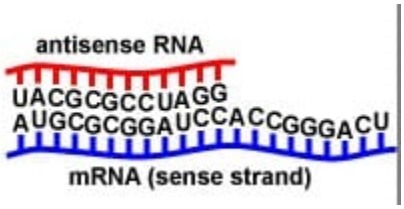


***Figure** 14.3.9**:** Antisense RNA (microRNA or miRNA). When an antisense RNA (microRNA or miRNA) that is complementary to a mRNA coding for a particular protein or enzyme binds to the mRNA by complementary base pairing, that mRNA cannot be*

translated and the protein or enzyme is not made.

Summary

1. Effector T4-lymphocytes called T_H1 cells coordinate immunity against intracellular bacteria and promote opsonization by macrophages.
2. Cytokines produced by T_H1 cells promote cell-mediated immunity against intracellular pathogens by activating macrophages and enhancing their antimicrobial effectiveness, increasing the production of opsonizing and complement activating IgG that enhances phagocytosis, and promoting diapedesis and chemotaxis of macrophages to the infection site.
3. Activation of natural killer T-lymphocytes (NKT cells) produces large amounts of IFN-gamma to activate macrophages.
4. Cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) produced by T_H1 lymphocytes activate NK cells.
5. Activated NK cells kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC).
6. Activated NK cells also use a duel receptor system in determining whether to kill or not kill cells such as cancer cells and infected cells that are displaying stress molecules and are not producing MHC-I molecules.
7. NK cells kill infected cells and cancer cells by inducing apoptosis, a programmed cell suicide.

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14: CELL-MEDIATED IMMUNITY

Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. Cellular immunity protects the body by:

- Activating antigen-specific cytotoxic T-lymphocytes (CTLs) that are able to lyse body cells displaying epitopes of foreign antigen on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens;
- Activating macrophages and NK cells, enabling them to destroy intracellular pathogens; and
- Stimulating cells to secrete a variety of cytokines that influence the function of other cells involved in adaptive immune responses and innate immune responses.

Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in destroying virus-infected cells, intracellular bacteria, and cancers. It also plays a major role in delayed transplant rejection.

14.1: Cell-Mediated Immunity - An Overview

14.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes

14.3: Activating Macrophages and NK Cells

14.4: Stimulating Cells to Secrete Cytokines

14.E: Cell-Mediated Immunity (Exercises)

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14.4: Stimulating Cells to Secrete Cytokines

Learning Objectives

1. Define cytokine and explain what is meant by "cytokines are pleiotropic, redundant, and multifunctional."
2. Name 3 cytokines that regulate innate immune responses by triggering an inflammatory response.
3. Name the group of cytokines that regulates innate immunity by preventing translation of viral mRNA and by degrading both viral and host cell RNA.
4. Name 4 cytokines that regulate adaptive immune responses.
5. Name 2 cytokines that stimulate hematopoiesis.

Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems. They are produced by virtually all cells involved in innate and adaptive immunity, but especially by T helper (T_H) lymphocytes. The activation of cytokine-producing cells triggers them to synthesize and secrete their cytokines. The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity in some manner. Cytokines are pleiotropic, redundant, and multifunctional.

- Pleiotropic means that a particular cytokine can act on a number of different types of cells rather than a single cell type.
- Redundant refers to to the ability of a number of different cytokines to carry out the same function.
- Multifunctional means the same cytokine is able to regulate a number of different functions.

Some cytokines are antagonistic in that one cytokine stimulates a particular defense function while another cytokine inhibits that function. Other cytokines are synergistic wherein two different cytokines have a greater effect in combination than either of the two would by themselves. There are three functional categories of cytokines:

1. Cytokines that regulate innate immune responses,
2. Cytokines that regulate adaptive Immune responses, and
3. Cytokines that stimulate hematopoiesis.

Cytokines that Regulate Innate Immunity

a. Cytokines that regulate innate immunity are produced primarily by mononuclear phagocytes such as macrophages and dendritic cells, although they can also be produced by T-lymphocytes, NK cells, endothelial cells, and mucosal epithelial cells. They are produced primarily in response to pathogen-associated molecular patterns (PAMPs) such as LPS, peptidoglycan monomers, teichoic acids, unmethylated cytosine-guanine dinucleotide or CpG sequences in bacterial and viral genomes, and double-stranded viral RNA. Cytokines produced in response to PRRs on cell surfaces, such as the inflammatory cytokines IL-1, IL-6, IL-8, and TNF-alpha, mainly act on leukocytes and the endothelial cells that form blood vessels in order to promote and control early inflammatory responses (Figure 14.4.1).

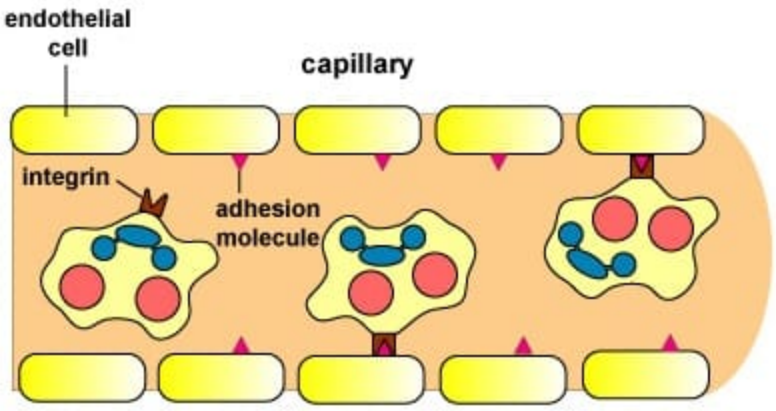


Figure 14.4.1: Diapedesis During Inflammation. Integrins on the surface of the leukocyte bind to adhesion molecules on the inner surface of the vascular endothelial cells. The leukocytes flatten out and squeeze between the endothelial cells to leave the blood vessels and enter the tissue. The increased capillary permeability also allows plasma to enter the tissue.

Cytokines produced in response to PRRs that recognize viral nucleic acids, such as type I interferons, primarily block viral replication within infected host cells (Figure 14.4.2).

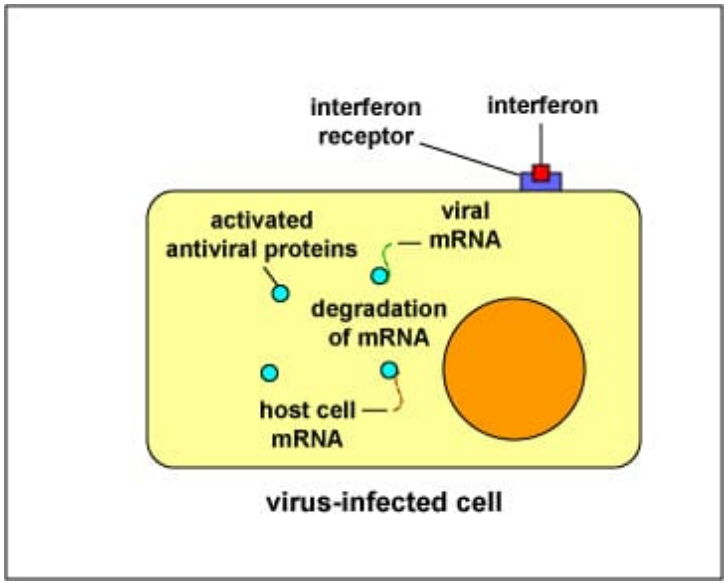


Figure 14.4.2: Antiviral Action of Interferon. Step 1 (left) Viral replication stimulates the infected host cell to produce type I interferons. Step 2 (right) Produced by immune-activated cells or virus-infected cells in response to the double-stranded RNA (dsRNA) that many viruses produce as a part of their life cycle, interferons exert their antiviral activity by binding to uninfected neighboring cells and inducing them to produce enzymes that degrade mRNA. This not only prevents translation of viral mRNA into viral protein it also eventually kills the host cell, the factory producing the viruses. Interferons also enhance body defenses against viruses by enhancing the activities of CTLs, macrophages, NK cells, and antibody-producing cells.

Examples include:

1. Tumor necrosis factor-alpha (TNF-a): TNF-a is the principle cytokine that mediates acute inflammation. In excessive amounts it also is the principal cause of systemic complications such as the shock cascade. Functions include acting on endothelial cells to stimulate inflammation and the coagulation pathway; stimulating endothelial cells to produce selectins and ligands for leukocyte integrins (Figure 14.4.1) during diapedesis; stimulating endothelial cells and macrophages to produce chemokines that contribute to diapedesis, chemotaxis, and the recruitment of leukocytes; stimulating macrophages to secrete interleukin-1 (IL-1) for redundancy; activating neutrophils and promoting extracellular killing by neutrophils; stimulating the liver to produce acute phase proteins, and acting on muscles and fat to stimulate catabolism for energy conversion. In addition, TNF is cytotoxic for some tumor cells; interacts with the hypothalamus to induce fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; and activates macrophages. TNF is produced by monocytes,macrophages, dendritic cells, T_H1 cells, and other cells.

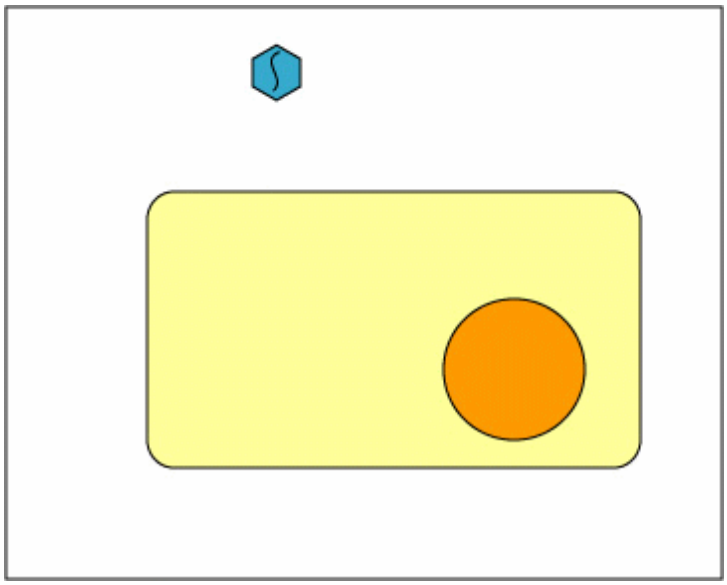
2. Interleukin-1 (IL-1): IL-1 function similarly to TNF in that it mediates acute inflammatory responses. It also works synergistically with TNF to enhance inflammation. Functions of IL-1 include promoting inflammation; activating the coagulation pathway, stimulating the liver to produce acute phase proteins, catabolism of fat for energy conversion, inducing fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; stimulates the synthesis of adhesion factors on endothelial cells and leukocytes (Figure 14.4.1) for diapedesis; and activates macrophages. IL-1 is produced primarily by monocytes, macrophages, dendritic cells, endothelial cells, and some epithelial cell.
3. Chemokines: Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation. They increase the affinity of integrins on leukocytes for ligands on the vascular wall (Figure 14.4.1) during diapedesis, regulate the polymerization and depolymerization of actin in leukocytes for movement and migration, and function as chemoattractants for leukocytes. In addition, they trigger some WBCs to release their killing agents for extracellular killing and induce some WBCs to ingest the remains of damaged tissue. Chemokines also regulate the movement of B-lymphocytes, T-lymphocytes, and dendritic cells through the lymph nodes and the spleen. When produced in excess amounts, chemokines can lead to damage of healthy tissue as seen in such disorders as rheumatoid arthritis, pneumonia, asthma, adult respiratory distress syndrome (ARDS), and septic shock. Examples of chemokines include IL-8, MIP-1a, MIP-1b, MCP-1, MCP-2, MCP-3, GRO-a, GRO-b, GRO-g, RANTES, and eotaxin. Chemokines are produced by many cells including leukocytes, endothelial cells, epithelial cells, and fibroblasts.
4. Interleukin-12 (IL-12): IL-12 is a primary mediator of early innate immune responses to intracellular microbes. It is also an inducer of cell-mediated immunity. It functions to stimulate the synthesis of interferon-gamma by T-lymphocytes and NK cells; increases the killing activity of cytotoxic T-lymphocytes and NK cells; and stimulates the differentiation of naive T4-lymphocytes into interferon-gamma producing T_H1 cells. It is produced mainly by macrophages and dendritic cells.
5. Type I Interferons: Interferons modulate the activity of virtually every component of the immune system. Type I interferons include 13 subtypes of interferon-alpha, interferon-beta, interferon omega, interferon-kappa, and interferon tau. (There is only one type II interferon, interferon-gamma, which is involved in the inflammatory response.)

The most powerful stimulus for type I interferons is the binding of viral DNA or RNA to toll-like receptors TLR-3, TLR-7, and TLR-9 in endosomal membranes.

a. TLR-3 - binds double-stranded viral RNA;
b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs;
c. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes but uncommon or masked in human DNA and RNA.

Signaling pattern recognition receptors located in the cytoplasm of cells such as RIG-1 and MDA-5 also signal synthesis and secretion of type-I interferons.

Type I interferons, produced by virtually any virus-infected cell, provide an early innate immune response against viruses. Interferons induce uninfected cells to produce enzymes capable of degrading mRNA. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade both viral and cellular mRNA. This not only blocks viral protein synthesis, it also eventually kills the infected cell (Figure 14.4.2). In addition, type I interferons also cause infected cells to produce enzymes that interfere with transcription of viral RNA or DNA. They also promote body defenses by enhancing the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-producing cells.



Antiviral Action of Interferon Interferon induces uninfected cells to produce enzymes capable of degrading mRNA. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade both viral and cellular mRNA. This not only blocks viral protein synthesis, it also eventually kills the infected cell.

Type I interferons also induce MHC-I antigen expression needed for recognition of antigens by cytotoxic T-lymphocytes; augment macrophage, NK cell, cytotoxic T-lymphocytes, and B-lymphocyte activity; and induce fever. Interferon-alpha is produced by T-lymphocytes, B-lymphocytes, NK cells, monocytes/macrophages; interferon-beta by virus-infected cells, fibroblasts, macrophages, epithelial cells, and endothelial cells.

6. Interleukin-6 (IL-6): IL-6 functions to stimulate the liver to produce acute phase proteins; stimulates the proliferation of B-lymphocytes; and increases neutrophil production. IL-6 is produced by many cells including T-lymphocytes, macrophages, monocytes, endothelial cells, and fibroblasts.

7. Interleukin-10 (IL-10): IL-10 is an inhibitor of activated macrophages and dendritic cells and as such, regulates innate immunity and cell-mediated immunity. IL-10 inhibits their production of IL-12, co-stimulator molecules, and MHC-II molecules, all of which are needed for cell-mediated immunity. IL-10 is produced mainly by macrophages, and T_H2 cells.

8. Interleukin 15 (IL-15): IL-15 stimulates NK cell proliferation and proliferation of memory T8-lymphocytes. IL-15 is produced by various cells including macrophages.

9. Interleukin-18 (IL-18): IL-18 stimulates the production of interferon-gamma by NK cells and T-lymphocytes and thus induces cell-mediated immunity. It is produced mainly by macrophages.

Cytokines that Regulate Adaptive Immune Responses (Humoral Immunity and Cell-Mediated Immunity)

Cytokines that regulate adaptive immunity are produced primarily by T-lymphocytes that have recognized an antigen specific for that cell. These cytokines function in the proliferation and differentiation of B-lymphocytes and T-lymphocytes after antigen recognition and in the activation of effector cells.

Examples include:

1. Interleukin-2 (IL-2): IL-2 is a growth factor for NK cells and antigen-stimulated T-lymphocytes and B-lymphocytes. IL-2 also increases the killing ability of NK cells; increases the synthesis of other cytokines; increases Fas-mediated apoptosis; and stimulates antibody synthesis by B-lymphocytes. IL-2 is produced mainly by T4-lymphocytes and to a lesser extent T8-lymphocytes.

2. Interleukin-4 (IL-4): IL-4 is a major stimulus for production of the antibody isotype IgE and the development of T_h2 cells for defense against helminths and arthropods. It also antagonizes the effects of interferon-gamma and thus inhibits cell-mediated immunity. IL-4 is produced mainly by T_H2 cells and mast cells.
3. Interleukin-5 (IL-5): IL-5 is a growth and activating factor for eosinophils as a defense against helminths and arthropods. It also stimulates the proliferation and differentiation of antigen-activated B-lymphocytes and the production of IgA. IL-5 is produced mainly by T_H2 cells.
4. Interferon-gamma (IFN-?):Interferons modulate the activity of virtually every component of the immune system. Type I interferons include more than 20 types of interferon-alpha, interferon-beta, interferon omega, and interferon tau. There is only one type II interferon, interferon-gamma. Type II interferon is produced by activated T-lymphocytes as part of an immune response and functions mainly to promote the activity of the components of the cell-mediated immune system such as CTLs, macrophages, and NK cells. IFN-? is the principal cytokine for activating macrophages. It also induces the production of MHC-I molecules, MHC-II molecules, and co-stimulatory molecules by APCs in order to promote cell-mediated immunity and activates and increases the antimicrobial and tumoricidal activity of monocytes, macrophages, neutrophils, and NK cells. IFN-? stimulates the differentiation of T4-lymphocytes into T_H1 cells and inhibits the proliferation of T_H2 cells; stimulates the production of IgG subclasses that activate the complement pathway and promote opsonization; and augments or inhibits other cytokine activities. IFN-? is produced primarily by T_H1 cells, $CD8^+$ cells, and NK cells.
5. Transforming growth factor-beta (TGF-ß): TGF-ß functions to inhibit the proliferation and effector function of T-lymphocytes; inhibit the proliferation of B-lymphocytes; and inhibits macrophage function. It also promotes tissue repair. TGF-ß is produced by T-lymphocytes, macrophages, and other cells.
6. Lymphotoxin (LT): LT plays a role in the recruitment and activation of neutrophils and in lymphoid organogenesis. Being chemically similar to TNF, LT is also a mediator of acute inflammatory responses. LT is made by T-lymphocytes.
7. Interleukin-13 (IL-13): IL-13 increases the production of IgE by B-lymphocytes, inhibits macrophages, and increases mucus production. IL-13 is made primarily by T_H2 cells.

Cytokines that Stimulate Hematopoiesis

Produced by bone marrow stromal cells, these cytokines stimulate the growth and differentiation of immature leukocytes.

Examples include:

1. *Colony-stimulating factors (CSF)*: Promote the production of colonies of the different leukocytes in the bone marrow and enhance their activity. Examples include granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), and macrophage colony stimulating factor (M-CSF). In addition to their role in promoting production of leukocyte colonies, the CSFs also appear to promote their function. For example, when GM-CSF binds to receptors on neutrophils, eosinophils, and monocytes, it activates these cells and inhibits their apoptosis. GM-CSF increases adhesion of these cells to capillary walls during diapedesis, enhances their phagocytosis and extracellular killing, and increases both superoxide anion generation and antibody-dependent cytotoxicity. The various CSFs are produced by T-lymphocytes, macrophages, and other cells.
2. *Stem cell factor*: Stem cell factor makes stem cells in the bone marrow mor responsive to the various CSFs. It is made mainly by bone marrow stromal cells.
3. *Interleukin-3 (IL-3)*: IL-3 supports the growth of multilineage bone marrow stem cells. IL-3 is made primarily by T-lymphocytes.
4. *Interleukin-7 (IL-7)*: IL-7 plays a role in the survival and proliferation of immature B-lymphocyte and T-lymphocyte precursors. Il-7 is produced mainly my fibroblasts and bone marrow stromal cells.

Some viruses cause infected host cells to secrete molecules that bind and tie up cytokines, preventing them from binding to normal cytokine receptors on host cells.

- Poxviruses cause infected host cells to secrete molecules that bind interleukin-1 (IL-1) and interferon-gamma (IFN-gamma).
- Cytomegaloviruses (CMV) cause infected host cells to secrete molecules that bind chemokines.

Summary

1. Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
2. Cytokines are pleiotropic, meaning that a particular cytokine can act on a number of different types of cells rather than a single cell type.

3. Cytokines are redundant, meaning that a number of different cytokines to carry out the same function.
4. Cytokines are multifunctional, meaning the same cytokine is able to regulate a number of different functions.
5. There are three functional categories of cytokines: Cytokines that regulate innate immune responses; cytokines that regulate adaptive Immune responses; and cytokines that stimulate hematopoiesis.
6. Type I interferons provide an early innate immune response against viruses. Interferons induce uninfected cells to produce enzymes capable of degrading mRNA. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade both viral and cellular mRNA. This not only blocks viral protein synthesis, it also eventually kills the infected cell.

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14.E: Cell-Mediated Immunity (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

14.1: Cell-Mediated Immunity: An Overview

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State three different ways by which cell-mediated immunity protects the body.
   A.
   B.
   C.
2. Define gene translocation.
3. Relate gene translocation to each T-lymphocyte being able to produce a T-cell receptor with a unique shape.
4. Define the following:
   a. combinatorial diversity
5. In terms of humoral immunity, discuss what is meant by anamnestic response.
6. Briefly describe why there is a heightened secondary response during anamestic response.

14.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. The role of cytotoxic T-lymphocytes (CTLs) in body defense.
   a. State from what cells cytotoxic T-lymphocytes are derived.
   b. Describe how they can react with and destroy virus-infected cells, cells containing intracellular bacteria, and cancer cells without harming normal cells. (Indicate the role of following: TCR, CD4, MHC-I, and peptides from endogenous antigens.)
   c. State the mechanism by which cytotoxic T-lymphocytes kill the cells to which they bind. (Indicate the role of the following: perforins, granzymes, caspases, and macrophages in the process.)

14.3: Activating Macrophages and NK Cells

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Viruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. This enables them to resist destruction by cytoyoxic T-lymphocytes. However the body is still able to kill these infected cells and tumor cells. Describe how.
2. Describe how T_H1 effector cells are able to interact with and activate macrophages.

14.4: Stimulating Cells to Secrete Cytokines

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Name 4 cytokines that regulate adaptive immune responses.
2. Name 3 cytokines that regulate innate immune responses by triggering an inflammatory response.

3. Name 2 cytokines that stimulate hematopoiesis.
4. Name the group of cytokines that regulates innate immunity by preventing translation of viral mRNA and by degrading both viral and host cell RNA.

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15.1: Primary Immunodeficiency

Learning Objectives

1. Define primary immunodeficiency.
2. Compare and contrast conventional and novel primary immunodeficiencies.
3. Name four categories of conventional immunodeficiencies and give an example of each.

A primary immunodeficiency is usually an immunodeficiency that one is born with. Until recently, primary immunodeficiencies were defined as a rare recessive genetic defect in the immune responses that involved the development of B-lymphocytes, T-lymphocytes, or both and resulted in multiple, recurrent infections during infancy. Depending on the disorder, the lymphocytes in question were either completely absent, present in very low levels, or present but not functioning normally. These disorders represent the conventional immunodeficiencies.

However, based on our increased understanding of the human genome and immune responses it now appears that there are a multitude of common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses. These so called novel primary immunodeficiencies involve the decreased ability to combat just a single type of infection or a narrow range of infections. The conventional primary immunodeficiencies were grouped as follows:

Conventional: B-lymphocyte Disorders

In the case of B-lymphocyte disorders, there may be may be greatly decreased humoral immunity but cell-mediated immunity , mediated by T-lymphocytes, remains normal.

1. Agammaglobulinemias: Few if any antibodies are produced and there are reduced B-lymphocyte numbers. The person is very susceptible to recurrent infections by common pyogenic bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Neisseria meningitidis,* and *Hemophilus influenzae. These* bacteria have antiphagocytic capsules that are normally eliminated by antibodies through opsonization. Examples include X-linked agammaglobulinemia and Autosomal recessive agammaglobulinemia.

2. Hypogammaglobulinemias /Isotype Defects: Decreased general antibody production or decrease production of a single isotype of antibody. Examples include:

- *IgG2 subclass deficiency:* A person is unable to produce the subclass of IgG called IgG2 but can produce other classes of antibodies. There is increased susceptibility to bacterial infections.
- *Selective IgA deficiency:* A person is unable to make IgA but can produce other classes of antibodies. There is increased susceptibility to bacterial infections and certain protozoan infections.
- *Combined Variable Immunodeficiency* (CVID): Hypogammaglobulinemia with normal or decreased numbers of B-lymphocytes.

More severe forms such as agammaglobulinemia are treated with artificially-acquired passive immunization - periodic injections of large amounts of immune globulin (IG or IVIG).

Conventional: T-lymphocyte Disorders

In the case of T-lymphocyte disorders, there is little or no cell-mediated immunity if the disorder involves T8-lymphocytes and/or T4-lymphocytes. There may also be decreased humoral immunity if there is a disorder involves T4-lymphocytes.

1. MHC Expression Defects

- MHC-I deficiency. Decreased levels of MHC-I production and reduced T8-lymphocyte numbers.
- Bare lymphocyte syndrome. Decreased levels of MHC-II, decreased numbers of T4-lymphocytes, and decreased T4-dependent antibody production by B-lymphocytes.

2. T-Lymphocyte Signaling Defects

- Wiskott-Aldrich syndrome. Defective T-lymphocyte activation and defective leukocyte mobility.
- Proximal TCR signaling defects. Defective cell-mediated immunity and defective T4-dependent antibody production by B-lymphocytes.

3. Familial Hemophagocytic Lymphohistiocytosis

- Perforin deficiencies. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs.
- Granule fusion defects. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs.
- X-linked lymphoproliferative syndrome. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs. Uncontrolled Epstein-Barr virus - induced B-lymphocyte proliferation.

Conventional: Combined B- and T-lymphocyte Disorders (Severe Combined Immunodeficiency Disease or SCID)

Severe combined immunodeficiency disease or SCID affects both humoral immunity and cell-mediated immunity . There is a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.

1. Cytokine-Signaling Defects

- Autosomal recessive SCID. Shows a marked decrease in T-lymphocytes but normal to increased levels of B-lymphocytes. There is reduced antibody levels due to the lack of T4-helper lymphocytes.
- X-linked recessive SCID. Shows a marked decrease in T-lymphocytes but normal to increased levels of B-lymphocytes. There is reduced antibody levels due to the lack of T4-helper lymphocytes.

2. Defects in Nucleotide Salvage Pathways

- PNP deficiency. Shows a progressive decrease in both T-lymphocytes, B-lymphocytes, and NK cells, as well as reduced antibody levels.
- ADA deficiency. Shows a progressive decrease in both T-lymphocytes, B-lymphocytes, and NK cells, as well as reduced antibody levels.

3. Defects in V(D)J Recombination (Combinatorial Diversity)

- RAG1 or RAG2 deficiency. Shows an absence or deficiency of both T-lymphocytes and B-lymphocytes, as well as reduced antibody levels.
- ARTEMIS defects. Shows an absence or deficiency of both T-lymphocytes and B-lymphocytes, as well as reduced antibody levels.

4. Defective Thymus Development

The thymus is needed for the development of T-lymphocytes from stem cells.

- DiGeorge syndrome. Shows decreased levels of T-lymphocytes, normal levels of B-lymphocytes, and reduced antibody levels.
- Defective pre-TCR checkpoint. Shows decreased levels of T-lymphocytes, normal or reduced levels of B-lymphocytes, and reduced antibody levels.

Conventional: Innate Immunity Disorders

- Chronic granulomatous disease. No oxygen-dependant killing pathway in phagocytes. Recurrent intracellular bacterial and fungal infections.
- Leukocyte adhesion deficiencies. Defective leukocyte adhesion, diapedesis , and migration. Recurrent bacterial and fungal infections.
- Chediak-Higashi syndrome. Defective vesicle fusion and lysosomal function in neutrophils, dendritic cells, macrophages and

other cells. Recurrent infections by pyogenic bacteria.

Novel Immunodeficiencies

While the rare conventional primary immunodeficiencies mentioned above are still very important, based on our increased understanding of the human genome and immune responses it now appears that there are a multitude of common, less severe primary immunodeficiencies. These so called novel *primary immunodeficiencies* relate to an individual's own unique genetics and can involve one or more of many immunity genes, ranging from any of the huge number of genes conferring protective immunity in general, to individual genes conferring specific immunity to a single pathogen.

It is now thought that almost every person suffers from one form of primary immunodeficiency or another. Unlike the classical primary immunodeficiencies, however, these primary Examples include:

- Disorders of the interleukin-12/interferon-gamma pathway appear to make individuals more susceptible to *Mycobacterium* and *Salmonella* infections.
- Disorders of the TLR-3 pathway makes individuals more susceptible to herpes simplex virus encephalitis.
- Disorders of the toll-interleukin 1 receptor/nuclear factor kappa B pathway makes individuals more susceptible to staphylococcal and pneumococcal infections.
- Disorders of properdin and terminal components of the complement pathways make individuals more susceptible to *Neisseria* infections.
- People with chronic sinusitis that does not respond well to treatment have decreased activity of TLR-9 and produce reduced levels of human beta-defensin 2, as well as mannan-binding lectin needed to initiate the lectin complement pathway.

Summary

1. Immunodeficiency results in an inability to combat certain diseases.
2. A primary immunodeficiency is usually an immunodeficiency that one is born with.
3. Conventional primary immunodeficiencies are rare recessive genetic defect in the immune responses that involved the development of B-lymphocytes, T-lymphocytes, or both and resulted in multiple, recurrent infections during infancy. Depending on the disorder, the lymphocytes in question were either completely absent, present in very low levels, or present but not functioning normally.
4. Conventional primary immunodeficiencies include B-lymphocyte disorders, T-lymphocyte disorders, Severe combined immunodeficiency disease or SCID,and innate immunity disorders.
5. B-lymphocyte disorders may result in greatly decreased humoral immunity but cell-mediated immunity, mediated by T-lymphocytes, remains normal.
6. T-lymphocyte disorders may result in little or no cell-mediated immunity if the disorder involves T8-lymphocytes and/or T4-helper lymphocytes. There may also be decreased humoral immunity if there is a disorder involves T4-helper lymphocytes.
7. Severe combined immunodeficiency disease deficiencies affect both humoral immunity and cell-mediated immunity may result in a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.
8. Innate immunity disorders are due to defects in genes that play a role in innate immune responses.
9. Novel primary immunodeficiencies include a multitude of common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses resulting in the decreased ability to combat just a single type of infection or a narrow range of infections.

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15.2: Secondary Immunodeficiency

Learning Objectives

1. State what is meant by secondary immunodeficiency and list four possible contributing factors.
2. Briefly give at least four mechanisms of HIV-induced immunodeficiency.

In the case of secondary immunodeficiency, one is born with normal immune responses but some secondary factor or occurrence causes a decrease in immune responses. Secondary immunodeficiency is induced by factors such as:

- Malnutrition. Inhibits lymphocyte maturation and function.
- Some viruses, e.g., HIV. Depletes T4-lymphocytes.
- Irradiation - exposure to X-rays and gamma rays. Causes a decreased production of lymphocyte precursors in the bone marrow.
- Cytotoxic drugs such as many used in cancer chemotherapy. Causes a decreased production of lymphocyte precursors in the bone marrow.
- Corticosteroids – anti-inflammatory steroids. Damages lymphocytes.
- Leukemias, cancers of the lymphoid system, metastases. Reduces areas for lymphocyte development.
- Aging. Adaptive immunity, especially cell-mediated immunity, tends to diminish with aging.
- Removal of the spleen. Decreased ability to remove microbes that enter the blood.

A secondary immunodeficiency of current notoriety is of course Acquired Immunodeficiency Syndrome or AIDS, a secondary immunodeficiency caused by Human Immunodeficiency Virus (HIV). As we saw in Unit 4, HIV, via its gp120, primarily infects cells with CD4 molecules and chemokine receptors on their surface, namely, T4-lymphocytes, macrophages, and dendritic cells. The median incubation period for AIDS is around 10 years.

During early or acute HIV infection the virus primarily infects and destroys memory T4-lymphocytes which express the chemokine receptor CCR5 and are very abundant in mucosal lymphoid tissues. Here HIV also encounters the dendritic cells located throughout the epithelium of the skin and the mucous membranes where in their immature form called Langerhans cells they are attached by long cytoplasmic processes. The envelope glycoproteins gp41 and gp120 of HIV contain mannose-rich glycans that bind to mannan-binding proteins (pattern recognition receptors; also called lectin receptors) on the dendritic cells.

Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by pro-inflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, the dendritic cells have matured and are now able to present antigens of HIV to naive T-lymphocytes located in the the lymph nodes in order to induce adaptive immune responses.

At this point the infection has transitioned from the acute phase to the chronic phase. The chronic phase of HIV infection is characterized by viral dissemination, viremia, and induction of adaptive immune responses. The viremia allows the viruses to spread and infect T4-helper lymphocytes, macrophages, and dendritic cells found in peripheral lymphoid tissues.

During the chronic phase of HIV infection, the lymph nodes and the spleen become sites for continuous viral replication and host cell destruction. During most of this phase, the immune system remains active and competent and there are few clinical symptoms. A steady state-infection generally persists where T4-lymphocyte death and T4-lymphocyte replacement by the body are in equilibrium. In a person infected with HIV, somewhere between one and two billion of these T4-cells die each day as a result of HIV infection and must be replaced by the body's lymphopoietic system in the bone marrow. It is estimated that 10 billion virions are produced and cleared in an infected individual each day. However, the enormous turnover of T4-lymphocytes eventually exhausts the lymphopoietic system and it becomes unable to replace the T4-cells being destroyed. A variety of mechanisms then eventually lead to immunodeficiency.

Mechanisms of HIV-induced immunodeficiency include:

- Direct HIV-induced cytopathic effect on infected T4-lymphocytes. This can occur through:
  - Increased cell permeability as a result of gp41 expression in the host cell membrane and viral release by budding;
  - Inhibition of host cell protein synthesis as a result of viral replication within the infected cell; and

    - Fusion of infected T4-cells with numerous uninfected T4-cells resulting in syncytia formation.
- Killing of HIV-infected T4-cells by cytotoxic T-lymphocytes or CTLs.
- Killing of HIV-infected T4-cells by antibody-dependent cytotoxicity or ADCC.
- Apoptosis of T4-cells as a result of chronic activation by HIV and by cytokines.
- Shedding of gp120 molecules by HIV. This subsequently triggers a series of events that cause the adaptive immune system to become less and less effective, primarily by altering the normal balance of immunoregulatory T_H1 and T_H2 cells in the body.
- Impaired function of HIV infected macrophages and dendritic cells.

To further complicate problems, during the replication of HIV the reverse transcriptase of HIV exhibits a high error rate as it transcribes the RNA genome into DNA. As a result, HIV readily mutates to become more immunoresistant, more drug resistant, and able to change the preferred cell type it is able to infect, e.g., M-tropic to T-tropic as shown in Figure 15.2.2.

Progression to AIDS is marked by a viral load that progressively increases in number while the immune system weakens as a result of the destruction of increasing numbers of T4-lymphocytes and the inability of the body to continually replace these destroyed cells. The loss of T4-helper lymphocytes leads to a marked decline in cells called cytotoxic T-lymphocytes (CTLs), the primary cells the body's immune responses use to destroy virus-infected cells. Once a person progresses to full-blown AIDS he or she becomes susceptible to a variety of opportunistic infections by:

- bacteria such as *Mycobacterium avium* complex (MAC), *Salmonella*, and *Nocardia*;
- protozoa such as *Cryptosporidium* and *Toxoplasma*;
- viruses such as cytomegalovirus (CMV), herpes simplex viruses types 1 and 2 (HSV-1, HSV-2), and varicella zoster virus (VZV);
- *Candida, Cryptococcus, Coccidioides, Histoplasma*, and *Pneumocystis*.

There is also an increased incidence of tumors, such Epstein-Barr virus-associated B-cell lymphomas, other lymphomas, cervical cancer, and Kaposi’s sarcoma. Wasting syndrome and encephalopathy are also common.

Summary

A secondary immunodeficiency is one in which a person is born with normal immune responses but some secondary factor or occurrence causes a decrease in immune responses. Causes of secondary immunodeficiencies include malnutrition, some viruses such as HIV, irradiation, cytotoxic drugs used in cancer chemotherapy, anti-inflammatory steroids, leukemias, aging, and removal of the spleen. HIV infects and destroys T4-lymphocytes and when the body becomes unable to replace the T4-lymphocytes as fast as they are being destroyed, secondary immunodeficiency results.

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15.E: Immunodeficiency (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

15.1: Primary Immunodeficiency

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

   ____ Rare but severe primary immunodeficiencies occuring as the result of a rare recessive genetic defect in the immune responses that involves the development of B-lymphocytes, T-lymphocytes, or both and results in multiple, recurrent infections during infancy.

   ____ Common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses. They involve the decreased ability to combat just a single type of infection or a narrow range of infections and relate to an individual's own unique genetics.

   _____ There may be greatly decreased humoral immunity but cell-mediated immunity remains normal. X-linked agammaglobulinemia and selective IgA deficiency are examples. May be treated with artificially-acquired passive immunization.

   _____ Primary immunodeficiencies that affect both humoral immunity and cell-mediated immunity. There is a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.

   a. B-lymphocyte disorder
   b. combined B-lymphocyte and T-lymphocyte disorder
   c. novel primary immunodeficiency
   d. conventional primary immunodeficiency
2. Infants born with a nonfunctional thymus develop frequent and severe infections. Explain.

15.2: Secondary Immunodeficiency

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what is meant by secondary immunodeficiency and list 4 possible contributing factors.
2. Briefly give three mechanisms of HIV-induced immunodeficiency.

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16.1: Immediate Hypersensitivities: Type I

Describe the mechanism for Type I (IgE-mediated) hypersensitivity and give 3 examples. State how they are treated symptomatically.

- Describe how desensitization (allergy) shots work to lessen the severity of Type I hypersensitivities.
- Briefly describe how monoclonal antibodies against the Fc portion of IgE may someday be used to prevent Type I allergies.
- When a person has hay fever, common symptoms include runny eyes, runny nose, swollen sinuses, and difficulty in breathing. In terms of humoral immunity, discuss the mechanism behind these symptoms. Also state the reason for giving antihistamines.

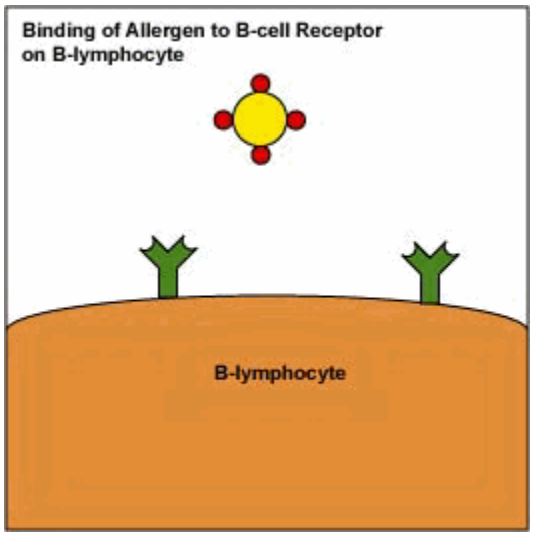


Figure 16.1.3: Type-I Hypersensitivity, Step-3. Allergen cross reacting with IgE on mast cell.

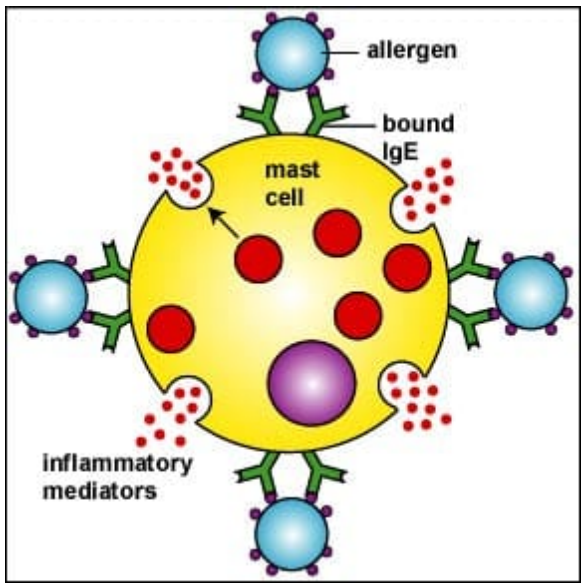


Figure 16.1.4: *Type-I Hypersensitivity, Step-4 . The next time the allergen enters the body, it cross-links the Fab portions of the IgE bound to the mast cell. This triggers the mast cell to degranulate, that is, release its histamine and other inflammatory mediators. The inflammatory mediators are now able to bind to receptors on target cells which leads to dilation of blood vessels, constriction of bronchioles, excessive mucus secretion, and other symptoms of allergy.*

Flash animation showing the mechanism behind Type-1 hypersensitivity.

html5 version of animation for iPad showing the mechanism behind Type-1 hypersensitivity.

For More Information: Five Classes of Human Antibodies from Unit 6

For More Information: TH1 and TH2 cells from Unit 6

For More Information: Inflammation from Unit 5

Late phase allergic reactions may begin several hours after exposure to antigen. It is thought that basophils play a major role here. Cell-bound IgE on the surface of basophils of sensitive individuals binds a substance called histamine releasing factor (possibly produced by macrophages and B-lymphocytes) causing further histamine release.

The inflammatory agents released or produced cause the following:

a. Dilation of blood vessels. This causes local redness (erythema) at the site of allergen delivery. If dilation is widespread, this can contribute to decreased vascular resistance, a drop in blood pressure, and shock.
b. Increased capillary permeability. This causes swelling of local tissues (edema). If widespread, it can contribute to decreased blood volume and shock.
c. Constriction of bronchial airways. This leads to wheezing and difficulty in breathing.
d. Stimulation of mucous secretion. This leads to congestion of airways.
e. Stimulation of nerve endings. This leads to itching and pain in the skin.

In a systemic anaphylaxis, the allergin is usually picked up by the blood and the reactions occur throughout the body. Examples include severe allergy to insect stings, drugs, and antisera. With a localized anaphylaxis, the allergin is usually found localized in the mucous membranes or the skin. Examples include allergy to hair, pollen, dust, dander, feathers, and food.

Type I hypersensitivity is treated symptomatically with such agents as:

a. Epinephrine. Epinephrine relaxes smooth muscle, constricts blood vessels, and stimulates the heart. It is used for severe systemic reactions.
b. Histamine H1-receptor antagonists. Antihistamines block the binding of histamine to histamine H1-receptors on target cells, e.g., loratadine, fexofenadine, cetirizine.
c. Beta2- agonists. Increase cyclic AMP levels leading to relaxation of bronchial smooth muscles and inhibit mast cell degranulation, e.g., albuterol, salmeterol, formoterol.
d. Leukotriene receptor antagonists. Block smooth muscle constriction, e.g., pranlukast.
e. Sodium cromoglycate. Sodium cromoglycate prevents mast cells from releasing histamines.
f. Nasally administered steroids. Corticosteroids are potent antiinflammatory agents.

Severity may be reduced by desensitization shots (allergy shots). It is thought that when very dilute allergen is given by injection, it stimulates the production of IgG and IgA. IgG and IgA then act as blocking antibodies to bind and neutralize much of the allergen in secretions before it can bind to the deeper cell-bound IgE on the mast cells in the connective tissue. The shots also appear to suppress production of IgE by inducing tolerance and/or by activating T8-suppressor cells.

A new experimental approach to treating and preventing Type-I hypersensitivity involves giving the person with allergies injections of monoclonal antibodies that have been made against the Fc portion of human IgE. This, in turn, blocks the attachment of the IgE to the Fc receptors on mast cells and basophils and the subsequent release of histamine by those cells upon exposure to allergen. In addition, the anti-IgE binds to IgE-producing B-lymphocytes causing apoptosis. The monoclonal antibody is a humanized hybrid molecule consisting of a mouse binding (Fab) portion attached to a human constant (Fc) portion and is known as rhuMab (recombinant human monoclonal antibody).

Flash animation showing the use of monoclonal antibodies to block the attachment of IgE to mast cells.

html5 version of animation for iPad showing the use of monoclonal antibodies to block the attachment of IgE to mast cells.

Summary

1. Immediate hypersensitivities refer to humoral immunity (antigen/antibody reactions) causing harm.
2. During Type I (IgE mediated or anaphylactic-type) hypersensitivity, IgE is made in response to an allergen.
3. In allergic individuals, the levels of IgE may be thousands of times higher than in those without allergies.
4. The Fc portion of IgE binds to the surface of mast cells and basophils and when the allergen subsequently cross-links the Fab portions of the mast cell-bound IgE, this triggers the release of inflammatory mediators such as histamine release by the mast cell, as well as the synthesis of other inflammatory mediators such as platelet-activating factor, leukotrienes, bradykinins, prostaglandins, and cytokines that contribute to inflammation.
5. The inflammatory agents then lead to dilation of blood vessels (redness or erythema, increased capillary permeability (swelling or edema), constriction of bronchial airways (wheezing and difficulty in breathing), stimulation of mucous secretion (congestion of airways), and stimulation of nerve endings (itching and pain in the skin).
6. In a systemic anaphylaxis, the allergin is usually picked up by the blood and the reactions occur throughout the body and can lead to shock. Examples include severe allergy to insect stings, drugs, and antisera.
7. With a localized anaphylaxis, the allergin is usually found localized in the mucous membranes or the skin. Examples include allergy to hair, pollen, dust, dander, feathers, and food.
8. Type I hypersensitivity is treated symptomatically with anti-inflammatory agents such antihistamines and epinephrine.
9. Desensitization shots (allergy shots) are thought to stimulate the production of IgG and IgA which then act as blocking antibodies to bind and neutralize much of the allergen in secretions before it can bind to the deeper cell-bound IgE on the mast cells in the connective tissue.
10. Monoclonal antibodies that have been made against the Fc portion of human IgE have also been used in treatment. They block the attachment of the IgE to the Fc receptors on mast cells and basophils and the subsequent release of histamine by those cells upon exposure to allergen.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe the mechanism for Type I (IgE-mediated) hypersensitivity and give two examples. State how they are treated symptomatically. *(ans)*
2. When a person has hay fever, common symptoms include runny eyes, runny nose, swollen sinuses, and difficulty in breathing. In terms of humoral immunity, discuss the mechanism behind these symptoms. Also state the reason for giving antihistamines and describe how allergy shots may lessen the severity of this type of hypersensitivity. *(ans)*
3. Researchers are hoping that the injection of monoclonal antibodies against IgE may someday be used to prevent virtually any Type I hypersensitivity. Explain. *(ans)*

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15: IMMUNODEFICIENCY

15.1: Primary Immunodeficiency
15.2: Secondary Immunodeficiency
15.E: Immunodeficiency (Exercises)

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16: HYPERSENSITIVITIES

Hypersensitivities are a set of undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Immediate hypersensitivities refer to humoral immunity (antigen/antibody reactions) causing harm. Delayed hypersensitivities refer to cell-mediated immunity (cytotoxic T-lymphocytes, macrophages, and cytokines) leading to harm.

16.1: Immediate Hypersensitivities: Type I

16.2: Immediate Hypersensitivities: Type II

16.3: Immediate Hypersensitivities: Type III

16.4: Immediate Hypersensitivities - Type V

16.5: Delayed Hypersensitivities - Type IV

16.6: Superantigens

16.E: Hypersensitivities (Exercises)

Template:HideTOC

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16.2: Immediate Hypersensitivities: Type II

Describe the mechanism for Type II (antibody-dependent cytotoxicity) hypersensitivity and give 2 examples.

Mechanism: Either IgG or IgM is made against normal self antigens as a result of a failure in immune tolerance , or a foreign antigen resembling some molecule on the surface of host cells enters the body and IgG or IgM made against that antigen then cross reacts with the host cell surface. The binding of these antibodies to the surface of host cells then leads to:

a. Opsonization of the host cells whereby phagocytes stick to host cells by way of IgG, C3b, or C4b and discharge their lysosomes (see Figure 16.2.1 and Figure 16.2.2);

Flash animation showing opsonization of cells during Type-II hypersensitivity.

html5 version of animation for iPad showing opsonization of cells during Type-II hypersensitivity.

b. Activation of the classical complement pathway causing MAC lysis of the cells (see Figure 16.2.3 and Figure 16.2.4); and

Flash animation showing MAC lysis of cells during Type-II hypersensitivity.

html5 version of animation for iPad showing MAC lysis of cells during Type-II hypersensitivity.

c. ADCC destruction of the host cells whereby NK cells attach to the Fc portion of the antibodies. The NK cell then release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. (see Figure 16.2.5 , Figure 16.2.5A, and Figure 16.2.6).

Flash animation showing ADCC destruction of cells during Type-II hypersensitivity.

html5 version of animation for iPad showing ADCC destruction of cells during Type-II hypersensitivity.

Flash animation showing apoptosis of cells during Type-II hypersensitivity.

html5 version of animation for iPad showing apoptosis of cells during Type-II hypersensitivity.

For More Information: Five Classes of Human Antibodies from Unit 6

For More Information: Opsonization from Unit 6

For More Information: MAC Cytolysis from Unit 6

For More Information: ADCC from Unit 6

Examples include:

- AB and Rh blood group reactions;
- autoimmune diseases such as:
  - rheumatic fever where antibodies result in joint and heart valve damage;
  - idiopathic thrombocytopenia purpura where antibodies result in the destruction of platelets;
  - myasthenia gravis where antibodies bind to the acetylcholine receptors on muscle cells causing faulty enervation of muscles;
  - Goodpasture's syndrome where antibodies lead to destruction of cells in the kidney;
  - multiple sclerosis where antibodies are made against the oligodendroglial cells that make myelin, the protein that forms the myelin sheath that insulates the nerve fiber of neurons in the brain and spinal cord; and
- some drug reactions.

Type II hypersensitivity also participates in early transplant rejections.

Summary

1. During type II (antibody-dependent cytotoxicity) hypersensitivity, either IgG or IgM is made against normal self antigens as a result of a failure in immune tolerance, or a foreign antigen resembling some molecule on the surface of host cells enters the body and IgG or IgM made against that antigen then cross reacts with the host cell surface.
2. The binding of these antibodies to the surface of host cells then leads to opsonization of the host cells, membrane attack complex (MAC) lysis of the cells, and antibody-dependent cellular cytotoxicity (ADCC) destruction of the host cells.
3. Examples include AB and Rh blood group reactions and autoimmune diseases such as rheumatic fever, acute glomerulonephritis, myasthenia gravis, and multiple sclerosis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe the mechanism for Type II (antibody-dependent cytotoxicity) hypersensitivity and give 2 examples. *(ans)*

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16.3: Immediate Hypersensitivities: Type III

Describe the mechanism for Type III (immune complex-mediated) hypersensitivity and give 2 examples.

Mechanism: This is caused when soluble antigen-antibody (IgG or IgM) complexes, which are normally removed by macrophages in the spleen and liver, form in large amounts and overwhelm the body (see Figure 16.3.1). These small complexes lodge in the capillaries, pass between the endothelial cells of blood vessels - especially those in the skin, joints, and kidneys - and become trapped on the surrounding basement membrane beneath these cells (see Figure 16.3.2). The antigen/antibody complexes then activate the classical complement pathway (see Figure 16.3.3). This may cause:

a. Massive inflammation, due to complement protein C5a triggering mast cells to release inflammatory mediators;

b. Influx of neutrophils, due to complement protein C5a, resulting in neutrophils discharging their lysosomes and causing tissue destruction through extracellular killing and causing further inflammation (see Figure 16.3.4 and Figure 16.3.5);

c. MAC lysis of surrounding tissue cells, due to the membrane attack complex, $C5_b6789_n$;

d. Aggregation of platelets, resulting in more inflammation and the formation of microthrombi that block capillaries; and

e. Activation of macrophages, resulting in production of inflammatory cytokines and extracellular killing causing tissue destruction.

GIF animation showing inflammation and tissue death during Type-III hypersensitivity.

This can lead to tissue death and hemorrhage.

For More Information: Five Classes of Human Antibodies from Unit 6

For More Information:The Classical Complement Pathway from Unit 5

Examples include:

- serum sickness, a combination type I and type III hypersensitivity;
- autoimmune acute glomerulonephritis;
- rheumatoid arthritis;
- systemic lupus erythematosus;
- some cases of chronic viral hepatitis; and
- the skin lesions of syphilis and leprosy.

Summary

1. Type III (immune complex-mediated) hypersensitivity is caused when soluble antigen-antibody (IgG or IgM) complexes, which are normally removed by macrophages in the spleen and liver, form in large amounts and overwhelm the body.
2. These small complexes lodge in the capillaries, pass between the endothelial cells of blood vessels - especially those in the skin, joints, and kidneys - and become trapped on the surrounding basement membrane beneath these cells.
3. The antigen/antibody complexes then trigger excessive activation of the classical complement pathway leading to a massive inflammatory response, influx of neutrophils with extracellular killing of body tissue, MAC lysis of tissue, and aggregation of platelets and macrophages.
4. Examples include Serum sickness, autoimmune acute glomerulonephritis, rheumatoid arthritis, and systemic lupus

erythematosus.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe the mechanism for Type III (immune complex-mediated) hypersensitivity and give 2 examples. *(ans)*

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16.4: Immediate Hypersensitivities - Type V

Describe the mechanism for Type V (Stimulatory) hypersensitivity and give an example.

Type V (Stimulatory Hypersensitivity) invovles making Antibodies are made against a particular hormone receptor on a hormone-producing cell. This leads to the overstimulation of those hormone-producing cells. An example is Graves' disease where antibodies are made against thyroid-stimulating hormone receptors of thyroid cells. The binding of the antibodies to the TSH receptors results in constant stimulation of the thyroid leading to hyperthyroidism.

Summary

1. During type V (stimulatory hypersensitivity) antibodies are made against a particular hormone receptor of a hormone-producing cell leading to the overstimulation of those hormone-producing cells.
2. An example is Graves' disease where antibodies are made against thyroid-stimulating hormone receptors of thyroid cells.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe the mechanism for Type V (Stimulatory) hypersensitivity and give an example. *(ans)*

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16.5: Delayed Hypersensitivities - Type IV

Learning Objectives

1. Describe the mechanism for Type IV (delayed) hypersensitivity and give two examples.

Delayed hypersensitivity is *cell-mediated* rather than *antibody-mediated*. The underlying Mechanism of delayed hypersensitivity is the same mechanism as cell-mediated immunity. T8-lymphocytes become sensitized to an antigen and differentiate into cytotoxic T-lymphocytes while effector T4-lymphocytes become sensitized to an antigen and produce cytokines . CTLs, cytokines, eosinophils, and/or macrophages then cause harm rather than benefit (Figure 16.5.1).

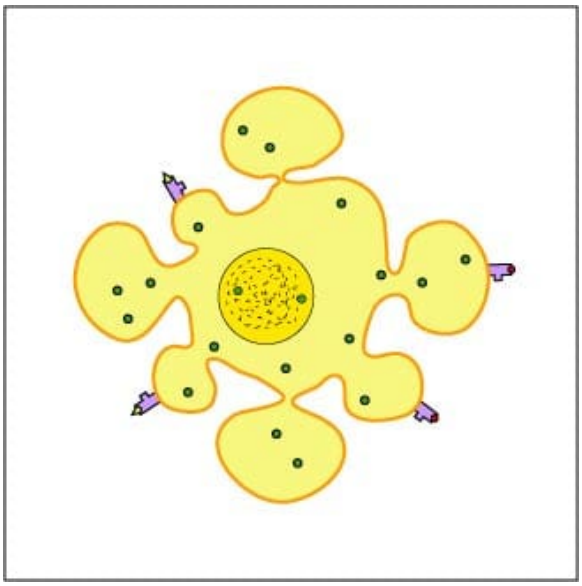


Figure 16.5.1: (left) Cytotoxic T-lymphocyte (CTL)-Induced Apoptosis of a Cross-Reacting Normal Cell during Type IV Hypersensitivity, step-1 (right) Binding of the CTL to a cross-reacting normal cell triggers the CTL to release pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the perforin pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes.

- CTLs use their TCR/CD8 to bind to peptide epitopes bound to MHC-I on infected cells or normal cells having cross-reacting epitopes and kill them through apoptosis.
- T_H1 cells activate macrophages causing the production of inflammatory cytokines and extracellular killing by the macrophages leading to tissue damage.
- T_H2 cells produce interleukin-4 (IL-4) and interleukin-5 (IL-5) to promote extracellular killing by eosinophils and causing tissue damage.

Examples include:

- the cell or tissue damage done during diseases like tuberculosis, leprosy, smallpox, measles, herpes infections, candidiasis, and histoplasmosis;
- the skin test reactions seen for tuberculosis and other infections;
- contact dermatitis like poison ivy;
- type-1 insulin-dependent diabetes where CTLs destroy insulin-producing cells;
- multiple sclerosis, where T-lymphocytes and macrophages secrete cytokines that destroy the myelin sheath that insulates the nerve fibers of neurons;
- Crohn's disease and ulcerative colitis; and
- psoriasis.

Delayed hypersensitivity also plays a major role in chronic transplant rejection as a result of CTL destruction of donor cells (host versus graft rejection) or recipient cells (graft versus host rejection). Immunosuppressive drugs such as cyclosporin A or FK-506 (Tacrolimus) are given in an attempt to prevent rejection. Both of these drugs prevent T-lymphocyte proliferation and differentiation by inhibiting the transcription of IL-2.

Summary

1. During delayed hypersensitivity,T8-lymphocytes become sensitized to an antigen and differentiate into cytotoxic T-lymphocytes (CTLs) while effector T4-lymphocytes become sensitized to an antigen and produce cytokines.
2. CTLs, cytokines, eosinophils, and/or macrophages then cause harm rather than benefit.
3. Examples include the cell or tissue damage done during diseases like tuberculosis, leprosy, smallpox, measles, herpes infections, candidiasis, and histoplasmosis, the skin test reactions seen for tuberculosis and other infections, contact dermatitis like poison ivy, type-1 insulin-dependent diabetes where CTLs destroy insulin-producing cells, multiple sclerosis, where T-lymphocytes and macrophages secrete cytokines that destroy the myelin sheath that insulates the nerve fibers of neurons, and Crohn's disease and ulcerative colitis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe the mechanism for Type IV (delayed) hypersensitivity and give 2 examples. *(ans)*

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16.6: Superantigens

Learning Objectives

1. Define superantigen.
2. Briefly describe the mechanism by which superantigens cause harm to the body.
3. Name 2 superantigens and give an example of a bacterium that produces each.

As was learned earlier under Bacterial Pathogenicity, superantigens are type I toxins that can trigger a harmful immune response. Exotoxins are toxins, often proteins in nature, secreted from a living bacterium but also released upon bacterial lysis. In addition, some bacteria use a type 3 secretion system or a type 4 secretion system to inject toxins directly into human cells. There are three main types of exotoxins:

1. Superantigens (Type I toxins),
2. Exotoxins that damage host cell membranes (Type II toxins)
3. A-B toxins and other toxin that interfere with host cell function (TypeIII toxins).

We will look at superantigens and their role in hypersensitivity.

Learning Objectives

1. Define superantigen.
2. Briefly describe the mechanism by which superantigens cause harm to the body.
3. Name 2 superantigens and give an example of a bacterium that produces each.

Highlighted Bacterium

1. Read the description of *Streptococcus pyogenes* and match the bacterium with the description of the organism and the infection it causes.

Superantigens are unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes. They bind to the surface of the target cell but do not enter the cell.

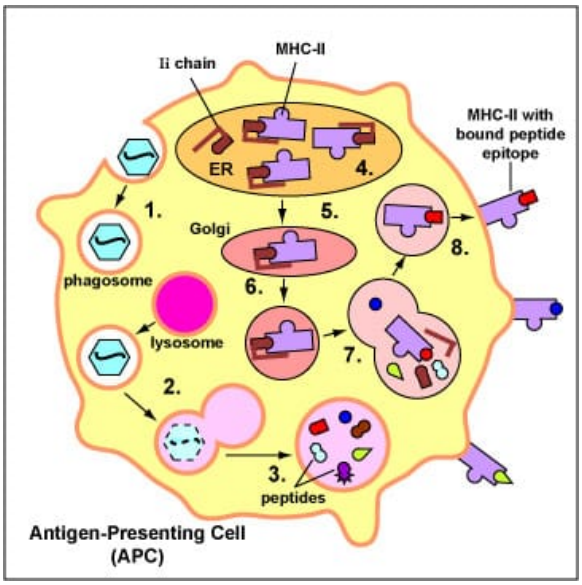


Figure 16.6.1: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules. 1. Exogenous antigens, such as viruses, are engulfed and placed in a phagosome. 2. Lysosomes fuse with the phagosome forming an phagolysosome. 3. Protein antigens are degraded into a series of peptides. 4. MHC-II molecules are synthesized in the endoplasmic reticulum and transported to the Golgi complex. Once assembled, within the endoplasmic reticulum, a protein called the invarient chain (Ii) attaches to the the peptide-binding groove of the MHC-II molecules and in this way prevents peptides designated for binding to MHC-I molecules within the ER from attaching to the MHC-II. 5&6. The MHC-II molecules with bound Ii chain are now transported to the Golgi complex, and placed in vesicles. 7. The vesicles containing the MHC-II molecules fuse with the peptide-containing phaglysosomes. The Ii chain is removed and the peptides are now free to bind to the grooves of the MHC-II molecules. 8. The MHC-II molecules with bound peptides are transported to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-II complexes can be recognized by T4-lymphocytes by way of TCRs and CD4 molecules having a complementary shape.

Conventional antigens are engulfed by antigen presenting cells (APCs), degraded into epitopes, bind to the peptide groove of MHC-II molecules, and are put on the surface of the APC (Figure 16.6.1). Here they are recognized by specific T4-lymphocytes having a TCR with a corresponding shape (Figure 16.6.2).

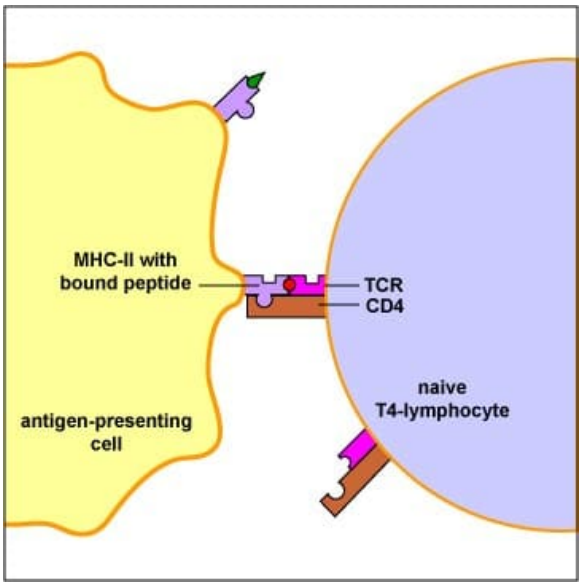


Figure 16.6.2: Binding of T4-Lymphocytes to Conventional Antigens. Conventional antigens are only recognized by specific T4-lymphocytes having a TCR with a shape that corresponds to a peptide of that antigen bound to MHC-II molecules.

Superantigens, however, bind directly to the outside of MHC-II molecules and activate large numbers of T4-lymphocytes (Figure 16.6.3). This activation of very large numbers of T4-lymphocytes results in the secretion of excessive amounts of a cytokine called interleukin-2 (IL-2) as well as the activation of self-reactive T-lymphocytes. The normal response to a conventional antigen results in the activation of maybe 1 in 10,000 T-lymphocytes; superantigens can activate as many as 1 in 5 T-lymphocytes.

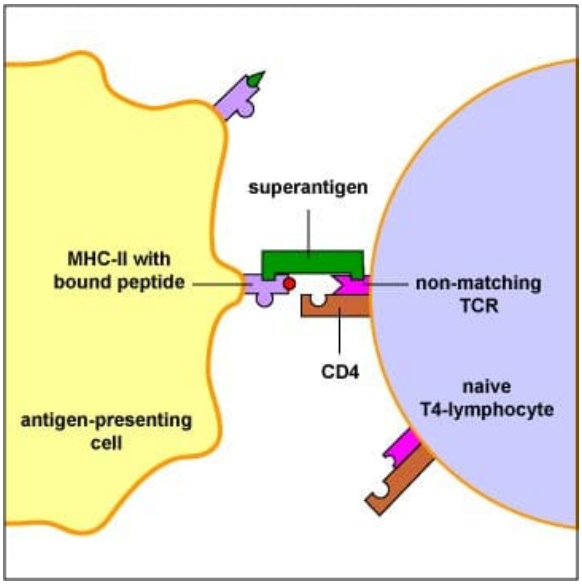


Figure 16.6.3: Binding of Superantigens. Conventional antigens are only recognized by specific T4-lymphocytes having a TCR with a shape that corresponds to a peptide of that antigen bound to MHC-II molecules. Superantigens, on the other hand, bind directly to the outside of MHC-II molecules and the TCRs and activate many T4-lymphocytes. A specific TCR is not required for activation.

Production of high levels of IL-2 can result in circulation of IL-2 in the blood leading to symptoms such as fever, nausea, vomiting, diarrhea, and malaise. However, excess stimulation of IL-2 secretion can also lead to production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), inflammatory chemokines such as IL-8, and platelet-activating factor (PAF), and can lead to the same endothelial damage, acute respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiple organ system failure seen above with LPS and other bacterial cell wall factors. Activation of self-reactive T-lymphocytes can also lead to autoimmune attack.

The following are examples of superantigens.

1. Toxic shock syndrome toxin-1 (TSST-1), produced by some strains of *Staphylococcus aureus.* This exotoxin causes toxic shock syndrome (TSS). Excessive cytokine production leads to fever, rash, and shock.
2. Streptococcal pyrogenic exotoxin (Spe), produced by rare invasive strains and scarlet fever strains of *Streptococcus pyogenes* (the group A beta streptococci). *S pyogenes* produces a number of SPEs that are cytotoxic, pyrogenic, enhance the lethal effects of endotoxins, and contribute to cytokine-induced inflammatory damage. SPEs are responsible for causing streptococcal toxic shock syndrome (STSS) whereby excessive cytokine production leads to fever, rash, and triggering the shock cascade. The SPEs also appear to be responsible for inducing necrotizing fasciitis, a disease that can destroy the skin, fat, and tissue covering the muscle (the fascia). SPE B is also a precursor for a cysteine protease that can destroy muscles tissue.

> Read the description of *Streptococcus pyogenes*, and be able to match the bacterium with its description on an exam.

3. Staphylococcal enterotoxins (SE), producedby many strains of *Staphylococcus aureus.* These exotoxins cause staphylococcal food poisoning. Excessive Il-2 production results in fever, nausea, vomiting,and diarrhea. The vomiting may also be due to these toxins stimulating the vagus nerve in the stomach lining that controls vomiting.
4. ETEC enterotoxin, produced by enterotoxogenic *E. coli* (ETEC), one of the most common causes of traveler's diarrhea.

Exercise: Think-Pair-Share Questions

What is the mechanism by which superantigens ultimately lead to SIRS?

Summary

1. Conventional antigens are only recognized by specific T4-cells having a TCR with a corresponding shape.
2. Superantigens are unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes.
3. Activation of very large numbers of T4-lymphocytes results in the secretion of excessive amounts of a cytokine called interleukin-2 (IL-2).
4. Excess stimulation of IL-2 secretion can also lead to production of inflammatory and can lead to the same endothelial damage, acute respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiple organ system failure seen with PAMP-induced inflammation.
5. Examples of superantigens include toxic shock syndrome toxin-1 (TSST-1), Streptococcal pyrogenic exotoxins (SPE), Staphylococcal enterotoxins (SE), and enterotoxogenic E. coli (ETEC) enterotoxin.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define superantigen *(ans)*.
2. Briefly describe the mechanism by which superantigens cause harm to the body. *(ans)*
3. Name 2 superantigens and give an example of a bacterium that produces each.
   A. *(ans)*
   B. *(ans)*
4. Multiple Choice *(ans)*

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- 6.2A: Type I Toxins: Superantigens by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

16.E: Hypersensitivities (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

1. When humoral immunity (antigen/antibody reactions) cause harm to the body it is termed _____.

2. When cell-mediated immunity (cytotoxic T-lymphocytes, macrophages, and cytokines) cause harm to the body it is termed _____.

3. **Describe** the mechanism for Type I (IgE-mediated) hypersensitivity and give two examples. State how they are treated symptomatically.

4. When a person has hay fever, common symptoms include runny eyes, runny nose, swollen sinuses, and difficulty in breathing. In terms of humoral immunity, discuss the mechanism behind these symptoms. Also state the reason for giving antihistamines and describe how allergy shots may lessen the severity of this type of hypersensitivity.

5. Researchers are hoping that the injection of monoclonal antibodies against IgE may someday be used to prevent virtually any Type I hypersensitivity. Explain.

6. Describe the mechanism for Type II (antibody-dependent cytotoxicity) hypersensitivity and give 2 examples.

7. Describe the mechanism for Type III (immune complex-mediated) hypersensitivity and give 2 examples.

8. Describe the mechanism for Type IV (Stimulatory) hypersensitivity and give an example.

9. Describe the mechanism for Type IV (delayed) hypersensitivity and give 2 examples.

10. Define superantigen .

11. Briefly describe the mechanism by which superantigens cause harm to the body.

12. Name 2 superantigens and give an example of a bacterium that produces each.

A.

B.

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17: BACTERIAL GROWTH AND ENERGY PRODUCTION

17.1: Bacterial Growth
17.2: Factors that Influence Bacterial Growth
17.3: Energy
17.4: Adenosine Triphosphate (ATP)
17.5: Phosphorylation Mechanisms for Generating ATP
17.6: The Flow of Energy in Nature
17.E: Bacterial Growth and Energy Production (Exercises)

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17.1: Bacterial Growth

Briefly describe the process of binary fission in bacteria, stating the functions of Par proteins, the divisome, and FtsZ proteins.

- Define the following:
  a. generation time
  b. geometric progression
- Draw a generalized bacterial growth curve, label the phases, and briefly describe what is happening during each phase.

Bacterial Growth

Bacteria replicate by binary fission, a process by which one bacterium splits into two. Therefore, bacteria increase their numbers by geometric progression whereby their population doubles every generation time.Generation time is the time it takes for a population of bacteria to double in number. For many common bacteria, the generation time is quite short, 20-60 minutes under optimum conditions. For most common pathogens in the body, the generation time is probably closer to 5-10 hours. Because bacteria grow by geometric progression and most have a short generation time, they can astronomically increase their number in a short period of time.

The relationship between the number of bacteria in a population at a given time (N_t), the original number of bacterial cells in the population (N_O), and the number of divisions those bacteria have undergone during that time (n) can be expressed by the following equation:

$$N_t = N_o \times 2^n \tag{17.1.1}$$

For example, *Escherichia coli*, under optimum conditions, has a generation time of 20 minutes. If one started with only 10 *E. coli* (N_O = 10) and allowed them to grow for 12 hours (n = 36; with a generation time of 20 minutes they would divide 3 times in one hour and 36 times in 12 hours), then plugging the numbers in the formula, the number of bacteria after 12 hours (N_t) would be

$$10 \times 2^{36} = N_t = 687,194,767,360\ E.\ coli \tag{17.1.2}$$

In general it is thought that during DNA replication (discussed in Unit 6), each strand of the replicating bacterial DNA attaches to proteins at what will become the cell division plane. For example, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells.

In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission (see Figure 17.1.1 and Figure 17.1.2).

- electron micrograph of a divisome: see under Bacterial Cell Division, Jon Beckwith's Lab.

The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum. The function of a number of divisome proteins have been identified, including:

- MinE: Directs formation of the FtsZ ring and divisome complex at the bacterium's division plane.
- FtsZ: Similar to tubulin in eukaryotic cells, FtsZ forms a constricting ring at the division site. As FtsZ depolymerizes, it directs an inward growth of the cell wall to form the division septum. It is found in both *Bacteria* and *Archaea*, as well as in mitochondria and chloroplasts.
- ZipA: A protein that connects the FtsZ ring to the bacterial cytoplasmic membrane.
- FtsA: An ATPase that breaks down ATP to provide energy for cell division and also helps connect the FtsZ ring to the bacterial cytoplasmic membrane.
- FtsK: Helps in separating the replicated bacterial chromosome.
- FtsI: Needed for peptidoglycan synthesis.

YouTube movie of binary fission in bacteria, #1.

YouTube movie of binary fission in bacteria, #2.

YouTube movie of fluorescing imaging of binary fission in bacteria.

- Scanning electron micrograph of dividing *Escherichia coli*; courtesy of CDC.

- Scanning electron micrograph of dividing *Salmonella typhimurium*; courtesy of CDC.

- To view an transmission electron micrograph of dividing streptococci, see the Rockefeller University home page.

The Population Growth Curve

Although bacteria are capable of replicating geometrically as a result of binary fission, in reality this only occurs as long as their is space to grow, sufficient nutrients, and a way to dispose of waste products. Because these factors limit the ability to replicate geometrically, over time in a closed growth system a bacterial population usually exhibits a predictable pattern of growth - its growth curve - that follows several stages or phases:

1. The lag phase

During the lag phase growth is relatively flat and the population appears either not to be growing or growing quite slowly (see Figure 17.1.3). During this phase the newly inoculated cells are adapting to their new environment and synthesizing the molecules they will need in order to grow rapidly.

2. The exponential growth phase (also called the logarithmic or log phase)

This is the phase where the population increases geometrically as long as there is sufficient food and space for growth (see Figure 17.1.3).

3. The stationary growth phase

Here the population grows slowly or stops growing (see Figure 17.1.3) because of decreasing food, increasing waste, and lack of space. The rate of replication is balanced out by the rate of inhibition or death.

4. The decline or death phase

Here the population dies exponentially from the accumulation of waste products (see Figure 17.1.3), although the rate of death depends on the degree of toxicity and the resistance of the species and viable cells may remain for weeks to months.

For more information: Lab 4, Enumeration of Microorganisms

Summary

1. Bacteria replicate by binary fission, a process by which one bacterium splits into two.
2. Generation time is the time it takes for a population of bacteria to double in number. For many bacteria the generation time ranges from minutes to hours.
3. Because of binary fission, bacteria increase their numbers by geometric progression whereby their population doubles every generation time.
4. Par proteins function to separate bacterial chromosomes to opposite poles of the cell during bacterial cell division.
5. The bacterial divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.

6. Although bacteria are capable of replicating geometrically as a result of binary fission, this only occurs as long as their is space to grow, sufficient nutrients, and a way to dispose of waste products.
7. In a closed growth system, a bacterial population usually exhibits a predictable pattern of growth - its growth curve - that follows several stages or phases.
8. During the lag phase growth is relatively flat and the population appears either not to be growing or growing quite slowly as newly inoculated cells are adapt to their new environment.
9. During the exponential growth phase (log phase) the population increases geometrically as long as there is sufficient food and space for growth.
10. During the stationary phase the population grows slowly or stops growing because of decreasing food, increasing waste, and lack of space.
11. During the death (decline) phase the population dies exponentially from the accumulation of waste products.

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17.2: Factors that Influence Bacterial Growth

Define the following:

a. psychrophile
b. psychrotroph
c. mesophile
d. thermophile
e. obligate aerobe
f. obligate anaerobe
g. aerotolerant anaerobe
h. facultative anaerobe

- State the optimum pH range for most bacteria and compare this range with the optimum pH for fungi.
- Define the following:

a. phototroph
b. chemotroph
c. autotroph
d. heterotroph
e. fastidious

Physical requirements

a. Temperature

Bacteria have a minimum, optimum, and maximum temperature for growth and can be divided into 3 groups based on their optimum growth temperature:

1. Psychrophiles are cold-loving bacteria. Their optimum growth temperature is between -5C and 15C. They are usually found in the Arctic and Antarctic regions and in streams fed by glaciers.

2. Mesophiles are bacteria that grow best at moderate temperatures. Their optimum growth temperature is between 25C and 45C. Most bacteria are mesophilic and include common soil bacteria and bacteria that live in and on the body.

3. Thermophiles are heat-loving bacteria. Their optimum growth temperature is between 45C and 70C and are commonly found in hot springs and in compost heaps.

4. Hyperthermophiles are bacteria that grow at very high temperatures. Their optimum growth temperature is between 70C and 110C. They are usually members of the Archaea and are found growing near hydrothermal vents at great depths in the ocean.

b. Oxygen requirements

Bacteria show a great deal of variation in their requirements for gaseous oxygen. Most can be placed in one of the following groups:

1. Obligate aerobes are organisms that grow only in the presence of oxygen. They obtain their energy through aerobic respiration .

2. Microaerophils are organisms that require a low concentration of oxygen (2% to 10%) for growth, but higher concentrations are inhibitory. They obtain their energy through aerobic respiration .

3. Obligate anaerobes are organisms that grow only in the absence of oxygen and, in fact, are often inhibited or killed by its presence. They obtain their energy through anaerobic respiration or fermentation .

4. Aerotolerant anaerobes , like obligate anaerobes, cannot use oxygen to transform energy but can grow in its presence. They obtain energy only by fermentation and are known as obligate fermenters.

5. Facultative anaerobes are organisms that grow with or without oxygen, but generally better with oxygen. They obtain their energy through aerobic respiration if oxygen is present, but use fermentation or anaerobic respiration if it is absent. Most bacteria are facultative anaerobes.

c. pH

Microorganisms can be placed in one of the following groups based on their optimum pH requirements:

1. Neutrophiles grow best at a pH range of 5 to 8.

2. Acidophiles grow best at a pH below 5.5.

3. Alkaliphiles grow best at a pH above 8.5.

d. Osmosis

Osmosis is the diffusion of water across a membrane from an area of higher water concentration (lower solute concentration) to lower water concentration (higher solute concentration). Osmosis is powered by the potential energy of a concentration gradient and does not require the expenditure of metabolic energy. While water molecules are small enough to pass between the phospholipids in the cytoplasmic membrane, their transport can be enhanced by water transporting transport proteins known as aquaporins . The aquaporins form channels that span the cytoplasmic membrane and transport water in and out of the cytoplasm.

To understand osmosis, one must understand what is meant by a solution . A solution consists of a solute dissolved in a solvent . In terms of osmosis, solute refers to all the molecules or ions dissolved in the water (the solvent). When a solute such as sugar dissolves in water, it forms weak hydrogen bonds with water molecules. While free, unbound water molecules are small enough to pass through membrane pores, water molecules bound to solute are not (see Figure 17.2.4 C and Figure 17.2.4D).Therefore, the higher the solute concentration, the lower the concentration of free water molecules capable of passing through the membrane.

A cell can find itself in one of three environments: isotonic , hypertonic , or hypotonic . (The prefixes iso-, hyper-, and hypo- refer to the solute concentration).

- In an isotonic environment (see Figure 17.2.5A), both the water and solute concentration are the same inside and outside the cell and water goes into and out of the cell at an equal rate.

Flash animation showing osmosis in an isotonic environment.

http5 version of animation for iPad showing osmosis in an isotonic environment.

- If the environment is hypertonic (see Figure 17.2.5B), the water concentration is greater inside the cell while the solute concentration is higher outside (the interior of the cell is hypotonic to the surrounding hypertonic environment). Water goes out of the cell.

Flash animation showing osmosis in a hypertonic environment.

html5 version of animation for iPad showing osmosis in a hypertonic environment.

- In an environment that is hypotonic (see Figure 17.2.5C), the water concentration is greater outside the cell and the solute concentration is higher inside (the interior of the cell is hypertonic to the hypotonic surroundings). Water goes into the cell.

Flash animation showing osmosis in a hypotonic environment.

html5 version of animation for iPad showing osmosis in a hypotonic environment.

Most bacteria require an isotonic environment or a hypotonic environment for optimum growth. Organisms that can grow at relatively high salt concentration (up to 10%) are said to be osmotolerant . Those that require relatively high salt concentrations for growth, like some of the Archaea that require sodium chloride concentrations of 20 % or higher halophiles .

Nutritional requirements

In addition to a proper physical environment, microorganisms also depend on an available source of chemical nutrients. Microorganisms are often grouped according to their energy source and their source of carbon.

a. Energy source

1. Phototrophs use radiant energy (light) as their primary energy source.

2. Chemotrophs use the oxidation and reduction of chemical compounds as their primary energy source.

b. Carbon source

Carbon is the structural backbone of the organic compounds that make up a living cell. Based on their source of carbon bacteria can be classified as autotrophs or heterotrophs.

1. Autotrophs : require only carbon dioxide as a carbon source. An autotroph can synthesize organic molecules from inorganic nutrients.

2. Heterotrophs : require organic forms of carbon. A Heterotroph cannot synthesize organic molecules from inorganic nutrients.

Combining their nutritional patterns, all organisms in nature can be placed into one of four separate groups: photoautotrophs, photoheterotrophs, chemoautotrophs, and chemoheterotrophs.

1. Photoautotrophs use light as an energy source and carbon dioxide as their main carbon source. They include photosynthetic bacteria (green sulfur bacteria, purple sulfur bacteria, and cyanobacteria), algae, and green plants. Photoautotrophs transform carbon dioxide and water into carbohydrates and oxygen gas through photosynthesis .

Cyanobacteria, as well as algae and green plants, use hydrogen atoms from water to reduce carbon dioxide to form carbohydrates, and during this process oxygen gas is given off (an oxygenic process). Other photosynthetic bacteria (the green sulfur bacteria and purple sulfur bacteria) carry out an anoxygenic process, using sulfur, sulfur compounds or hydrogen gas to reduce carbon dioxide and form organic compounds.

2. Photoheterotrophs use light as an energy source but cannot convert carbon dioxide into energy. Instead they use organic compounds as a carbon source. They include the green nonsulfur bacteria and the purple nonsulfur bacteria.

3. Chemolithoautotrophs use inorganic compounds such as hydrogen sulfide, sulfur, ammonia, nitrites, hydrogen gas, or

iron as an energy source and carbon dioxide as their main carbon source.

4. Chemooganoheterotrophs use organic compounds as both an energy source and a carbon source. Saprophytes live on dead organic matter while parasites get their nutrients from a living host. Most bacteria, and all protozoans, fungi, and animals are chemoorganoheterotrophs.

c. Nitrogen source

Nitrogen is needed for the synthesis of such molecules as amino acids, DNA, RNA and ATP . Depending on the organism, nitrogen, nitrates, ammonia, or organic nitrogen compounds may be used as a nitrogen source.

d. Minerals

1. Sulfur

Sulfur is needed to synthesizes sulfur-containing amino acids and certain vitamins. Depending on the organism, sulfates, hydrogen sulfide, or sulfur-containing amino acids may be used as a sulfur source.

2. Phosphorus

Phosphorus is needed to synthesize phospholipids , DNA, RNA, and ATP . Phosphate ions are the primary source of phosphorus.

3. Potassium, magnesium, and calcium

These are required for certain enzymes to function as well as additional functions.

4. Iron

Iron is a part of certain enzymes.

5. Trace elements

Trace elements are elements required in very minute amounts, and like potassium, magnesium, calcium, and iron, they usually function as cofactors in enzyme reactions. They include sodium, zinc, copper,molybdenum, manganese, and cobalt ions. Cofactors usually function as electron donors or electron acceptors during enzyme reactions.

e. Water

f. Growth factors

Growth factors are organic compounds such as amino acids , purines , pyrimidines , and vitamins that a cell must have for growth but cannot synthesize itself. Organisms having complex nutritional requirements and needing many growth factors are said to be fastidious .

Summary

1. Bacteria have a minimum, optimum, and maximum temperature for growth and can be divided into 3 groups based on their optimum growth temperature: psychrophils, mesophils, thermophils, or hyperthermophils.
2. Bacteria show a great deal of variation in their requirements for gaseous oxygen. Most can be placed in one of the following groups: obligate aerobes, microaerophils, obligate anaerobes, aerotolerant anaerobes, or facultative anaerobes.
3. Microorganisms can be placed in one of the following groups based on their optimum pH requirements: neutrophiles, acidophiles, or alkaliphiles.
4. A bacterium's osmotic environment can affect bacterial growth.
5. Bacteria can be grouped according to their energy source as phototrophs or chemotrophs.
6. Bacteria can be grouped according to their carbon source as autotrophs or heterotrophs.

7. Combining their nutritional patterns, all organisms in nature can be placed into one of four separate groups: photoautotrophs, photoheterotrophs, chemoautotrophs, and chemoheterotrophs.
8. Bacteria also need a nitrogen source, various minerals, and water for growth.
9. Organisms having complex nutritional requirements and needing many growth factors are said to be fastidious.

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17.3: Energy

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17.4: Adenosine Triphosphate (ATP)

State what the letters ADP and ATP stand for and how the two molecules differ.

- Briefly describe how energy that is released from energy-containing compounds is trapped and stored as ATP and how energy stored in ATP is released to do cellular work.

Adenosine triphosphate (ATP) links most cellular exergonic and endergonic chemical reactions. To obtain energy to do cellular work, organisms take energy-rich compounds such as glucose into the cell and enzymatically break them down to release their potential energy. Therefore, the organism needs a way to trap some of that released energy and store the energy in a form that can be utilized by the cell to do cellular work. Principally, energy is trapped and stored in the form of adenosine triphosphate or ATP.

A tremendous amount of ATP is needed for normal cellular growth. For example,a human at rest uses about 45 kilograms (about 99 pounds) of ATP each day but at any one time has a surplus of less than one gram. It is estimated that each cell will generate and consume approximately 10,000,000 molecules of ATP per second. As can be seen, ATP production is an ongoing cellular process.

To trap energy released from exergonic catabolic chemical reactions, the cell uses some of that released energy to attach an inorganic phosphate group on to adenosine diphosphate (ADP) to make adenosine triphosphate (ATP). Because the phosphate groups are all negatively charged, they repel each other and stress the bond holding them together, much like a bent diving board. Thus, energy is trapped and stored in these stressed bonds known as high-energy phosphate bonds. To obtain energy to do cellular work during endergonic anabolic chemical reactions, the organism enzymatically removes the third phosphate from ATP thus releasing the stored energy and forming ADP and inorganic phosphate once again (see Figure 17.4.1).

Flash animation illustrating the formation of ATP from ADP and phosphate.

html5 version of animation for iPad illustrating the formation of ATP from ADP and phosphate.

Flash animation illustrating the hydrolysis of ATP to provide energy for cellular work.

html5 version of animation for iPad illustrating the hydrolysis of ATP to provide energy for cellular work.

Depending on the type of organism, cells transfer energy and generate ATP by photophosphorylation, by substrate-level phosphorylation, and/or by oxidative phosphorylation. (Phosphorylation refers to the attachment of a phosphate group to a molecule.)

Summary

1. Cellular energy is primarily trapped and stored in the form of adenosine triphosphate or ATP.
2. A tremendous amount of ATP is needed for normal cellular growth.
3. To trap energy released from exergonic catabolic chemical reactions, the cell uses some of that released energy to attach an inorganic phosphate group on to adenosine diphosphate (ADP) to make adenosine triphosphate (ATP). The energy is stored in these high-energy phosphate bonds.
4. To obtain energy to do cellular work during endergonic anabolic chemical reactions, the organism enzymatically removes the third phosphate from ATP thus releasing the stored energy and forming ADP and inorganic phosphate once again.
5. Depending on the type of organism, cells transfer energy and generate ATP by photophosphorylation, by substrate-level phosphorylation, and/or by oxidative phosphorylation.

Questions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. The acronym ATP stands for_____. *(ans)*
2. Describe how cells trap energy released from exergonic catabolic chemical reactions and store it as ATP. *(ans)*
3. Describe how cells obtain energy to do cellular work during endergonic anabolic chemical reactions. *(ans)*
4. The hydrolysis of ATP is:
    a. an exergonic reaction *(ans)*
    b. an endergonic reaction *(ans)*

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17.5: Phosphorylation Mechanisms for Generating ATP

Define photophosphorylation.

- Describe substrate-level phosphorylation and name to energy-generating pathways in which this occurs.
- Define oxidative phosphorylation.
- Name the two components of a hydrogen atom.
- Describe an oxidation-reduction reaction.
- Define dehydrogenation and hydrogenation.
- State the function of the following coenzymes and give their reduced form:

  a. NAD^+
  b. FAD
  c. $NADP^+$

- Briefly describe proton motive force and how it develops within a cell.
- Describe an electron transport chain and state its cellular function.
- Briefly describethe chemiosmotic theory of generation of ATP as a result of an electron transport chain.
- State the function of ATP synthases.

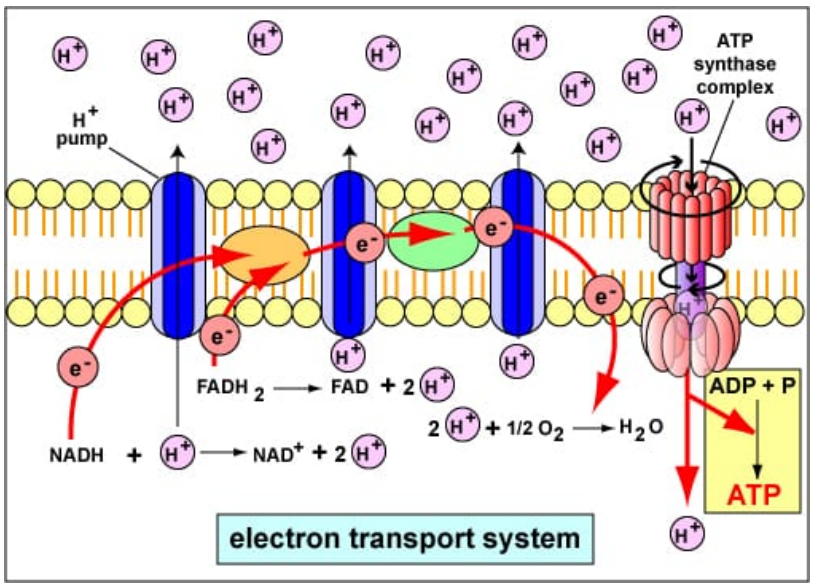


Figure 17.5.1: ATP Production during Aerobic Respiration by Oxidative Phosphorylation involving an Electron Transport System and Chemiosmosis. NADH and $FADH_2$ carry protons (H^+) and electrons (e^-) to the electron transport chain located in the membrane. The energy from the transfer of electrons along the chain transports protons across the membrane and creates an electrochemical gradient. As the accumulating protons follow the electrochemical gradient back across the membrane through an ATP synthase complex, the movement of the protons provides energy for synthesizing ATP from ADP and phosphate. At the end of the electron transport system, two protons, two electrons, and half of an oxygen molecule combine to form water. Since oxygen is the final electron acceptor, the process is called aerobic respiration.

YouTube movie illustrating the light reactions during photosynthesis including photophosphorylation.

Substrate-Level Phosphorylation

Substrate-level phosphorylation is the production of ATP from ADP by a direct transfer of a high-energy phosphate group from a phosphorylated intermediate metabolic compound in an exergonic catabolic pathway as shown in Figure 17.5.2. Such intermediate compounds are sometimes called high-energy transfer compounds (HETCs) and several HETCs are found as intermediates during glycolysis and aerobic respiration .

Flash animation illustrating substrate-level phosphorylation.

html5 version of animation for iPad illustrating substrate-level phosphorylation.

Oxidative Phosphorylation

Oxidative phosphorylation is the production of ATP using energy derived from the transfer of electrons in an electron transport system and occurs by chemiosmosis.

To understand oxidative phosphorylation, it is important to first review the hydrogen atom and the process of oxidation and reduction. An atom of hydrogen contains only one proton (H^+) and one electron (e^-). Therefore, the term proton and the term hydrogen ion (H^+) are interchangeable. Also remember that electrons have stored energy, or potential energy, ready to do work and when an atom or molecule loses that electron (becomes oxidized) that energy is released and able to do cellular work.

Oxidation-reduction reactions are **coupled chemical reactions** in which one atom or molecule loses one or more electrons (oxidation) while another atom or molecule gains those electrons (reduction). The compound that loses electrons becomes oxidized; the compound that gains those electrons becomes reduced. In covalent compounds, however, it is usually easier to lose a whole hydrogen (H) atom - a proton and an electron - rather than just an electron. An oxidation reaction during which both a proton and an electron are lost is called dehydrogenation . A reduction reaction during which both a proton and an electron are gained is called hydrogenation .

Cells use specific molecules to carry the electrons that are removed during the oxidation of an energy source. These molecules are called electron carriers and they alternately become oxidized and reduced during electron and proton transfer. These include three freely diffusible coenzymes known as NAD^+, FAD, and $NADP^+$. The reduced forms of these coenzymes (NADH, $FADH_2$, and NADPH) have reducing power because their bonds contain a form of usable energy.

- NAD^+ , or nicotinamide adenine dinucleotide, is a coenzyme that often works in conjunction with an enzyme called a dehydrogenase. The enzyme removes two hydrogen atoms ($2H^+$ and $2e^-$) from its substrate. Both electrons but only one proton are accepted by the NAD^+ to produce its reduced form, NADH, plus H^+. NADH is used to generate proton motive force (discussed below) that can drive the synthesis of ATP.
- FAD , or flavin adenine dinucleotide, is a coenzyme that also works in conjunction with an enzyme called a dehydrogenase. The enzyme removes two hydrogen atoms ($2H^+$ and $2e^-$) from its substrate. Both electrons and both protons are accepted by the FAD to produce its reduced form, $FADH_2$. $FADH_2$ is used to generate proton motive force (discussed below) that can drive the synthesis of ATP.
- $NADP^+$, or nicotinamide adenine dinucleotide phosphate, is a coenzyme that uses dehydrogenase to remove two hydrogen atoms ($2H^+$ and $2e^-$) from its substrate. Both electrons but only one proton are accepted by the $NADP^+$ to produce its reduced form, NADPH, plus H^+. NADPH is not used for ATP synthesis but its electrons provide the energy for certain biosynthesis reactions such as ones involved in photosynthesis.

During the process of aerobic respiration, discussed in the next section, coupled oxidation-reduction reactions and electron carriers are often part of what is called an electron transport chain , a series of electron carriers that eventually transfers electrons from NADH and $FADH_2$ to oxygen. The diffusible electron carriers NADH and $FADH_2$ carry hydrogen atoms (protons and electrons) from substrates in exergonic catabolic pathways such as glycolysis and the citric acid cycle to other electron carriers that are embedded in membranes. These membrane-associated electron carriers include flavoproteins, iron-sulfur proteins, quinones, and cytochromes. The last electron carrier in the electron transport chain transfers the electrons to the terminal electron acceptor, oxygen.

The chemiosmotic theory explains the functioning of electron transport chains. According to this theory, the transfer of electrons down an electron transport system through a series of oxidation-reduction reactions releases energy (Figure 17.5.1). This energy

allows certain carriers in the chain to transport hydrogen ions (H^+ or protons) across a membrane.

Flash animation illustrating energy release during oxidation-reduction reactions.

html5 version of animation for iPad illustrating energy release during oxidation-reduction reactions.

Depending on the type of cell, the electron transport chain may be found in the cytoplasmic membrane, the inner membrane of mitochondria, and the inner membrane of chloroplasts.

- In prokaryotic cells, the protons are transported from the cytoplasm of the bacterium across the cytoplasmic membrane to the periplasmic space located between the cytoplasmic membrane and the cell wall.
- In eukaryotic cells, protons are transported from the matrix of the mitochondria across the inner mitochondrial membrane to the intermembrane space located between the inner and outer mitochondrial membranes.
- In plant cells and the cells of algae, protons are transported from the stroma of the chloroplast across the thylakoid membrane into the interior space of the thylakoid.

As the hydrogen ions accumulate on one side of a membrane, the concentration of hydrogen ions creates an electrochemical gradient or potential difference (voltage) across the membrane. (The fluid on the side of the membrane where the protons accumulate acquires a positive charge; the fluid on the opposite side of the membrane is left with a negative charge.) The energized state of the membrane as a result of this charge separation is called proton motive force or PMF.

This proton motive force provides the energy necessary for enzymes called ATP synthases (Figure 17.5.5), also located in the membranes mentioned above, to catalyze the synthesis of ATP from ADP and phosphate. This generation of ATP occurs as the protons cross the membrane through the ATP synthase complexes and re-enter either the bacterial cytoplasm (Figure 17.5.5), the matrix of the mitochondria, or the stroma of the chloroplasts. As the protons move down the concentration gradient through the ATP synthase, the energy released causes the rotor and rod of the ATP synthase to rotate. The mechanical energy from this rotation is converted into chemical energy as phosphate is added to ADP to form ATP.

Flash animation from Sigma-Aldrich illustrating ATP synthase generating ATP.

Proton motive force is also used to transport substances across membranes during active transport and to rotate bacterial flagella.

At the end of the electron transport chain involved in aerobic respiration, the last electron carrier in the membrane transfers 2 electrons to half an oxygen molecule (an oxygen atom) that simultaneously combines with 2 protons from the surrounding medium to produce water as an end product (Figure 17.5.3). The electron transport chains involved in photosynthesis ultimately transfer 2 electrons to $NADP^+$ that simultaneously combines with 2 protons from the surrounding medium to produce NADPH.

Flash animation illustrating the development of proton motive force as a result of chemiosmosis and ATP production by ATP synthase.

html5 version of animation for iPad illustrating the development of proton motive force as a result of chemiosmosis and ATP production by ATP synthase.

Flash animation from Sigma-Aldrich illustrating ATP synthase generating ATP.

Flash animation illustrating ATP production by chemiosmosis during aerobic respiration in a prokaryotic bacterium.

html5 version of animation for iPad illustrating ATP production by chemiosmosis during aerobic respiration in a prokaryotic bacterium.

McGraw-Hill Flash animation illustrating ATP production by chemiosmosis in a eukaryotic mitochondrion.

Summary

1. Photophosphorylation uses the radiant energy of the sun to drive the synthesis of ATP.
2. This is a process seen only in cells capable of photosynthesis.
3. Substrate-level phosphorylation is the production of ATP from ADP by a direct transfer of a high-energy phosphate group from a phosphorylated intermediate metabolic compound in an exergonic catabolic pathway.

1. Oxidative phosphorylation is the production of ATP using energy derived from the transfer of electrons in an electron transport system and occurs by chemiosmosis.
2. An atom of hydrogen contains only one proton (H^+) and one electron.
3. Electrons have stored energy, or potential energy, ready to do work. When an atom or molecule loses that electron (becomes oxidized) that energy is released and able to do cellular work.
4. Oxidation-reduction reactions are coupled chemical reactions in which one atom or molecule loses one or more electrons (oxidation) while another atom or molecule gains those electrons (reduction).
5. An oxidation reaction during which both a proton and an electron are lost is called dehydrogenation.
6. A reduction reaction during which both a proton and an electron are gained is called hydrogenation.
7. Cells use specific molecules such as NAD^+, FAD, and $NADP^+$ to carry the electrons that are removed during the oxidation of an energy source. These molecules are called electron carriers and they alternately become oxidized and reduced during electron and proton transfer.
8. Coupled oxidation-reduction reactions and electron carriers are often part of what is called an electron transport chain.
9. The chemiosmotic theory explains the functioning of electron transport chains. According to this theory, the transfer of electrons down an electron transport system through a series of oxidation-reduction reactions releases energy. This energy allows certain carriers in the chain to transport hydrogen ions (H^+ or protons) across a membrane.
10. In prokaryotic cells, the protons are transported from the cytoplasm of the bacterium across the cytoplasmic membrane to the periplasmic space located between the cytoplasmic membrane and the cell wall; in eukaryotic cells, protons are transported from the matrix of the mitochondria across the inner mitochondrial membrane to the intermembrane space located between the inner and outer mitochondrial membranes; in plant cells and the cells of algae, protons are transported from the stroma of the chloroplast across the thylakoid membrane into the interior space of the thylakoid.
11. As the hydrogen ions accumulate on one side of a membrane, the concentration of hydrogen ions creates an electrochemical gradient or potential difference (voltage) across the membrane called proton motive force (PMF).
12. This proton motive force provides the energy necessary for enzymes called ATP synthases to catalyze the synthesis of ATP from ADP and phosphate.

Questions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define photophosphorylation. *(ans)*
2. Briefly describe the process of substrate-level phosphorylation. *(ans)*
3. Briefly describe the process of oxidative phosphorylation. *(ans)*
4. Another name for a hydrogen ion (H^+) is: *(ans)*
5. An atom or molecule gains an electron. This best describes:
   a. oxidation *(ans)*
   b. reduction *(ans)*
   c. dehydrogenation *(ans)*
   d. hydrogenation *(ans)*
6. When a molecule gains electrons or both protons and electrons, we say it becomes:

a. oxidized *(ans)*
b. reduced *(ans)*

7. Cells use specific molecules to carry the electrons that are removed during the oxidation of an energy source. These molecules are called electron carriers and they alternately become oxidized and reduced during electron and proton transfer. Name three freely diffusible coenzymes and give both their oxidized and reduced state. *(ans)*
8. A coenzyme that often works in conjunction with an enzyme called a dehydrogenase. The enzyme removes two hydrogen atoms ($2H^+$ and $2e^-$) from its substrate. Both electrons but only one proton are accepted to produce its reduced form that is used to generate proton motive force for driving the synthesis of ATP. This best describes:
   a. NAD^+(ans)
   b. FAD *(ans)*
   c. $NADP^+$ *(ans)*
9. $NADH + H^+$ is the _____ form of NAD^+. *(ans)*
10. Describe an electron transport chain. *(ans)*
11. Based on the chemiosmotic theory, briefly describe proton motive force and how it develops within a cell. *(ans)*
12. Based on the chemiosmotic theory, briefly describe how proton motive force leads to the generation of ATP. *(ans)*

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17.6: The Flow of Energy in Nature

Describe the relationship between photosynthesis and aerobic respiration and relate this to the first law of thermodynamics.

For the vast majority of life on earth, the flow of energy begins with sunlight and involves a cycle involving photoautotrophs and chemoorganoheterotrophs. Photoautotrophs use sunlight as a source of energy and through the process of photosynthesis, reduce carbon dioxide to form carbohydrates such as glucose. The radient energy is converted to the chemical bond energy within glucose.

The overall reaction for photosynthesis (in the presence of light and chlorophyll) is as follows:

$$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2 \tag{17.6.1}$$

Note that carbon dioxide (CO_2) is reduced to produce glucose ($C_6H_{12}O_6$) and water (H_2O) is oxidized to produce oxygen (O_2).

Both chemoorganoheterotrophs and photoautotrophs then convert the chemical bond energy of glucose to the chemical bond energy of ATP, the form of energy required to do most cellular work. This is done through the process called aerobic respiration.

The overall reaction for aerobic respiration is:

$C_6H_{12}O_6$ + 6O_2 yields 6CO_2 + 6H_2O + energy (as ATP)

Note that glucose ($C_6H_{12}O_6$) is oxidized to produce carbon dioxide (CO_2) and oxygen (O_2) is reduced to produce water (H_2O).

As can be seen, the end products for aerobic respiration, carbon dioxide and water, are the reactants for photosynthesis while the end products of photosynthesis, glucose and oxygen, are the reactants for aerobic respiration. In other words, the nutrients are continuously recycled between the two processes. Energy, however, is converted from one form to another: from radiant energy to the chemical bond energy of glucose to the chemical bond energy of ATP, the first law of thermodynamics.

Summary

1. The overall reaction for photosynthesis is 6CO_2 + 6H_2O in the presence of light and chlorophyll yields $C_6H_{12}O_6$ + 6O_2.
2. The overall reaction for aerobic respiration is $C_6H_{12}O_6$ + 6O_2 yields 6CO_2 + 6H_2O + energy (as ATP).
3. As can be seen, the end products for aerobic respiration, carbon dioxide and water, are the reactants for photosynthesis while the end products of photosynthesis, glucose and oxygen, are the reactants for aerobic respiration. In other words, the nutrients are continuously recycled between the two processes.
4. Energy, however, is not recycled but rather is converted from one form to another: from radiant energy to the chemical bond energy of glucose to the chemical bond energy of ATP.

Questions

Study the material in this section and then **write out the answers** to these question. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. 6CO_2 + 6H_2O are the reactants for _____ and the products of _____.
   a. aerobic respiration / photosynthesis *(ans)*
   b. photosynthesis / aerobic respiration *(ans)*
2. $C_6H_{12}O_6$ + 6O_2 are the reactants for _____ and the products of _____.
   a. aerobic respiration / photosynthesis *(ans)*
   b. photosynthesis / aerobic respiration *(ans)*

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17.E: Bacterial Growth and Energy Production (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

17.1: Bacterial Growth

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

   _____ A population doubles every generation time.

   _____ One cell splits in two.

   _____ The time it takes for a population of organisms to double in number.

   a. binary fission
   b. generation time
   c. geometric progression

2. If you started with 1000 *E. coli* with a generation time of 30 minutes, how many bacteria would you have after 3 hours?
3. Match the following:

   ____ Phase where the population grows slowly or stops growing because of decreasing food, increasing waste, and lack of space. The rate of replication is balanced out by the rate of inhibition or death.

   ____ Phase where the population dies exponentially from the accumulation of waste products, although the rate of death depends on the degree of toxicity and the resistance of the species.

   ____ Phase where growth is relatively flat and the population appears either not to be growing or growing quite slowly. During this phase the newly inoculated cells are adapting to their new environment and synthesizing the molecules they will need in order to grow rapidly.

   ____ Phase where the population increases geometrically as long as there is sufficient food and space for growth.

   A. Lag phase
   B. Exponential (log) growth phase
   C. Stationary phase
   D. Death (decline) phase

17.2: Factors that Influence Bacterial Growth

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching

   _____ Bacteria that grow best at moderate temperatures. Their optimum growth temperature is between 25C and 45C.

   _____ Cold-loving bacteria. Their optimum growth temperature is between -5C and 15C. They are usually found in the Arctic and Antarctic regions and in streams fed by glaciers.

_____ Organisms that grow with or without oxygen, but generally better with oxygen.

_____ Organisms that grow onlyin the absense of oxygen and, in fact, are often inhibited or killed by its presense.

_____ An environment where the water concentration is greater outside the cell and the solute concentration is higher inside. Water goes into the cell.

_____ Organisms that use the oxidation and reduction of chemical compounds as their primary energy source.

____ Organisms that use light as an energy source and carbon dioxideas their main carbon source.

_____ Organisms that use organic compounds as both an energy source and a carbon source.

_____ Organisms that use light as an energy source but cannot convert carbon dioxide into energy. Instead they use organic compounds as a carbon source.

A. photoautotrophs
B. photoheterotrophs
C. chemolithoautotrophs
D. chemooganoheterotrophs
E. phototroph
F. heterotroph
G. hypertonic
H. hypotonic
I. obligate aerobe
J. facultative anaerobe
K. obligate anaerobe
L. psychrophile
M. mesophile
N. thermophile

17.3: Energy Conversion in Microorganisms

17.4: Cellular Respiration

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. An exergonic processes by which energy released by the breakdown of organic compounds such as glucose can be used to synthesize ATP, the form of energy required to do cellular work. This best describes:
   a. anabolism
   b. catabolism
2. Intermediate molecules that link catabolic and anabolic pathways; can be either oxidized to generate ATP or can be used to synthesize macromolecular subunits such as amino acids, lipids, and nucleotides.
3. Define cellular respiration.
4. Pathways that do not require oxygen are said to be:
   a. aerobic
   b. anaerobic
5. Name an exergonic pathway that requires molecular oxygen (O_2).
6. Name two anaerobic exergonic forms of cellular respiration.

17.5: Photosynthesis

1. Organisms that absorb and convert light energy into the stored energy of chemical bonds in organic molecules through a process called photosynthesis best describes:

   a. anoxygenic photoautotrophs

b. oxygenic photoautotrophs

2. Name the two stages of photosynthesis.

3. Define photon.

4. Describe what happens when photons of visible light energy strike certain atoms of pigments during photosynthesis and how this can lead to the generation of ATP.

5. Fill in the blank.

The inner membrane of a chloroplast encloses a fluid-filled region called the _____ that contains enzymes for the light-independent reactions of photosynthesis. Infolding of this inner membrane forms interconnected stacks of disk-like sacs called _____ , often arranged in stacks called _____ .

6. Name three different types of pigments that play a role in photosynthesis by absorbing light energy.

7. State the reactants and the products for photosynthesis and indicate which are oxidized and which are reduced.

8. Briefly describe the overall function of the light-dependent reactions in photosynthesis.

9. Where in the chloroplasts do the light-dependent reactions occur?

a. In the thylakoids.
b. In the stroma.

10. The parts of a photosystem that are able to trap light and transfer energy to a complex of chlorophyll molecules and proteins called the reaction center are called _____.

11. In Photosystem II, the electrons lost by chlorophyll P680 molecules are replaced by:

a. the electrons traveling down the electron transport system of Photosystem I
b. the electrons released by the splitting of water

12. The primary function of Photosystem II is to produce:

a. ATP
b. NADPH

13. Briefly describe how ATP is generated by chemiosmosis during the light-dependent reactions of photosynthesis.

14. In Photosystem I, the electrons lost by chlorophyll P700 molecules are replaced by:

a. the electrons traveling down the electron transport system of Photosystem II
b. the electrons released by the splitting of water

15. The primary function of Photosystem I is to produce:

a. ATP
b. NADPH

16. Involves only Photosystem I and generates ATP but not NADPH. This best describes:

a. cyclic photophosphorylation
b. noncyclic photophosphorylation

17. Briefly describe the overall function of the light-independent reactions in photosynthesis.

18. Where in the chloroplasts do the light-independent reactions occur?

a. In the thylakoids.

b. In the stroma.

19. State how the light-dependent and light-independent reactions are linked during photosynthesis.

20. Briefly describe the following stages of the Calvin cycle:

a. CO_2 fixation
b. production of G3P
c. regeneration of RuBP

21. State the significance of glyceraldehyde-3-phosphate (G3P) in the Calvin cycle.

22. Is the following statement true or false?

During the C4 pathway for fixing CO_2, CO_2 from the air combines with ribulose bisphosphate to begin the Calvin cycle.

23. Plants that live in very dry condition and, unlike other plants, open their stomata to fix CO_2 only at night best describes:

a. C4 plants
b. C3 plants
c. CAM plants

24. C4 and CAM pathways evolved for plants that live in _____ climates.

a. hot, humid
b. cold, dry
c. hot, dry

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18.2: Overview of Cellular Respiration

Define catabolism and anabolism and state which is exergonic and which is endergonic.

- Define precursor metabolites and state their functions in metabolism.
- Define the following:

  a. cellular respiration
  b. aerobic
  c. anaerobic

- Name one aerobic and two anaerobic forms of cellular respiration.

As mentioned previously, to grow, function, and reproduce, cells must synthesize new cellular components such as cell walls, cell membranes, nucleic acids, ribosomes, proteins, flagella, etc., and harvest energy and convert it into a form that is usable to do cellular work.

Catabolism refers to the exergonic process by which energy released by the breakdown of organic compounds such as glucose can be used to synthesize ATP, the form of energy required to do cellular work. Anabolism is the endergonic process that uses the energy stored in ATP to synthesize the building blocks of the macromolecules that make up the cell. As can be seen, these two metabolic processes are closely linked. Another factor that links catabolic and anabolic pathways is the generation of precursor metabolites. Precursor metabolites are intermediate molecules in catabolic and anabolic pathways that can be either oxidized to generate ATP or can be used to synthesize macromolecular subunits such as amino acids, lipids, and nucleotides.

In this section we will concentrate primarily on harvesting energy and converting it to energy stored in ATP through the process of cellular respiration, but we will also look at some of the key precursor metabolites that are produced during this process.

Cellular respiration is the process cells use to convert the energy in the chemical bonds of nutrients to ATP energy. Depending on the organism, cellular respiration can be aerobic, anaerobic, or both. Aerobic respiration is an exergonic pathway that requires molecular oxygen (O_2). Anaerobic exergonic pathways do not require oxygen and include anaerobic respiration and fermentation. We will now look at these three pathways.

Summary

1. Catabolism refers to the exergonic process by which energy released by the breakdown of organic compounds such as glucose can be used to synthesize ATP, the form of energy required to do cellular work.
2. Anabolism is the endergonic process that uses the energy stored in ATP to synthesize the building blocks of the macromolecules that make up the cell.
3. Precursor metabolites are intermediate molecules in catabolic and anabolic pathways that can be either oxidized to generate ATP or can be used to synthesize macromolecular subunits such as amino acids, lipids, and nucleotides.
4. Cellular respiration is the process cells use to convert the energy in the chemical bonds of nutrients to ATP energy.
5. Aerobic respiration is an exergonic pathway that requires molecular oxygen (O_2).
6. Anaerobic exergonic pathways do not require oxygen and include anaerobic respiration and fermentation.

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18.3: AEROBIC RESPIRATION

Define aerobic respiration.

- Give the overall chemical reaction for aerobic respiration.
- Name the four stages of aerobic respiration.

Aerobic respiration is the aerobic catabolism of nutrients to carbon dioxide, water, and energy, and involves an electron transport system in which molecular oxygen is the final electron acceptor. Most eukaryotes and prokaryotes use aerobic respiration to obtain energy from glucose. The overall reaction is:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O \tag{18.3.1}$$

Note that glucose ($C_6H_{12}O_6$) is oxidized to produce carbon dioxide (CO_2) and oxygen (O_2) is reduced to produce water (H_2O). This reaction is a strongly driven reactions and "releases" energy as ATP molecules. This type of ATP production is seen in aerobes and facultative anaerobes. Obligate aerobes are organisms that require molecular oxygen because they produce ATP only by aerobic respiration. Facultative anaerobes, on the other hand are capable of aerobic respiration but can switch to fermentation, an anaerobic ATP-producing process, if oxygen is unavailable.

Aerobic respiration involves four stages:

- glycolysis,
- a transition reaction that forms acetyl coenzyme A,
- the citric acid (Krebs) cycle, and an electron transport chain and
- chemiosmosis.

We will now look at each of these stages.

Summary

1. Aerobic respiration is the aerobic catabolism of nutrients to carbon dioxide, water, and energy, and involves an electron transport system in which molecular oxygen is the final electron acceptor.
2. The overall reaction is: $C_6H_{12}O_6$ + $6O_2$ yields $6CO_2$ + $6H_2O$ + energy (as ATP). Glucose ($C_6H_{12}O_6$) is oxidized to produce carbon dioxide (CO_2) and oxygen (O_2) is reduced to produce water (H_2O).
3. This type of ATP production is seen in aerobes and facultative anaerobes.
4. Aerobic respiration involves four stages: glycolysis, a transition reaction that forms acetyl coenzyme A, the citric acid (Krebs) cycle, and an electron transport chain and chemiosmosis.

- Topic hierarchy

18.3A: Glycolysis

18.3B: Transition Reaction

18.3C: Citric Acid (Krebs) Cycle

18.3D: Electron Transport Chain and Chemisomosis

18.3E: Theoretical ATP Yield

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18.3A: Glycolysis

Learning Objectives

1. Briefly describethe function of glycolysis during aerobic respiration and indicate the reactants and products.
2. State whether or not glycolysis requires oxygen.
3. Compare where glycolysis occurs in prokaryotic cells and in eukaryotic cells.
4. State whether steps 1 and 3 of glycolysis are exergonic or endergonic and indicate why.
5. State why one molecule of glucose is able to produce two molecules of pyruvate during glycolysis.
6. Define substrate-level phosphorylation.
7. State the total number and the net number of ATP produced by substrate-level phosphorylation during glycolysis.
8. During aerobic respiration, state what happens to the 2 NADH produced during glycolysis.
9. During aerobic respiration, state what happens to the two molecules of pyruvate produced during glycolysis.

Glycolysis is a partial breakdown of a six-carbon glucose molecule into two, three-carbon molecules of pyruvate, 2NADH $+2H^+$, and 2 net ATP as a result of substrate-level phosphorylation, as shown in (Figures 1 and 2).

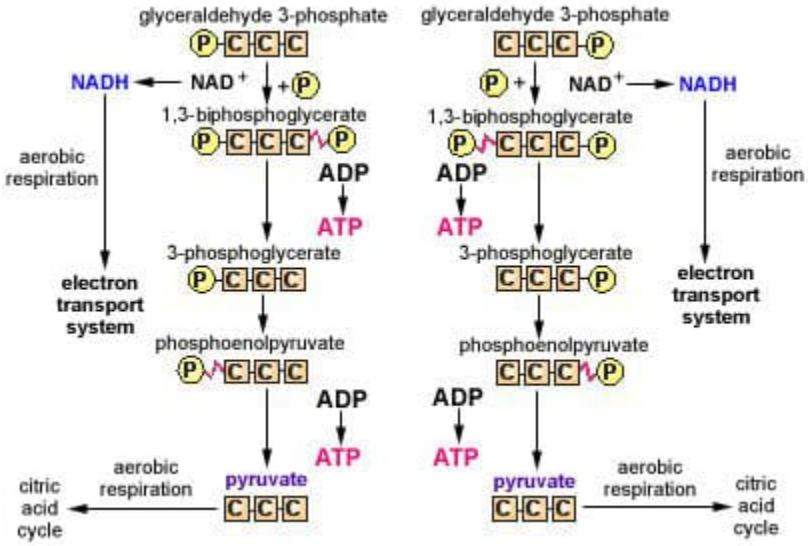


Figure 18.3A.1 and 2: A Summary of Glycolysis

Steps of Glycolysis

1. *A phosphate from the hydrolysis of a molecule of ATP is added to glucose, a 6-carbon sugar, to form glucose 6-phosphate.*
2. *The glucose 6-phosphate molecule is rearranged into an isomer called fructose 6-phosphate.*
3. *A second phosphate provided by the hydrolysis of a second molecule of ATP is added to the fructose 6-phosphate to form fructose 1,*
4. *The 6-carbon fructose 1,6-biphosphate is split into two molecules of glyceraldehyde 3-phosphate, a 3-carbon molecule.*
5. Oxidation and phosphorylation of each glyceraldehyde 3-phosphate produces 1,3-biphosphoglycerate with a high-energy phosphate bond (wavy red line) and NADH.
6. Through substrate-level phosphorylation, the high-energy phosphate is removed from each 1,3-biphosphoglycerate and transferred to ADP forming ATP and 3-phosphoglycerate.
7. Each 3-phosphoglycerate is oxidized to form a molecule of phosphoenolpyruvate with a high-energy phosphate bond.

8. Through substrate-level phosphorylation, the high-energy phosphate is removed from each phosphoenolpyruvate and transferred to ADP forming ATP and pyruvate.

In summary, one molecule of glucose produces two net ATPs (two ATPs were used at the beginning; four ATPs were produced through substrate-level phosphorylation), two molecules of NADH + $2H^+$, and two molecules of pyruvate.

Glycolysis occurs in the **cytoplasm** of the cell. The overall reaction is:

$$glucose(6C) + 2NAD + 2ADP + 2inorganicphosphates(P_i) \tag{18.3A.1}$$

$$\rightarrow 2pyruvate(3C) + 2NADH + 2H^+ + 2ATP \tag{18.3A.2}$$

Glycolysis also produces a number of key precursor metabolites, as shown in Figure $18.3A.3$. Glycolysis does not require oxygen and can occur under aerobic and anaerobic conditions. However, during aerobic respiration, the two reduced NADH molecules transfer protons and electrons to the electron transport chain to generate additional ATPs by way of oxidative phosphorylation.

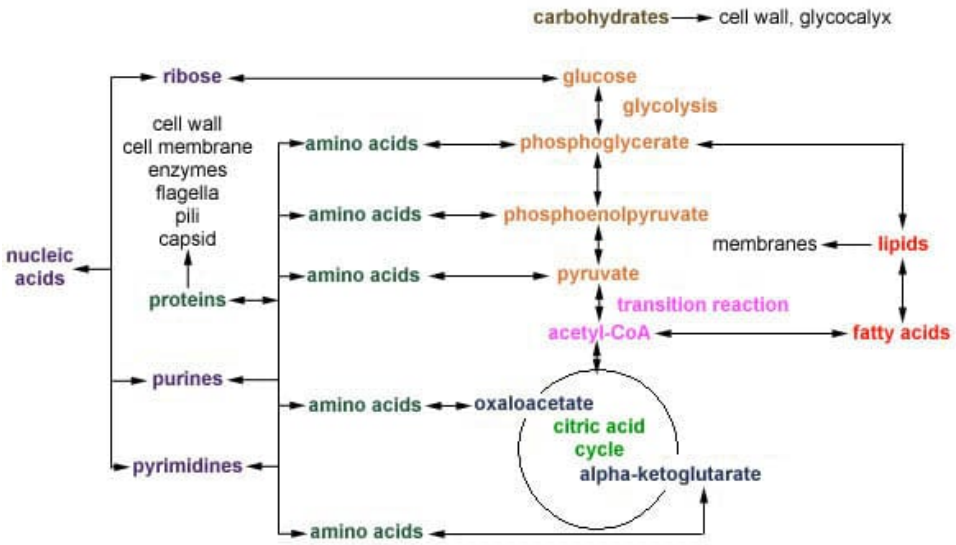


Figure $18.3A.3$: Integration of Metabolism - Precursor Metabolites.Carbohydrates, proteins, and lipids can be used as energy sources; metabolites involved in energy production can be used to synthesize carbohydrates, proteins, lipids, nucleic acids, and cellular structures.

The glycolysis pathway involves 9 distinct steps, each catalyzed by a unique enzyme. You are not responsible for knowing the chemical structures or enzymes involved in the steps below. They are included to help illustrate how the molecules in the pathway are manipulated by the enzymes in order to to achieve the required products.

Step 1

To initiate glycolysis in eukaryotic cells (Figure $18.3A.4$), a molecule of ATP is hydrolyzed to transfer a phosphate group to the number 6 carbon of glucose to produce glucose 6-phosphate. In prokaryotes, the conversion of phosphoenolpyruvate (PEP) to pyruvate provides the energy to transport glucose across the cytoplasmic membrane and, in the process, adds a phosphate group to glucose producing glucose 6-phosphate.

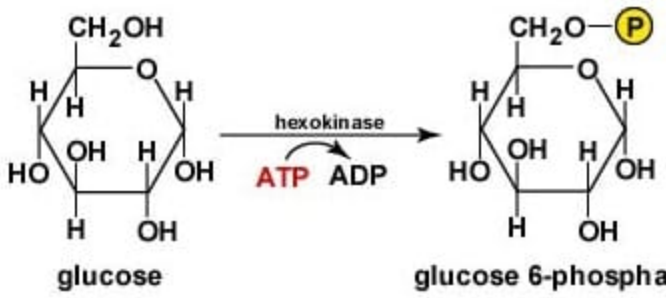


Figure 18.3A.4: Glycolysis, Step 1. To initiate glycolysis in eukaryotic cells, shown in this figure, a molecule of ATP is hydrolyzed to transfer a phosphate group to the number 6 carbon of glucose to produce glucose 6-phosphate. In prokaryotes, the conversion of phosphoenolpyruvate (PEP) to pyruvate provides the energy to transport glucose across the cytoplasmic membrane and, in the process, adds a phosphate group to glucose producing glucose 6-phosphate.

Step 2

The glucose 6-phosphate is rearranged to an isomeric form called fructose 6-phosphate (Figure 18.3A.5).

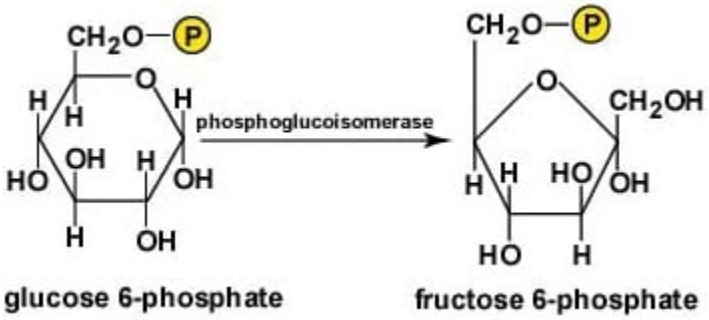


Figure 18.3A.5: Glycolysis, Step 2. The glucose 6-phosphate is rearranged to an isomeric form called fructose 6-phosphate.

Step 3

A second molecule of ATP is hydrolyzed to transfer a phosphate group to the number 1 carbon of fructose 6-phosphate to produce fructose 1,6-biphosphate (Figure 18.3A.6).

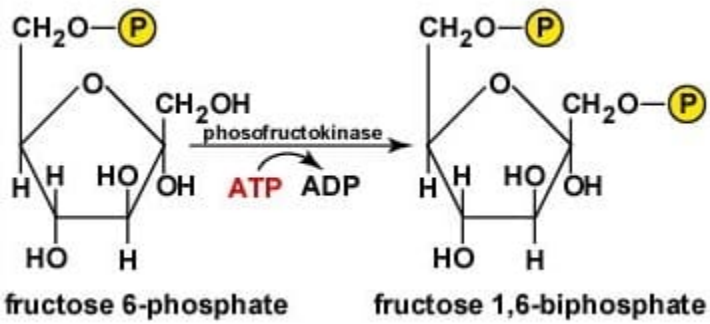


Figure 18.3A.6: Glycolysis, Step 3. A second molecule of ATP is hydrolyzed to transfer a phosphate group to the number 1 carbon of fructose 6-phosphate to produce fructose 1,6-biphosphate.

Step 4

The 6-carbon fructose 1,6 biphosphate is split to form two, 3-carbon molecules: glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. The dihydroxyacetone phosphate is then converted into a second molecule of glyceraldehyde 3-phosphate (Figure 18.3A.7). Two molecules of glyceraldehyde 3-phosphate will now go through each of the remaining steps in

glycolysis producing two molecules of each product.

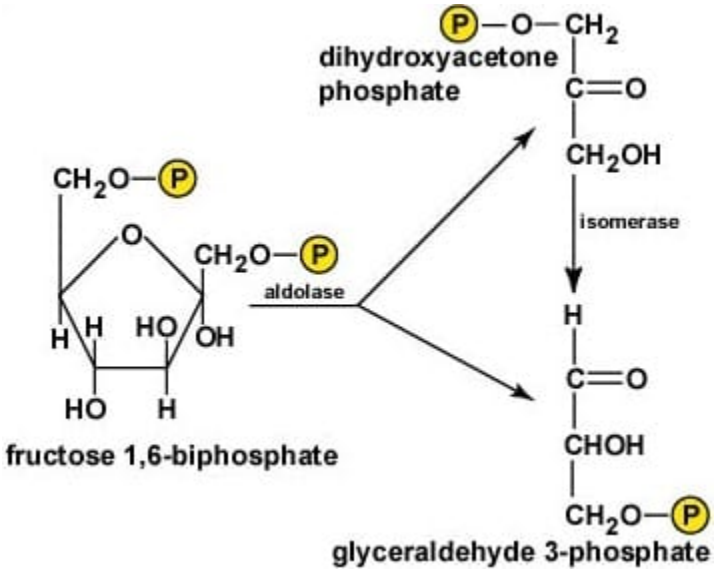


Figure 18.3A.7: Glycolysis, Step 4. The 6-carbon fructose 1,6 biphosphate is split to form two, 3-carbon molecules: glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. The dihydroxyacetone phosphate is then converted into a second molecule of glyceraldehyde 3-phosphate. Two molecules of glyceraldehyde 3-phosphate will now go through each of the remaining steps in glycolysis producing two molecules of each product.

Step 5

As each of the two molecules of glyceraldehyde 3-phosphate are oxidized, the energy released is used to add an inorganic phosphate group to form two molecules of 1,3-biphosphoglycerate, each containing a high-energy phosphate bond. During these oxidations, two molecules of NAD^+ are reduced to form 2NADH + $2H^+$ (Figure 18.3A.8). During aerobic respiration, the 2NADH + $2H^+$ carry protons and electrons to the electron transport chain to generate additional ATP by oxidative phosphorylation.

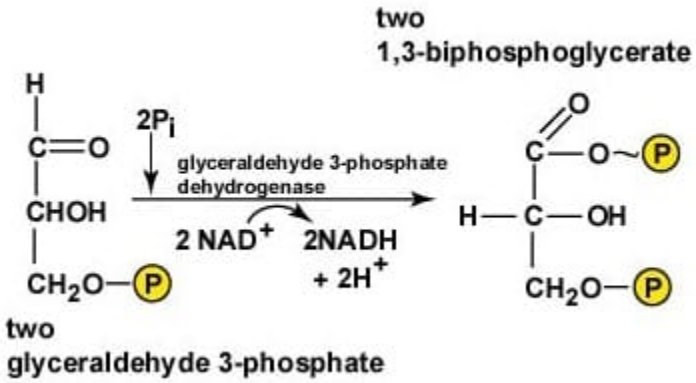


Figure 18.3A.8: Glycolysis, Step 5. As each of the two molecules of glyceraldehyde 3-phosphate are oxidized, the energy released is used to add an inorganic phosphate group to form two molecules of 1,3-biphosphoglycerate, each containing a high-energy phosphate bond. During these oxidations, two molecules of NAD^+ are reduced to form two NADH + $2H^+$.

Step 6

As each of the two molecules of 1,3-biphosphoglycerate are converted to 3-phosphoglycerate, the high-energy phosphate group is added to ADP producing 2 ATP by substrate-level phosphorylation, a shown in Figure 18.3A.9.

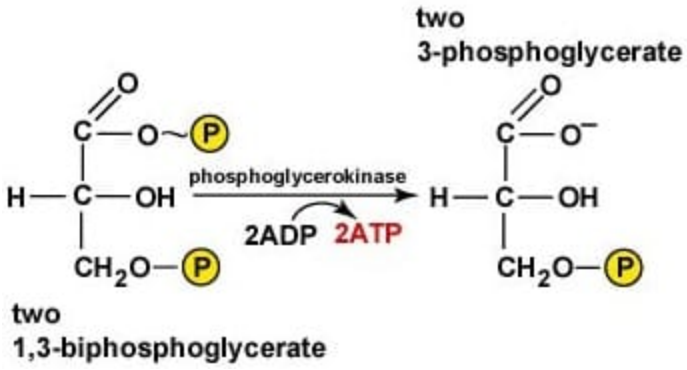


Figure 18.3A.9: Glycolysis, Step 6. As each of the two molecules of 1,3-biphosphoglycerate are converted to 3-phosphoglycerate, the high-energy phosphate group is added to ADP producing 2 ATP by substrate-level phosphorylation.

Step 7

The two molecules of 3-phosphoglycerate are rearranged to form two molecules of 2-phosphoglycerate (Figure 18.3A.10).

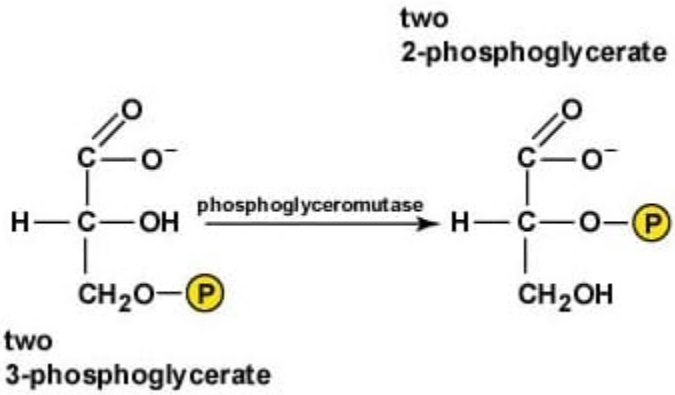


Figure 18.3A.10: Glycolysis, Step 7. The two molecules of 3-phosphoglycerate are rearranged to form two molecules of 2-phosphoglycerate.

Step 8

Water is removed from each of the two molecules of 2-phosphoglycerate converting the phosphate bonds to a high-energy phosphate bonds as two molecules of phosphoenolpyruvate are produced (Figure 18.3A.11).

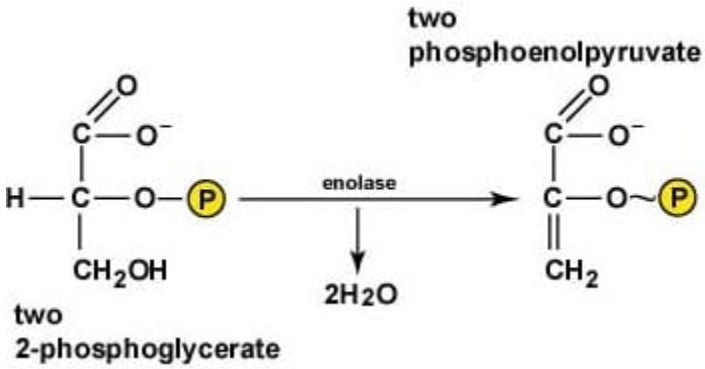


Figure 18.3A.11: Glycolysis, Step 8. Water is removed from each of the two molecules of 2-phosphoglycerate converting the phosphate bonds to a high-energy phosphate bonds as two molecules of phosphoenolpyruvate are produced.

Step 9

As the two molecules of phosphoenolpyruvate are converted to two molecules of pyruvate, the high-energy phosphate groups are added to ADP producing 2 ATP by substrate-level phosphorylation, a shown in Figure 18.3A.12.

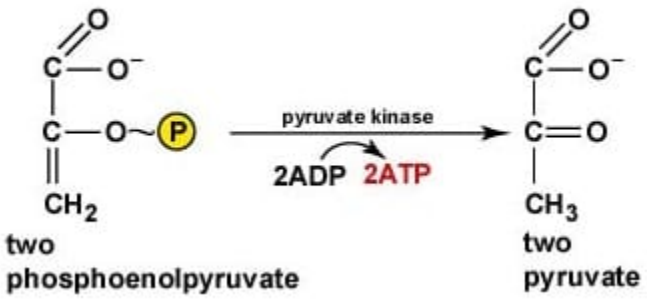


Figure 18.3A.12: Glycolysis, Step 9. As the two molecules of phosphoenolpyruvate are converted to two molecules of pyruvate, the high-energy phosphate groups are added to ADP producing 2 ATP by substrate-level phosphorylation.

Through an intermediate step called the transition reaction, the two molecules of pyruvate then enter the citric acid cycle to be further broken down and generate more ATPs by oxidative phosphorylation.

Overview

Glycolysis is a partial breakdown of a six-carbon glucose molecule into two, three-carbon molecules of pyruvate, 2NADH +2H^+, and 2 net ATP as a result of substrate-level phosphorylation. Glycolysis occurs in the cytoplasm of the cell.

Glycolysis

Glycolysis is the partial breakdown of one molecule of glucose into two molecules of pyruvic acid, two net molecules of ATP, two molecules of NADH, and $2H^+$.

The overall Glycolysis reaction is:

glucose (6C) + 2 NAD^+ 2 ADP +2 inorganic phosphates (P_i)

yields 2 pyruvate (3C) + 2 NADH + 2 H^+ + 2 net ATP

Outside Links

- YouTube movie of Glycolysis: Overview Reaction for Cellular Respiration
- YouTube movie: How Glycolysis Works

Summary

1. Aerobic respiration is the aerobic catabolism of nutrients to carbon dioxide, water, and energy, and involves an electron transport system in which molecular oxygen is the final electron acceptor.
2. Aerobic respiration involves four stages: glycolysis, a transition reaction that forms acetyl coenzyme A, the citric acid (Krebs) cycle, and an electron transport chain and chemiosmosis.
3. Glycolysis is a partial breakdown of a six-carbon glucose molecule into two, three-carbon molecules of pyruvate, 2NADH +2H^+, and 2 net ATP as a result of substrate-level phosphorylation.
4. The overall reaction for glycolysis is: glucose (6C) + 2 NAD^+ 2 ADP +2 inorganic phosphates (P_i) yields 2 pyruvate (3C) + 2 NADH + 2 H^+ + 2 net ATP.
5. Glycolysis does not require oxygen and can occur under aerobic and anaerobic conditions. However, during aerobic respiration, the two reduced NADH molecules transfer protons and electrons to the electron transport chain to generate additional ATPs by way of oxidative phosphorylation.
6. Glycolysis also produces a number of key precursor metabolites.
7. Through an intermediate step called the transition reaction, the two molecules of pyruvate then enter the citric acid cycle to be further broken down and generate more ATPs by oxidative phosphorylation.

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18.3B: Transition Reaction

Learning Objectives

1. Briefly describethe function of transition reaction during aerobic respiration and indicate the reactants and products.
2. During aerobic respiration, state what happens to the 2 NADH produced during the transition reaction.
3. Compare where the transition reaction occurs in prokaryotic cells and in eukaryotic cells.
4. During aerobic respiration, state what happens to the two molecules of Acetyl-CoA produced during the transition reaction.

Formation of Acetyl-CoA through the Transition Reaction

The transition reaction connects glycolysis to the citric acid (Krebs) cycle. Through a process called *oxidative decarboxylation*, the transition reaction converts the two molecules of the 3-carbon pyruvate from glycolysis (and other pathways) into two molecules of the 2-carbon molecule acetyl Coenzyme A (acetyl-CoA) and 2 molecules of carbon dioxide. First, a carboxyl group of each pyruvate is removed as carbon dioxide and then the remaining acetyl group combines with coenzyme A (CoA) to form acetyl-CoA.

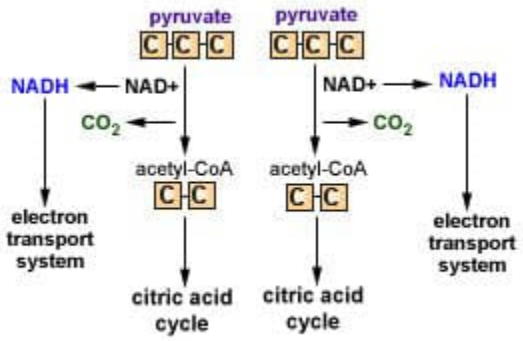


Figure $18.3B.1$**:** The Transition Reaction between Glycolysis and the Citric Acid Cycle. Before the pyruvates from glycolysis can enter the citric acid cycle, they must undergo a transition reaction. The 3-carbon pyruvate is converted into a 2-carbon acetyl group with a carboxyl being removed as CO_2. The acetyl group is attached to coenzyme A to form acetyl coenzyme A (acetyl-CoA), a key precursor metabolite. As the two acetyl groups become oxidized to acetyl-CoA, two molecules of NAD^+ are reduced to 2NADH + $2H^+$.

As the two pyruvates undergo oxidative decarboxylation, two molecules of NAD^+ become reduced to 2NADH + $2H^+$ (Figures $18.3B.1$ and $18.3B.2$). The 2NADH + $2H^+$ carry protons and electrons to the electron transport chain to generate additional ATP by oxidative phosphorylation.

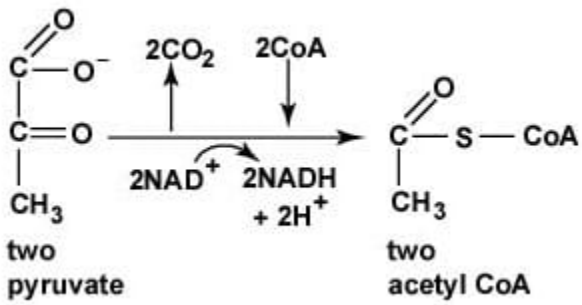


Figure $18.3B.2$**:** The Transition Reaction between Glycolysis and the Citric Acid Cycle

The two molecules of acetyl-CoA then enter the citric acid cycle. The 2NADH molecules that are produced carry electrons to the electron transport system for further production of ATPs by oxidative phosphorylation.

The overall reaction for the transition reaction is:

$$2 \text{ pyruvate} + 2 \text{ NAD}^+ + 2 \text{ coenzyme A}$$

$$\text{yields } 2 \text{ acetyl-CoA} + 2 \text{ NADH} + 2 \text{ H}^+ + 2 \text{ CO}_2$$

In prokaryotic cells, the transition step occurs in the cytoplasm; in eukaryotic cells the pyruvates must first enter the mitochondria because the transition reaction and the citric acid cycle take place in the matrix of the mitochondria.

The two molecules of acetyl-CoA can now enter the citric acid cycle. Acetyl-CoA is also a **precursor metabolite** for fatty acid synthesis, as shown in Figure $18.3B.3$.

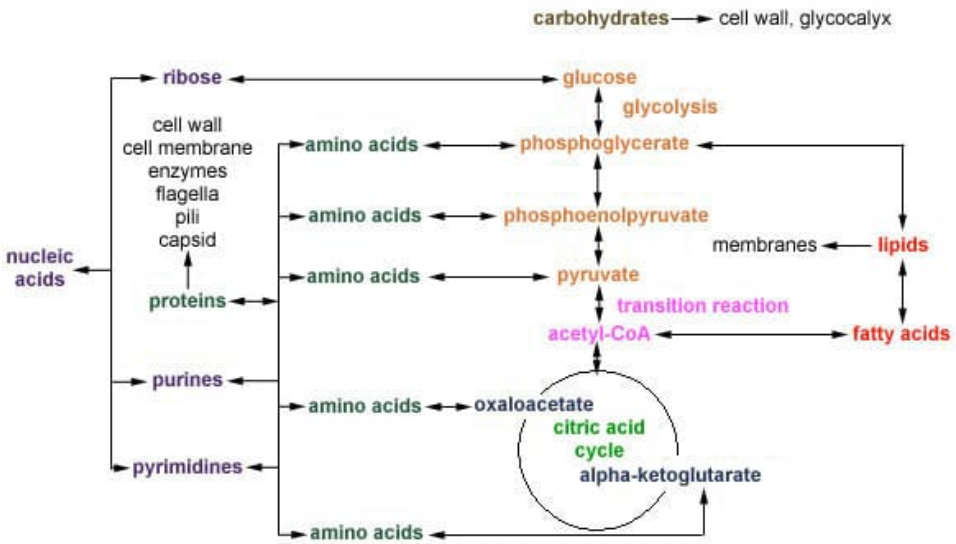


Figure $18.3B.3$**:** Integration of Metabolism - Precursor Metabolites. Carbohydrates, proteins, and lipids can be used as energy sources; metabolites involved in energy production can be used to synthesize carbohydrates, proteins, lipids, nucleic acids, and cellular structures.

Summary

1. Aerobic respiration involves four stages: glycolysis, a transition reaction that forms acetyl coenzyme A, the citric acid (Krebs) cycle, and an electron transport chain and chemiosmosis.
2. The transition reaction connects glycolysis to the citric acid (Krebs) cycle.
3. The transition reaction converts the two molecules of the 3-carbon pyruvate from glycolysis (and other pathways) into two molecules of the 2-carbon molecule acetyl Coenzyme A (acetyl-CoA) and 2 molecules of carbon dioxide.
4. As the two pyruvates undergo oxidative decarboxylation, two molecules of NAD^+ become reduced to $2NADH + 2H^+$ which carry protons and electrons to the electron transport chain to generate additional ATP by oxidative phosphorylation.
5. The overall reaction for the transition reaction is: 2 pyruvate + 2 NAD^+ + 2 coenzyme A yields 2 acetyl-CoA + 2 NADH + 2 H^+ + 2 CO_2.
6. The two molecules of acetyl-CoA can now enter the citric acid cycle.

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18.3C: Citric Acid (Krebs) Cycle

Learning Objectives

- State two other names for the citric acid cycle.
- Briefly describethe function of the citric acid cycle during aerobic respiration and indicate the reactants and products.
- Compare where the citric acid cycle occurs in prokaryotic cells and in eukaryotic cells.
- State the total number of ATP produced by substrate-level phosphorylation for each acetyl-CoA that enters the citric acid cycle.
- State the total number of NADH and $FADH_2$ produced for each acetyl-CoA that enters the citric acid cycle.
- During aerobic respiration, state what happens to the NADH and the $FADH_2$ produced during the citric acid cycle.

The citric acid cycle, also known as the tricarboxylic acid cycle and the Krebs cycle, completes the oxidation of glucose by taking the pyruvates from glycolysis (and other pathways), by way of the transition reaction mentioned previously, and completely breaking them down into CO_2 molecules, H_2O molecules, and generating additional ATP by oxidative phosphorylation. In prokaryotic cells, the citric acid cycle occurs in the cytoplasm; in eukaryotic cells the citric acid cycle takes place in the matrix of the mitochondria.

The overall reaction for the citric acid cycle is:

$$2 \text{ acetyl groups} + 6NAD^+ + 2FAD + 2ADP + 2P_i \tag{18.3C.1}$$

$$\rightarrow 4CO_2 + 6NADH + 6H^+ + 2FADH_2 + 2ATP \tag{18.3C.2}$$

The citric acid cycle (Figure Figure $18.3C.1$) provides a series of intermediate compounds that donate protons and electrons to the electron transport chain by way of the reduced coenzymes $NADH$ and $FADH_2$. The electron transport chain then generates additional ATPs by oxidative phosphorylation. The citric acid cycle also produces 2 ATP by substrate phosphorylation and plays an important role in the flow of carbon through the cell by supplying precursor metabolites for various biosynthetic pathways.

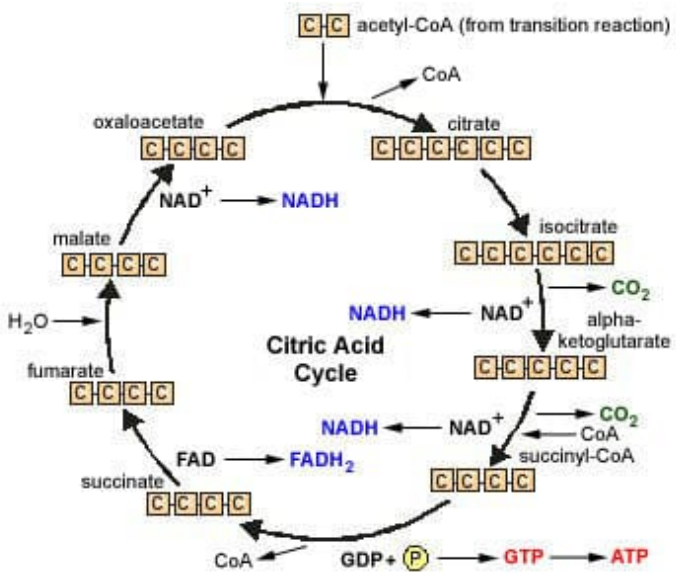


Figure $18.3C.1$: The Citric Acid Cycle (also Known as the Tricarboxylic Acid Cycle and the Krebs Cycle). The two molecules of acetyl-CoA from the transition reaction enter the citric acid cycle. This results in the formation of 6 molecules of $NADH$, two molecules of \(FADH_{-2\)}, two molecules of ATP, and four molecules of CO_2. *The NADH and $FADH_2$ molecules then carry electrons to the electron transport system for further production of ATPs by oxidative phosphorylation.*

The citric acid cycle involves 8 distinct steps, each catalyzed by a unique enzyme. You are not responsible for knowing the chemical structures or enzymes involved in the steps below. They are included to help illustrate how the molecules in the pathway

are manipulated by the enzymes in order to to achieve the required products.

Step 1: The citric acid cycle begins when Coenzyme A transfers its 2-carbon acetyl group to the 4-carbon compound oxaloacetate to form the 6-carbon molecule citrate (Figure Figure $18.3C.2$).

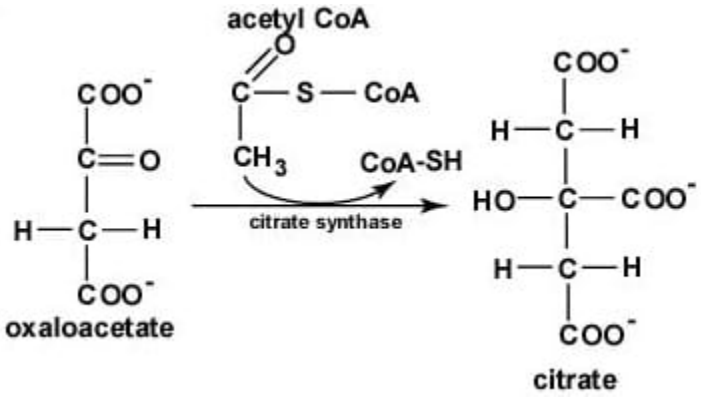


Figure $18.3C.2$: The Citric Acid Cycle, Step 1. The citric acid cycle begins when Coenzyme A transfers its 2-carbon acetyl group to the 4-carbon compound oxaloacetate to form the 6-carbon molecule citrate.

Step 2: The citrate is rearranged to form an isomeric form, isocitrate (Figure $18.3C.3$).

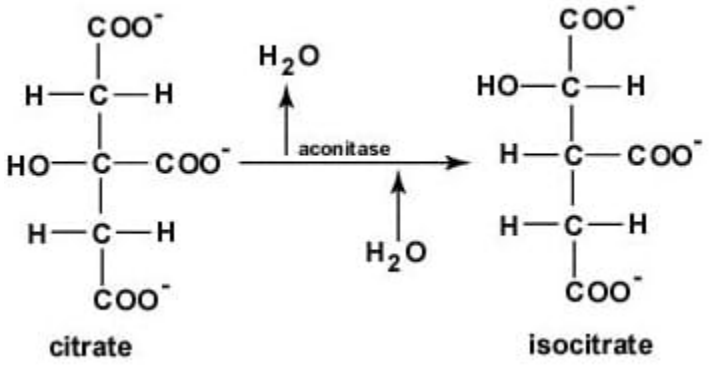


Figure $18.3C.3$: The Citric Acid Cycle, Step 2. The citrate is rearranged to form an isomeric form, isocitrate.

Step 3: The 6-carbon isocitrate is oxidized and a molecule of carbon dioxide is removed producing the 5-carbon molecule alpha-ketoglutarate. During this oxidation, NAD^+ is reduced to $NADH$ and H^+ (Figure $18.3C.4$).

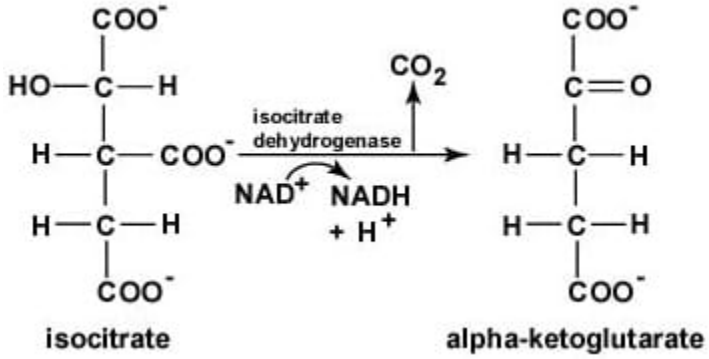


Figure $18.3C.4$: The Citric Acid Cycle, Step 3. The 6-carbon isocitrate is oxidized and a molecule of carbon dioxide is removed producing the 5-carbon molecule alpha-ketoglutarate. During this oxidation, NAD^+ is reduced to NADH + H^+.

Step 4: Alpha-ketoglutarate is oxidized, carbon dioxide is removed, and coenzyme A is added to form the 4-carbon compound succinyl-CoA. During this oxidation, NAD+ is reduced to NADH + H+ (Figure $18.3C.5$).

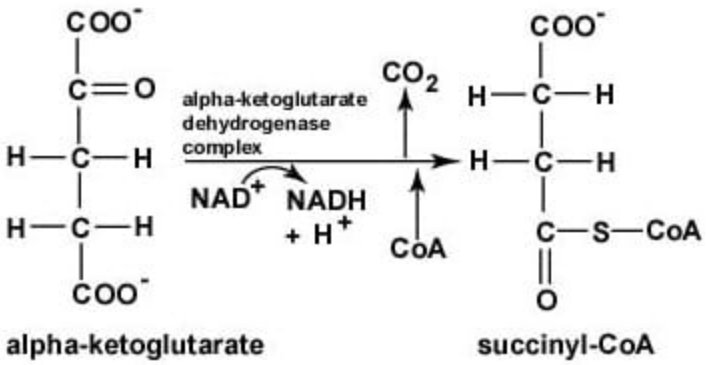


Figure $18.3C.5$: The Citric Acid Cycle, Step 4. Alpha-ketoglutarate is oxidized, carbon dioxide is removed, and coenzyme A is added to form the 4-carbon compound succinyl CoA. During this oxidation, NAD^+ is reduced to NADH + H^+.

Step 5: CoA is removed from succinyl-CoA to produce succinate. The energy released is used to make guanosine triphosphate (GTP) from guanosine diphosphate (GDP) and Pi by substrate-level phosphorylation. GTP can then be used to make ATP (Figure $18.3C.6$).

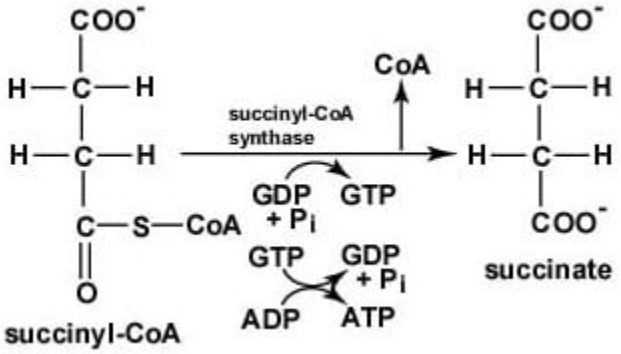


Figure $18.3C.6$: The Citric Acid Cycle, Step 5. CoA is removed from succinyl-CoA to produce succinate. The energy released is used to make guanosine triphosphate (GTP) from guanosine diphosphate (GDP) and P_i by substrate-level phosphorylation. GTP can then be used to make ATP.

Step 6: Succinate is oxidized to fumarate. During this oxidation, FAD is reduced to $FADH_2$ (Figure $18.3C.7$).

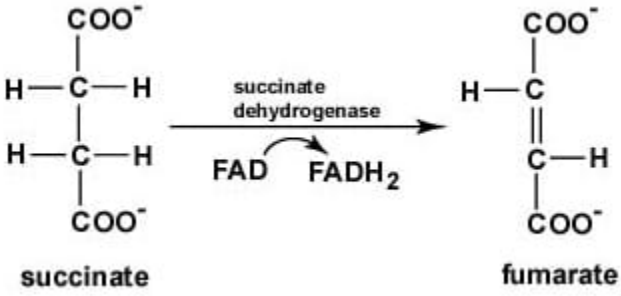


Figure $18.3C.7$: The Citric Acid Cycle, Step 6. Succinate is oxidized to fumarate. During this oxidation, FAD is reduced to $FADH_2$.

Step 7: Water is added to fumarate to form malate (Figure $18.3C.8$).

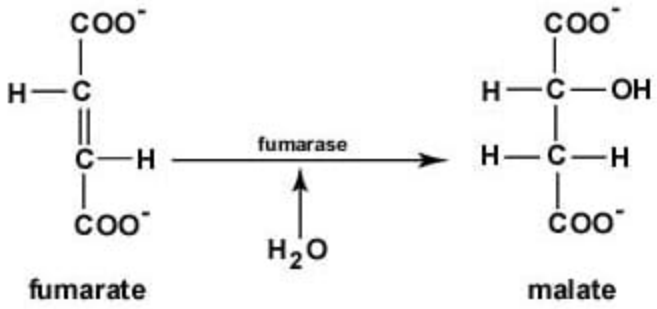


Figure $18.3C.8$: The Citric Acid Cycle, Step 7. Water is added to fumarate to form malate.

Step 8: Malate is oxidized to produce oxaloacetate, the starting compound of the citric acid cycle. During this oxidation, NAD^+ is reduced to NADH + H^+ (Figure $18.3C.9$).

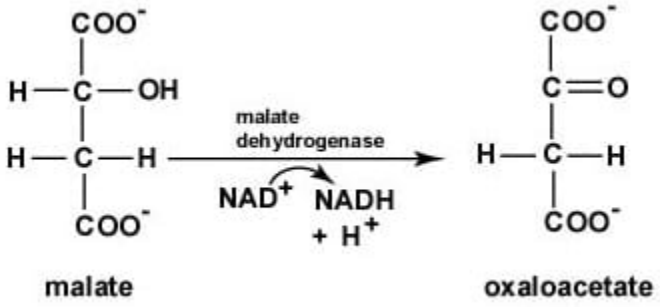


Figure $18.3C.9$: The Citric Acid Cycle, Step 8. Malate is oxidized to produce oxaloacetate, the starting compound of the citric acid cycle. During this oxidation, NAD^+ is reduced to NADH + H^+.

The NADH + H^+ and $FADH_2$ carry protons and electrons to the electron transport chain to generate additional ATP by oxidative phosphorylation.

Summary

1. Aerobic respiration involves four stages: glycolysis, a transition reaction that forms acetyl coenzyme A, the citric acid (Krebs) cycle, and an electron transport chain and chemiosmosis.
2. The citric acid cycle, also known as the tricarboxylic acid cycle and the Krebs cycle, completes the oxidation of glucose by taking the pyruvates from glycolysis, by way of the transition reaction, and completely breaking them down into CO_2 molecules, H_2O molecules, and generating additional ATP by oxidative phosphorylation.
3. The citric acid cycle provides a series of intermediate compounds that donate protons and electrons to the electron transport chain by way of the reduced coenzymes NADH and $FADH_2$. The electron transport chain then generates additional ATPs by oxidative phosphorylation. The citric acid cycle also produces 2 ATP by substrate phosphorylation.
4. The overall reaction for the citric acid cycle is:

$$2acetylgroups + 6NAD^+ + 2FAD + 2ADP + 2P_iyields4CO_2 + 6NADH + 6H^+ + 2FADH_2 + 2ATP. \quad (18.3C.3)$$

5. The citric acid cycle also plays an important role in the flow of carbon through the cell by supplying precursor metabolites for various biosynthetic pathways.

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18: MICROBIAL METABOLISM

- Topic hierarchy

18.2: Overview of Cellular Respiration

18.3: Aerobic Respiration

18.3A: Glycolysis

18.3B: Transition Reaction

18.3C: Citric Acid (Krebs) Cycle

18.3D: Electron Transport Chain and Chemisomosis

18.3E: Theoretical ATP Yield

18.4: Anaerobic Respiration

18.5: Fermentation

18.6: Precursor Metabolites: Linking Catabolic and Anabolic Pathways

18.7: Photosynthesis

18.7A: Introduction to Photosynthesis

18.7B: Oxygenic Photosynthesis: Light-Dependent Reactions

18.7C: Oxygenic Photosynthesis: Light-Independent Reactions

18.7D: C4 and CAM Pathways in Plants

18.E: Microbial Metabolism (Exercises)

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18.3D: Electron Transport Chain and Chemisomosis

Learning Objectives

1. Briefly describethe function of the electron transport chain during aerobic respiration.
2. Briefly describethe chemiosmotic theory of generation of ATP as a result of an electron transport chain.
3. Compare where the electron transport chain occurs in prokaryotic cells and in eukaryotic cells.
4. State what is meant by proton motive force.
5. State the function of ATP synthases in chemiosmosis.
6. State the final electron acceptor and the end product formed at the end of aerobic respiration.

During various steps in glycolysis and the citric acid cycle, the oxidation of certain intermediate precursor molecules causes the reduction of NAD^+ to NADH + H^+ and FAD to $FADH_2$. NADH and $FADH_2$ then transfer protons and electrons to the electron transport chain to produce additional ATPs by oxidative phosphorylation .

As mentioned in the previous section on energy, during the process of aerobic respiration, coupled oxidation-reduction reactions and electron carriers are often part of what is called an electron transport chain , a series of electron carriers that eventually transfers electrons from NADH and $FADH_2$ to oxygen. The diffusible electron carriers NADH and $FADH_2$ carry hydrogen atoms (protons and electrons) from substrates in exergonic catabolic pathways such as glycolysis and the citric acid cycle to other electron carriers that are embedded in membranes. These membrane-associated electron carriers include flavoproteins, iron-sulfur proteins, quinones, and cytochromes. The last electron carrier in the electron transport chain transfers the electrons to the terminal electron acceptor, oxygen.

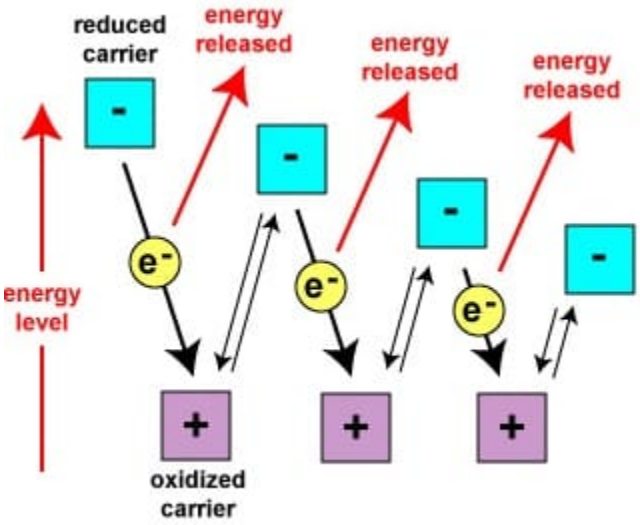


Figure $18.3D.1$: Energy Release from an Electron Transport System. In an electron transport system, electrons pass from carrier to carrier through a series of oxidation-reduction reactions. During each transfer, some energy is released.

The chemiosmotic theory explains the functioning of electron transport chains. According to this theory, the transfer of electrons down an electron transport system through a series of oxidation-reduction reactions releases energy (Figure $18.3D.1$). This energy allows certain carriers in the chain to transport hydrogen ions (H^+ or protons) across a membrane.

Depending on the type of cell, the electron transport chain may be found in the cytoplasmic membrane or the inner membrane of mitochondria.

- In prokaryotic cells, the protons are transported from the cytoplasm of the bacterium across the cytoplasmic membrane to the periplasmic space located between the cytoplasmic membrane and the cell wall .
- In eukaryotic cells, protons are transported from the matrix of the mitochondria across the inner mitochondrial membrane

to the intermembrane space located between the inner and outer mitochondrial membranes (Figure $18.3D.2$).

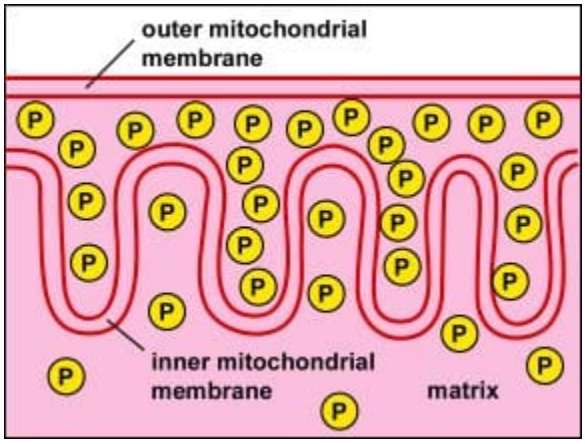


Figure $18.3D.2$: Accumulation of Protons within the Intermembrane Space of Mitochondria. In he mitochondria of eukaryotic cells, protons (H+) are transported from the matrix to the intermembrane space between the inner and outer mitochondrial membranes to produce proton motive force.

As the hydrogen ions accumulate on one side of a membrane, the concentration of hydrogen ions creates an electrochemical gradient or potential difference (voltage) across the membrane. (The fluid on the side of the membrane where the protons accumulate acquires a positive charge; the fluid on the opposite side of the membrane is left with a negative charge.) The energized state of the membrane as a result of this charge separation is called proton motive force or PMF.

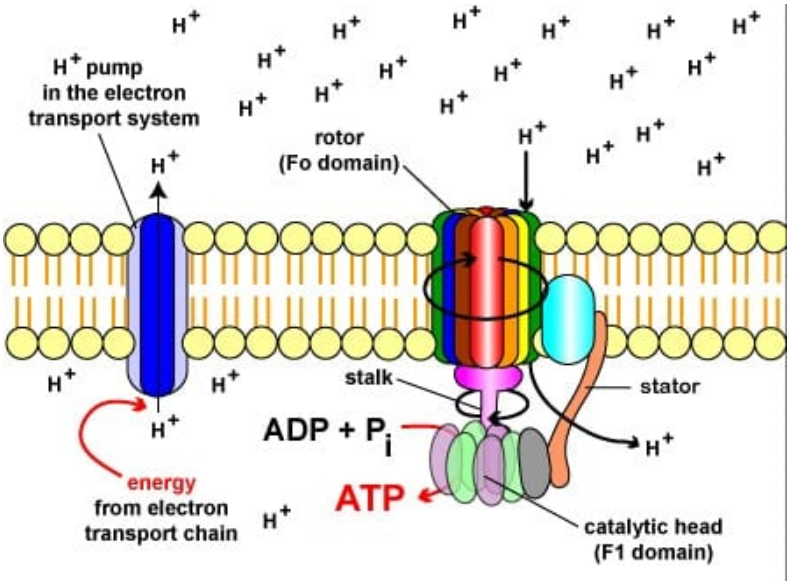


Figure $18.3D.3$: ATP Synthase Generating ATP. The chemiosmotic theory explains the functioning of electron transport chains. According to this theory, the tranfer of electrons down an electron transport system through a series of oxidation-reduction reactions releases energy. This energy allows certain carriers in the chain to transport hydrogen ions (H^+ or protons) across a membrane. As the hydrogen ions accumulate on one side of a membrane, the concentration of hydrogen ions creates an electrochemical gradient or potential difference (voltage) across the membrane. (The fluid on the side of the membrane where the protons accumulate acquires a positive charge; the fluid on the opposite side of the membrane is left with a negative charge.) The energized state of the membrane as a result of this charge separation is called proton motive force or PMF. This proton motive force provides the energy necessary for enzymes called ATP synthases, also located in the membranes mentioned above, to catalyze the synthesis of ATP from ADP and phosphate. This generation of ATP occurs as the protons cross the membrane through the ATP synthase complexes and re-enter either the bacterial cytoplasm or the matrix of the mitochondria. As the protons move down the concentration gradient through the ATP synthase, the energy released causes the rotor and rod of the ATP synthase to rotate. The mechanical energy from this rotation is converted into chemical energy as phosphate is added to ADP tform ATP.

This proton motive force provides the energy necessary for enzymes called ATP synthases (see Figure $18.3D.3$), also located in the membranes mentioned above, to catalyze the synthesis of ATP from ADP and phosphate. This generation of ATP occurs as the protons cross the membrane through the ATP synthase complexes and re-enter either the bacterial cytoplasm (Figure $18.3D.4$

) or the matrix of the mitochondria. As the protons move down the concentration gradient through the ATP synthase, the energy released causes the rotor and rod of the ATP synthase to rotate. The mechanical energy from this rotation is converted into chemical energy as phosphate is added to ADP to form ATP.

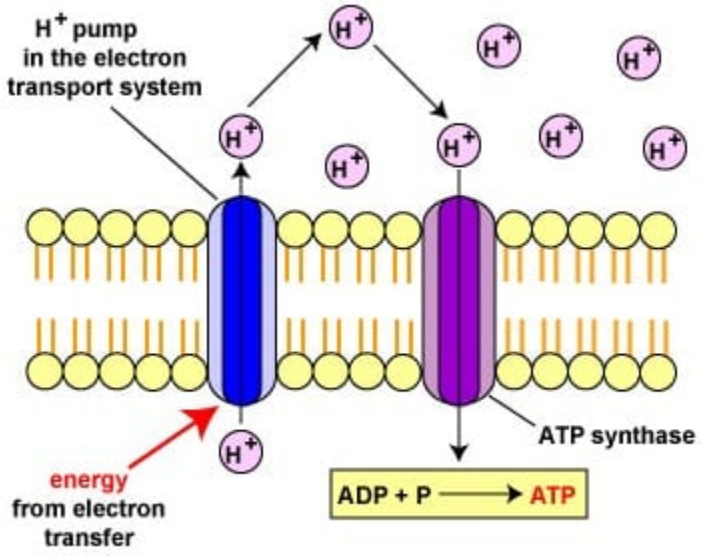


Figure 18.3D.4: Development of Proton Motive Force from Chemiosmosis and Generation of ATP. In an electron transport system, energy from electron transfer during oxidation-reduction reactions enables certain carriers to transport protons (H+) across a membrane. As the H+ concentration increases on one side of the membrane, an electrochemical gradient called proton motive force develops. Re-entry of the protons through an enzyme complex called ATP synthase provides the energy for the synthesis of ATP from ADP and phosphate.

Proton motive force is also used to transport substances across membranes during active transport and to rotate bacterial flagella.

At the end of the electron transport chain involved in aerobic respiration, the last electron carrier in the membrane transfers 2 electrons to half an oxygen molecule (an oxygen atom) that simultaneously combines with 2 protons from the surrounding medium to produce water as an end product (Figure 18.3D.5).

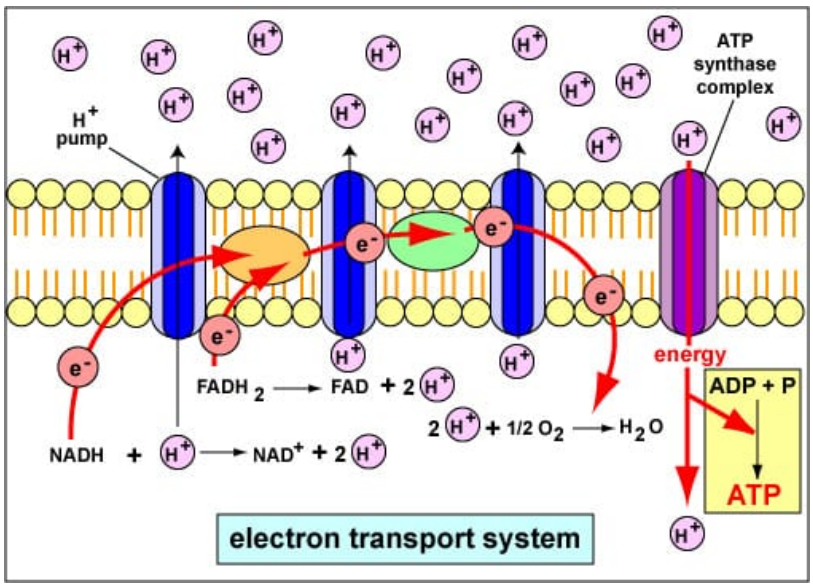


Figure 18.3D.5: ATP Production during Aerobic Respiration by Oxidative Phosphorylation involving an Electron Transport System and Chemiosmosis. NADH and $FADH_2$ carry protons (H^+) and electrons (e^-) to the electron transport chain located in the membrane. The energy from the transfer of electrons along the chain transports protons across the membrane and creates an electrochemical gradient. As the accumulating protons follow the electrochemical gradient back across the membrane through an ATP synthase complex, the movement of the protons provides energy for synthesizing ATP from ADP and phosphate. At the end of the electron transport system, two protons, two electrons, and half of an oxygen molecule combine to form water. Since oxygen is the final electron acceptor, the process is called aerobic respiration.

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

Movie illustrating the electron transport system in the mitochondria of eukaryotic cells.

Summary

1. Aerobic respiration involves four stages: glycolysis, a transition reaction that forms acetyl coenzyme A, the citric acid (Krebs) cycle, and an electron transport chain and chemiosmosis.
2. During various steps in glycolysis and the citric acid cycle, the oxidation of certain intermediate precursor molecules causes the reduction of NAD^+ to NADH + H^+ and FAD to $FADH_2$. NADH and $FADH_2$ then transfer protons and electrons to the electron transport chain to produce additional ATPs by oxidative phosphorylation.
3. The electron transport chain consists of a series of electron carriers that eventually transfer electrons from NADH and $FADH_2$ to oxygen.
4. The chemiosmotic theory states that the transfer of electrons down an electron transport system through a series of oxidation-reduction reactions releases energy. This energy allows certain carriers in the chain to transport hydrogen ions (H^+ or protons) across a membrane.
5. As the hydrogen ions accumulate on one side of a membrane, the concentration of hydrogen ions creates an electrochemical gradient or potential difference (voltage) across the membrane called proton motive force.
6. This proton motive force provides the energy necessary for enzymes called ATP synthases, also located in the membranes mentioned above, to catalyze the synthesis of ATP from ADP and phosphate.
7. During aerobic respiration, the last electron carrier in the membrane transfers 2 electrons to half an oxygen molecule (an oxygen atom) that simultaneously combines with 2 protons from the surrounding medium to produce water as an end product.

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18.3E: Theoretical ATP Yield

The theoretical maximum yield of ATP for the oxidation of one molecule of glucose during aerobic respiration is 38. In terms of substrate-level phosphorylation, oxidative phosphorylation, and the component pathways involved, briefly explain how this number is obtained.

Determining the exact yield of ATP for aerobic respiration is difficult for a number of reasons. In addition to generating ATP by oxidative phosphorylation in prokaryotic cells, proton motive force is also used for functions such as transporting materials across membranes and rotating flagella. Also, some bacteria use different carriers in their electron transport chain than others and the carriers may vary in the number of protons they transport across the membrane. Furthermore, the number of ATP generated per reduced NADH or $FADH_2$ is not always a whole number. For every pair of electrons transported to the electron transport chain by a molecule of NADH, between 2 and 3 ATP are generated. For each pair of electrons transferred by $FADH_2$, between 1 and 2 ATP are generated. In eukaryotic cells, unlike prokaryotes, NADH generated in the cytoplasm during glycolysis must be transported across the mitochondrial membrane before it can transfer electrons to the electron transport chain and this requires energy. As a result, between 1 and 2 ATP are generated from these NADH.

For simplicity, however, we will look at the theoretical maximum yield of ATP per glucose molecule oxidized by aerobic respiration. We will assume that for each pair of electrons transferred to the electron transport chain by NADH, 3 ATP will be generated; for each electron pair transferred by $FADH_2$, 2 ATP will be generated. Keep in mind, however, that less ATP may actually be generated.

As seen above, one molecule of glucose oxidized by aerobic respiration in prokaryotes yields the following:

Glycolysis

2 net ATP from substrate-level phosphorylation
2 NADH yields 6 ATP (assuming 3 ATP per NADH) by oxidative phosphorylation

Transition Reaction

2 NADH yields 6 ATP (assuming 3 ATP per NADH) by oxidative phosphorylation

Citric Acid Cycle

2 ATP from substrate-level phosphorylation
6 NADH yields 18 ATP (assuming 3 ATP per NADH) by oxidative phosphorylation
2 $FADH_2$ yields 4 ATP (assuming 2 ATP per $FADH_2$) by oxidative phosphorylation

Total Theoretical Maximum Number of ATP Generated per Glucose in Prokaryotes

38 ATP: 4 from substrate-level phosphorylation; 34 from oxidative phosphorylation.

In eukaryotic cells, the theoretical maximum yield of ATP generated per glucose is 36 to 38, depending on how the 2 NADH generated in the cytoplasm during glycolysis enter the mitochondria and whether the resulting yield is 2 or 3 ATP per NADH.

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18.4: Anaerobic Respiration

Define anaerobic respiration and state the pathways involved.

- State in what types or organism anaerobic respiration occurs.

Some prokaryotes are able to carry out anaerobic respiration, respiration in which an inorganic molecule other than oxygen (O_2) is the final electron acceptor. For example, some bacteria called sulfate reducers can transfer electrons to sulfate (SO_4^{2-}) reducing it to H_2S. Other bacteria, called nitrate reducers, can transfer electrons to nitrate (NO_3^-) reducing it to nitrite (NO_2^-). Other nitrate reducers can reduce nitrate even further to nitrous oxide (NO) or nitrogen gas (N_2).

Like aerobic respiration, anaerobic respiration involves glycolysis, a transition reaction, the citric acid cycle, and an electron transport chain. The total energy yield per glucose oxidized is less than with aerobic respiration with a theoretical maximum yield of 36 ATP or less.

Summary

1. Cellular respiration is the process cells use to convert the energy in the chemical bonds of nutrients to ATP energy.
2. Aerobic respiration is an exergonic pathway that requires molecular oxygen (O_2).
3. Anaerobic exergonic pathways do not require oxygen and include anaerobic respiration and fermentation.
4. Some prokaryotes are able to carry out anaerobic respiration, respiration in which an inorganic molecule other than oxygen (O_2) is the final electron acceptor.
5. Some bacteria called sulfate reducers can transfer electrons to sulfate (SO_4^{2-}) reducing it to H_2S. Other bacteria, called nitrate reducers, can transfer electrons to nitrate (NO_3^-) reducing it to nitrite (NO_2^-). Other nitrate reducers can reduce nitrate even further to nitrous oxide (NO) or nitrogen gas (N_2).
6. Like aerobic respiration, anaerobic respiration involves glycolysis, a transition reaction, the citric acid cycle, and an electron transport chain.

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18.5: Fermentation

Learning Objectives

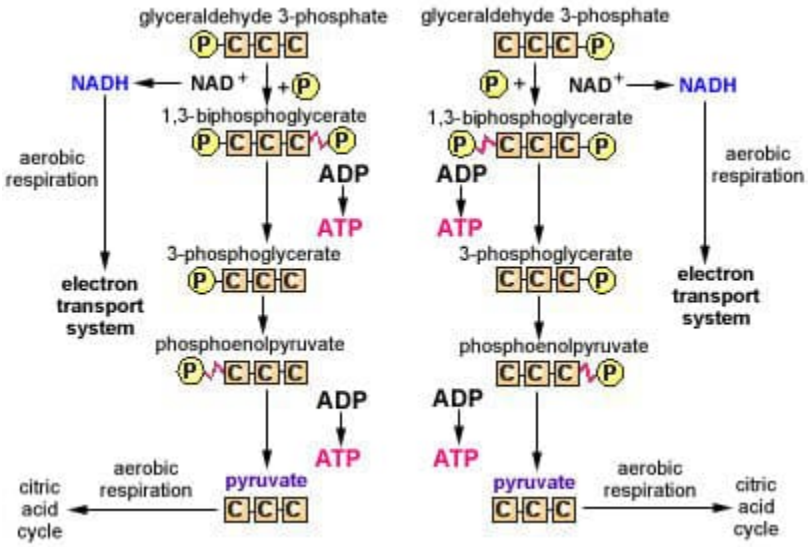
1. Define fermentation.
2. State the mechanism for ATP generation during fermentation.
3. Briefly describethe function of glycolysis during fermentation and indicate the reactants and products.
4. Compare the maximum yield of ATP from one molecule of glucose for aerobic respiration and for fermentation.

Fermentation is an anaerobic breakdown of carbohydrates in which an organic molecule is the final electron acceptor. It does not involve an electron transport system. Furthermore,:

a. Fermentation is a partial breakdown of glucose producing only 2 net ATP's per glucose by way of substrate-level phosphorylation ;
b. Fermentation involves only glycolysis; and
c. Fermentation is found in bacteria that are obligate anaerobes and facultative anaerobes.

Glycolysis during Fermentation

Function: As during aerobic respiration, glycolysis is a partial breakdown of a six-carbon glucose molecule into two, three-carbon molecules of pyruvate, 2NADH +2H$^+$, and 2 net ATP as a result of substrate-level phosphorylation, as shown in (see Figure 18.5.1 and Figure 18.5.2).



Figures 1 and 2: A Summary of Glycolysis. 1. A phosphate from the hydrolysis of a molecule of ATP is added to glucose, a 6-carbon sugar, to form glucose 6-phosphate. 2. The glucose 6-phosphate molecule is rearranged into an isomer called fructose 6-phosphate. 3. A second phosphate provided by the hydrolysis of a second molecule of ATP is added to the fructose 6-phosphate to form fructose 1,6-diphosphate. 4. The 6-carbon fructose 1,6-biphosphate is split into two molecules of glyceraldehyde 3-phosphate, a 3-carbon molecule. 4. Oxidation and phosphorylation of each glyceraldehyde 3-phosphate produces 1,3-biphosphoglycerate with a high-energy phosphate bond (wavy red line) and NADH. 5. Through substrate-level phosphorylation, the high-energy phosphate is removed from each 1,3-biphosphoglycerate and transferred to ADP forming ATP and 3-phosphoglycerate. 6. Each 3-phosphoglycerate is oxidized to form a molecule of phosphoenolpyruvate with a high-energy phosphate bond.7. Through substrate-level phosphorylation, the high-energy phosphate is removed from each phosphoenolpyruvate and transferred to ADP forming ATP and pyruvate.

Glycolysis occurs in the cytoplasm of the cell. As mentioned above, the overall reaction is:

glucose (6C) + 2 NAD^+ +2 ADP +2 inorganic phosphates (P_i)

yields 2 pyruvate (3C) + 2 NADH + 2 H^+ + 2 net ATP

Glycolysis also produces a number of key precursor metabolites, as shown in Figure 18.5.3.

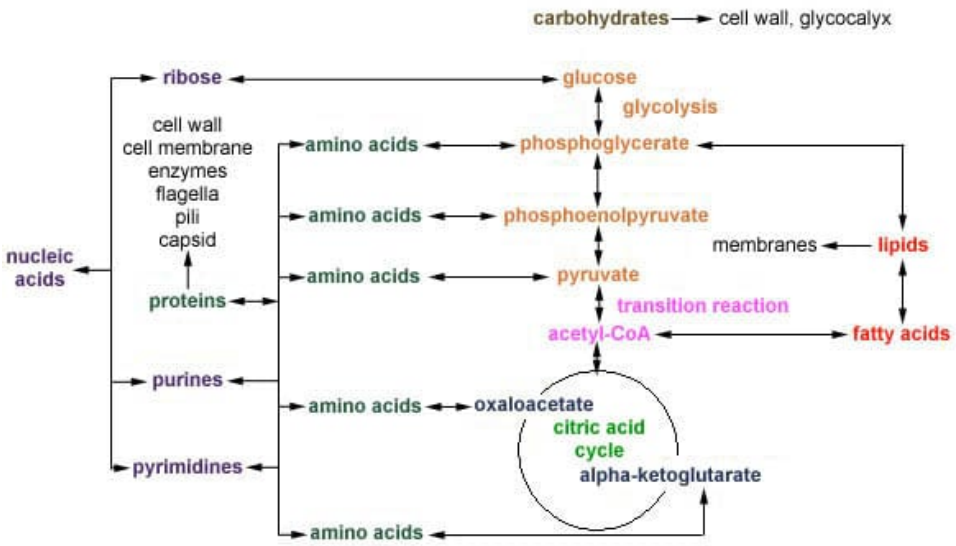
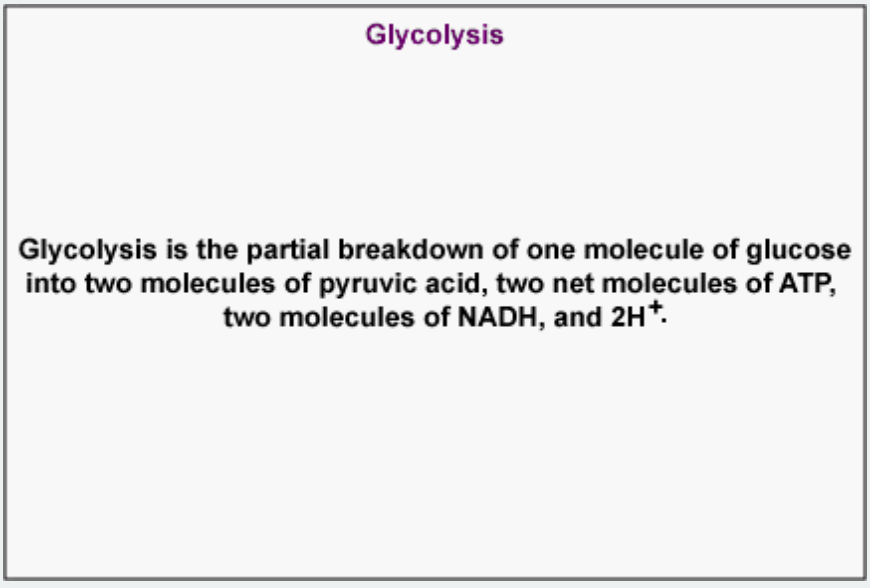


Figure 18.5.3: Integration of Metabolism - Precursor Metabolites. Carbohydrates, proteins, and lipids can be used as energy sources; metabolites involved in energy production can be used to synthesize carbohydrates, proteins, lipids, nucleic acids, and cellular structures.

Since there is no electron transport system, the protons and electrons donated by certain intermediate precursor molecules during glycolysis generate no additional molecules of ATP. Instead, they combine with the coenzyme NAD^+, the organic molecule which serves as the final electron and proton acceptor, reducing it to NADH + H^+ (see Figure 18.5.1 and Figure 18.5.2).

Glycolysis



Glycolysis is a partial breakdown of a six-carbon glucose molecule into two, three-carbon molecules of pyruvate, 2NADH +2H^+, and 2 net ATP as a result of substrate-level phosphorylation. Glycolysis occurs in the cytoplasm of the cell.

The 2 pyruvic acids are then converted into one of many different fermentation end products in several non-energy-producing steps.

Fermentation end products

Some fermentation end products produced by microorganisms are very beneficial to humans and are the basis of a number of industries (brewing industry, dairy industry, etc.). Fermentation is used in the production of many food products including bread, alcohol, yogurt, sour cream, cheeses, vinegar, sauerkraut, pickles, olives, soy sauce, poi, and kimchi. Examples of microbial fermentation end products include:

- *Saccharomyces*: ethyl alcohol and CO_2
- *Streptococcus* and *Lactobacillus*: lactic acid
- *Propionibacterium*: proprionic acid, acetic acid, and CO_2
- *Escherichia coli*: acetic acid, lactic acid, succinic acid, ethyl alcohol, CO_2, and H_2
- *Enterobacter*: formic acid, ethyl alcohol, 2,3-butanediol, lactic acid, CO_2, and H_2
- *Clostridium*: butyric acid, butyl alcohol, acetone, isopropyl alcohol, CO_2, and H_2

Summary

1. Fermentation is an anaerobic breakdown of carbohydrates in which an organic molecules the final electron acceptor and does not involve an electron transport system.
2. Fermentation is a partial breakdown of glucose producing only 2 net ATP's per glucose by way of substrate-level phosphorylation, involves only glycolysis, and is found in anaerobic and facultative anaerobic bacteria.
3. The overall reaction is glucose (6C) + 2 NAD^+ +2 ADP +2 inorganic phosphates (P_i) yields 2 pyruvate (3C) + 2 NADH + 2 H^+ + 2 net ATP.
4. Glycolysis also produces a number of key precursor metabolites.
5. Some fermentation end products produced by microorganisms are very beneficial to humans and are the basis of a number of industries (brewing industry, dairy industry, etc.).

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18.6: Precursor Metabolites: Linking Catabolic and Anabolic Pathways

Define precursor metabolites and indicate their importance in metabolism.

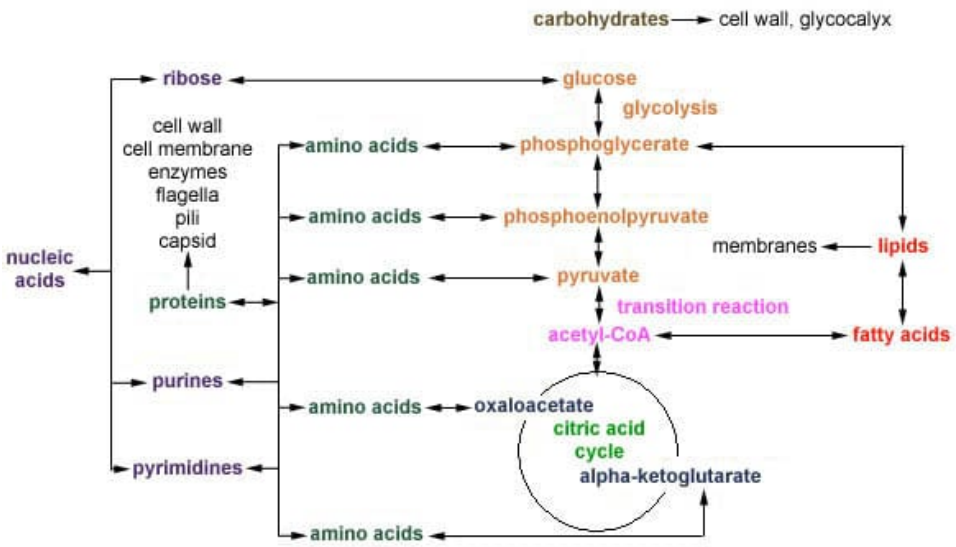


Figure 18.6.18.6.1: Integration of Metabolism - Precursor Metabolites. Carbohydrates, proteins, and lipids can be used as energy sources; metabolites involved in energy production can be used to synthesize carbohydrates, proteins, lipids, nucleic acids, and cellular structures.

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18.7: PHOTOSYNTHESIS

Photoautotrophs use sunlight as a source of energy and through the process of photosynthesis, reduce carbon dioxide to form carbohydrates such as glucose. The radiant energy is converted to the chemical bond energy within glucose and other organic molecules. Plants, algae, and cyanobacteria are known as oxygenic photoautotrophs because they synthesize organic molecules from inorganic materials, convert light energy into chemical energy, use water as an electron source, and generate oxygen as an end product of photosynthesis. The overall reaction for photosynthesis is as follows:

$$6CO_2 + 12H_2O \xrightarrow[\text{light}]{\text{chlorophyll}} C_6H_{12}O_6 + 6O_2 + 6H_2O \tag{18.7.1}$$

Note that photosyntehsis is a redox reaction with carbon dioxide (CO_2) reduced to produce glucose ($C_6H_{12}O_6$) and water (H_2O) oxidized to produce oxygen (O_2). Photosynthesis is composed of two stages: the light-dependent reactions and the light independent reactions.

- Topic hierarchy

18.7A: Introduction to Photosynthesis

18.7B: Oxygenic Photosynthesis: Light-Dependent Reactions

18.7C: Oxygenic Photosynthesis: Light-Independent Reactions

18.7D: C4 and CAM Pathways in Plants

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18.7A: Introduction to Photosynthesis

Define the following:

a. oxygenic photoautotroph
b. anoxygenic photoautotroph
c. photon

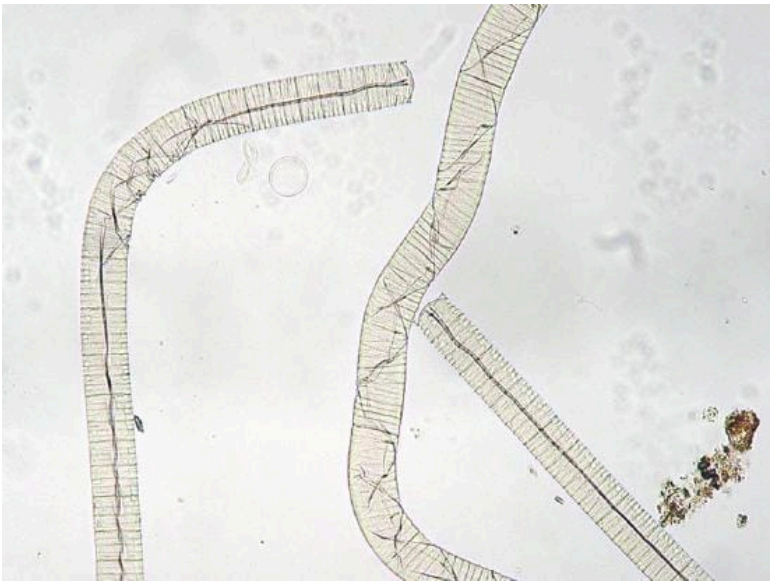
- Name the two stages of photosynthesis.
- State how all radiations in the electromagnetic spectrum travel.
- State what constitutes visible light.
- Define photon and describe what happens when photons of visible light energy strike certain atoms of pigments during photosynthesis and how this can lead to the generation of ATP.
- Describe the structure of a chloroplast and list the pigments it may contain.
- Give the overall reaction for photosynthesis.
- State the reactants and the products for photosynthesis and indicate which are oxidized and which are reduced.

Autotrophs are organisms that are able to synthesize organic molecules from inorganic materials. Photoautotrophs absorb and convert light energy into the stored energy of chemical bonds in organic molecules through a process called photosynthesis.

Plants, algae, and bacteria known as cyanobacteria are known as oxygenic photoautotrophs because they synthesize organic molecules from inorganic materials, convert light energy into chemical energy, use water as an electron source, and generate oxygen as an end product of photosynthesis. Some bacteria, such as the green and purple bacteria, are known as anoxygenic phototrophs . Unlike the oxygenic plants, algae, and cyanobacteria, anoxygenic phototrophs do not use water as an electron source and, therefore, do not evolve oxygen during photosynthesis. The electrons come from compounds such as hydrogen gas, hydrogen sulfide, and reduced organic molecules. In this section on photosynthesis, we be concerned with the oxygenic phototrophs.

There are three major groups of photosynthetic bacteria: cyanobacteria, purple bacteria, and green bacteria.

1. The cyanobacteria carry out **oxygenic photosynthesis**, that is, they use water as an electron donor and generate oxygen during photosynthesis. The photosynthetic system is located in an extensive thylakoid membrane system that is lined with particles called phycobilisomes.





Cyanobacteria, as well as algae and green plants, use hydrogen atoms from water to reduce carbon dioxide to form carbohydrates, and during this process oxygen gas is given off (an oxygenic process). Cyanobacteria were the first organisms on earth to carry out oxygenic photosynthesis. (left) Anabaena flosaquae and (right) Oscillatoria princeps. Images used with permission (Anabaena is Public domain from the US Environmental Protection Agenca and Oscillatoria is CC BY-SA 3.0; Kristian Peters).

2. The green bacteria carry out **anoxygenic photosynthesis**. They use reduced molecules such as H_2, H_2S, S, and organic molecules as an electron source and generate NADH and NADPH. The photosynthetic system is located in ellipsoidal vesicles called **chlorosomes** that are independent of the cytoplasmic membrane.

3. The purple bacteria carry out **anoxygenic photosynthesis**. They use reduced molecules such as H_2, H_2S, S, and organic molecules as an electron source and generate NADH and NADPH. The photosynthetic system is located in spherical or lamellar membrane systems that are continuous with the cytoplasmic membrane.

In this section we will concentrate on oxygenic photosynthesis. Oxygenic photosynthesis is composed of two stages: the light-dependent reactions and the light-independent reactions.

1. The light-dependent reactions convert light energy into chemical energy, producing ATP and NADPH.

2. The light-independent reactions use the ATP and NADPH from the light-dependent reactions to reduce carbon dioxide and convert the energy to the chemical bond energy in carbohydrates such as glucose. Before we get to these photosynthetic reactions however, we need to understand a little about the electromagnetic spectrum and chloroplasts.

The Electromagnetic Spectrum

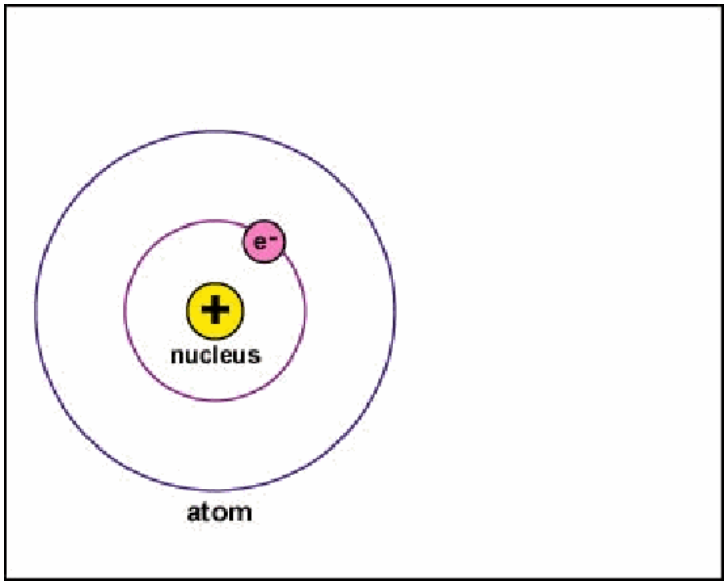


Figure 18.7A.2: Chloroplasts. Chloroplasts are surrounded by an inner and an outer membrane. The inner membrane encloses a fluid-filled region called the stroma that contains enzymes for the light-independent reactions of photosynthesis. Infolding of this inner membrane forms interconnected stacks of disk-like sacs called thylakoids, often arranged in stacks called grana. The thylakoid membrane, which encloses a fluid-filled thylakoid interior space, contains chlorophyll and other photosynthetic pigments as well as electron transport chains. The light-dependent reactions of photosynthesis occur in the thylakoids. The outer membrane of the chloroplast encloses the intermembrane space between the inner and outer chloroplast membranes. (CC BY 3.0; Kelvinsong).

The thylakoid membranes contain several pigments capable of absorbing visible light. Chlorophyll is the primary pigment of photosynthesis. Chlorophyll absorbs light in the blue and red region of the visible light spectrum and reflects green light. There are two major types of chlorophyll, chlorophyll *a* that initiates the light-dependent reactions of photosynthesis, and chlorophyll *b*, an accessory pigment that also participates in photosynthesis. The thylakoid membranes also contain other accessory pigments. Carotenoids are pigments that absorb blue and green light and reflect yellow, orange, or red. Phycocyanins absorb green and yellow light and reflect blue or purple. These accessory pigments absorb light energy and transfer it to chlorophyll.

Photosynthetic prokaryotic cells do not possess chloroplasts. Instead, thylakoid membranes are usually arranged around the periphery of the bacterium as infoldings of the cytoplasmic membrane.

Photosynthesis

As mentioned above, photoautotrophs use sunlight as a source of energy and through the process of photosynthesis, reduce carbon dioxide to form carbohydrates such as glucose. The radiant energy is converted to the chemical bond energy within glucose and other organic molecules.

The overall reaction for photosynthesis is as follows:

$$6\ CO_2 + 12\ H_2O \text{ in the presence of light and chlorophyll yields } C_6H_{12}O_6 + 6\ O_2 + 6\ H_2O$$

Note that carbon dioxide (CO_2) is reduced to produce glucose ($C_6H_{12}O_6$) while water (H_2O) is oxidized to produce oxygen (O_2).

Outside Links

- YouTube movie on the structure and functions of chloroplasts.

Summary

1. Autotrophs are organisms that are able to synthesize organic molecules from inorganic materials.

2. Photoautotrophs absorb and convert light energy into the stored energy of chemical bonds in organic molecules through a process called photosynthesis.
3. Plants, algae, and cyanobacteria are known as oxygenic photoautotrophs because they synthesize organic molecules from inorganic materials, convert light energy into chemical energy, use water as an electron source, and generate oxygen as an end product of photosynthesis.
4. Green and purple bacteria, are known as anoxygenic phototrophs that do not use water as an electron source and, therefore, do not evolve oxygen during photosynthesis. The electrons come from compounds such as hydrogen gas, hydrogen sulfide, and reduced organic molecules.
5. Oxygenic photosynthesis is composed of two stages: the light-dependent reactions and the light-independent reactions.
6. The light-dependent reactions convert light energy into chemical energy, producing ATP and NADPH.
7. The light-independent reactions use the ATP and NADPH from the light-dependent reactions to reduce carbon dioxide and convert the energy to the chemical bond energy in carbohydrates such as glucose.
8. Light and other types of radiation are composed of individual packets of energy called photons. When photons of visible light energy strike certain atoms of pigments during photosynthesis, that energy may push an electron from that atom to a higher energy level where it can be picked up by an electron acceptor in an electron transport chain.
9. In eukaryotic cells, photosynthesis takes place in organelles called chloroplasts.
10. The inner membrane of a chloroplast encloses a fluid-filled region called the stroma that contains enzymes for the light-independent reactions of photosynthesis.
11. Infolding of this inner membrane forms interconnected stacks of disk-like sacs called thylakoids. The thylakoid membrane, which encloses a fluid-filled thylakoid interior space, contains chlorophyll and other photosynthetic pigments as well as electron transport chains. The light-dependent reactions of photosynthesis occur in the thylakoids.
12. The overall reaction for photosynthesis is as follows: 6 CO_2 + 12 H_2O in the presence of light and chlorophyll yields $C_6H_{12}O_6$ + 6 O_2 + 6 H_2O.

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18.7B: Oxygenic Photosynthesis: Light-Dependent Reactions

Briefly describe the overall function of the light-dependent reactions in photosynthesis and state where in the chloroplast they occur.

- State the reactants and the products for the light-dependent reactions.
- Describe an antenna complex and state the function of the reaction center.
- Briefly describe the overall function of Photosystem II in the light-dependent reactions of photosynthesis.
- Briefly describe how ATP is generated by chemiosmosis during the light-dependent reactions of photosynthesis.
- Briefly describe the overall function of Photosystem I in the light-dependent reactions of photosynthesis.
- Compare noncyclic photophosphorylation and cyclic photophosphorylation in terms of Photosystems involved and products produced.

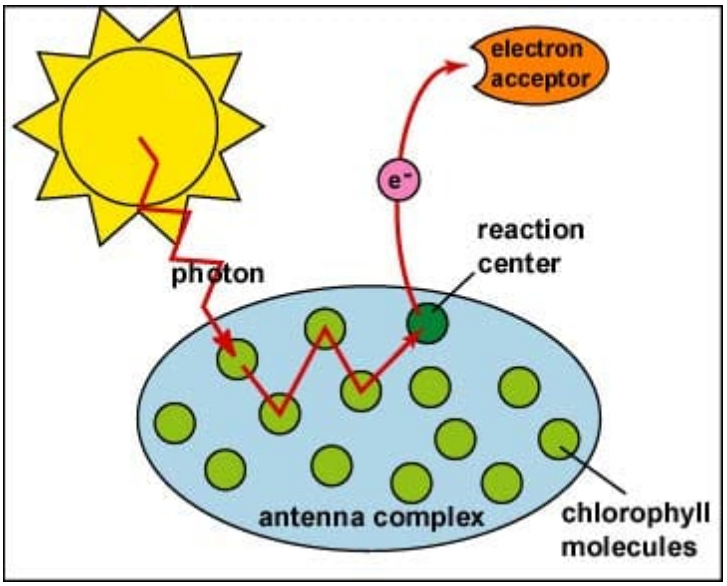


Figure 18.7B.1: Antenna Complex Each antenna complex is able to trap light and transfer energy to a complex of chlorophyll molecules and proteins called the reaction center. Photons are absorbed by chlorophyll and accessory pigments and that energy is eventually transfered to the reaction center where it is absorbed by an excitable electron moving it to a higher energy level. Here the electron can be accepted by an electron acceptor molecule of an electron transport chain where the light energy is converted to chemical energy by chemiosmosis

The most common light-dependent reaction in photosynthesis is called noncyclic photophosphorylation. Noncyclic photophosphorylation involves both Photosystem I and Photosystem II and produces ATP and NADPH. During noncyclic photophosphorylation, the generation of ATP is coupled to a one-way flow of electrons from H_2O to $NADP^+$. We will now look at Photosystems I and II and their roles in noncyclic photophosphorylation.

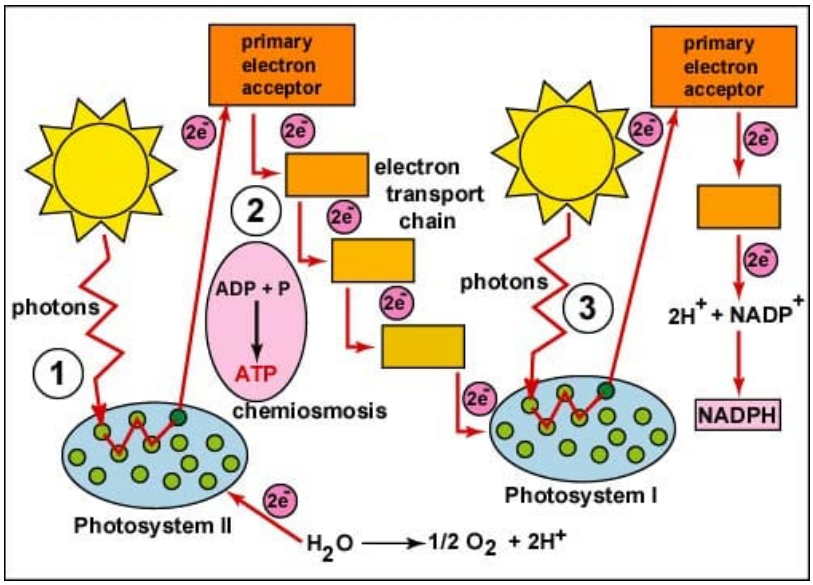


Figure $18.7B.3$: Electron Transport and Chemiosmosis during Photosynthesis 1. As photons are absorbed by pigment molecules in the antenna complexes of Photosystem II, excited electrons from the reaction center are picked up by the primary electron acceptor of the Photosystem II electron transport chain. During this process, Photosystem II splits molecules of H_2O into 1/2 O_2, $2H^+$, and 2 electrons. These electrons continuously replace the electrons being lost by the P680 chlorophyll a molecules in the reaction centers of the Photosystem II antenna complexes. 2. During this process, ATP is generated by the Photosystem II electron transport chain and chemiosmosis. According to the chemiosmosis theory, as the electrons are transported down the electron transport chain, some of the energy released is used to pump protons across the thylakoid membrane from the stroma of the chloroplast to the thylakoid interior space producing a proton gradient or proton motive force. As the accumulating protons in the thylakoid interior space pass back across the thylakoid membrane to the stroma through ATP synthetase complexes, this proton motive force is used to generate ATP from ADP and Pi. 3. Meanwhile, photons are also being absorbed by pigment molecules in the antenna complex of Photosystem I and excited electrons from the reaction center are picked up by the primary electron acceptor of the Photosystem I electron transport chain. The electrons being lost by the P700 chlorophyll a molecules in the reaction centers of Photosystem I are replaced by the electrons traveling down the Photosystem II electron transport chain. The electrons transported down the Photosystem I electron transport chain combine with $2H^+$ from the surrounding medium and $NADP^+$ to produce NADPH + H^+.

Flash animation illustrating the development of proton motive force as a result of chemiosmosis and ATP production by ATP synthase.

html5 version of animation for iPad illustrating the development of proton motive force as a result of chemiosmosis and ATP production by ATP synthase.

2. Meanwhile, photons are also being absorbed by pigment molecules in the antenna complex of Photosystem I and excited electrons from the reaction center are picked up by the primary electron acceptor of the Photosystem I electron transport chain. The electrons being lost by the P700 chlorophyll *a* molecules in the reaction centers of Photosystem I are replaced by the electrons traveling down the Photosystem II electron transport chain. The electrons transported down the Photosystem I electron transport chain combine with $2H^+$ from the surrounding medium and $NADP^+$ to produce NADPH + H^+ (Figure $18.7B.2$).

McGraw-Hill Flash animation illustrating photosynthetic electron transport and ATP production by ATP synthase.

Cyclic photophosphorylation occurs less commonly in plants than noncyclic photophosphorylation, most likely occurring when there is too little $NADP^+$ available. It is also seen in certain photosynthetic bacteria. Cyclic photophosphorylation involves only Photosystem I and generates ATP but not NADPH. As the electrons from the reaction center of Photosystem I are picked up by the electron transport chain, they are transported back to the reaction center chlorophyll. As the electrons are transported down the electron transport chain, some of the energy released is used to pump protons across the thylakoid membrane from the stroma of the chloroplast to the thylakoid interior space producing a proton gradient or proton motive force. As the accumulating protons in the thylakoid interior space pass back across the thylakoid membrane to the stroma through ATP synthetase complexes, this energy is used to generate ATP from ADP and P*i* (Figure $18.7B.4$).

McGraw-Hill Flash animation illustrating cyclic and non-cyclic photophosphorylation.

Summary

1. Plants, algae, and cyanobacteria are known as oxygenic photoautotrophs because they synthesize organic molecules from inorganic materials, convert light energy into chemical energy, use water as an electron source, and generate oxygen as an end product of photosynthesis.
2. The overall reaction for photosynthesis is as follows: 6 CO_2 + 12 H_2O in the presence of light and chlorophyll yields $C_6H_{12}O_6$ + 6 O_2 + 6 H_2O.
3. Oxygenic photosynthesis is composed of two stages: the light-dependent reactions and the light-independent reactions.
4. The light-dependent reactions convert light energy into chemical energy, producing ATP and NADPH.
5. The light-dependent reactions can be summarized as follows: 12 H_2O + 12 $NADP^+$ + 18 ADP + 18 P_i + light and chlorophyll yields 6 O_2 + 12 NADPH + 18 ATP.
6. The most common light-dependent reaction in photosynthesis is called noncyclic photophosphorylation.
7. During noncyclic photophosphorylation light-dependent reactions, photons are absorbed by pigment molecules in the antenna complexes of Photosystem II, and excited electrons from the reaction center are picked up by the primary electron acceptor of the Photosystem II electron transport chain. During this process, Photosystem II splits molecules of H_2O into 1/2 O_2, $2H^+$, and 2 electrons.
8. According to the chemiosmosis theory, as the electrons are transported down the electron transport chain, some of the energy released is used to pump protons across the thylakoid membrane from the stroma of the chloroplast to the thylakoid interior space producing a proton gradient or proton motive force. As the accumulating protons in the thylakoid interior space pass back across the thylakoid membrane to the stroma through ATP synthetase complexes, this proton motive force is used to generate ATP from ADP and Pi.
9. Meanwhile, photons are also being absorbed by pigment molecules in the antenna complex of Photosystem I and excited electrons from the reaction center are picked up by the primary electron acceptor of the Photosystem I electron transport chain. The electrons being lost by chlorophyll molecules in the reaction centers of Photosystem I are replaced by the electrons traveling down the Photosystem II electron transport chain. The electrons transported down the Photosystem I electron transport chain combine with $2H^+$ from the surrounding medium and $NADP^+$ to produce NADPH + H^+.

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18.7C: Oxygenic Photosynthesis: Light-Independent Reactions

Briefly describe the overall function of the light-independent reactions in photosynthesis and state where in the chloroplast they occur.

- State how the light-dependent and light-independent reactions are linked during photosynthesis.
- State the reactants and the products for the light-independent reactions.
- Briefly describe the following stages of the Calvin cycle:

  a. CO_2 fixation
  b. production of G3P
  c. regeneration of RuBP

- State the significance of glyceraldehyde-3-phosphate (G3P) in the Calvin cycle.

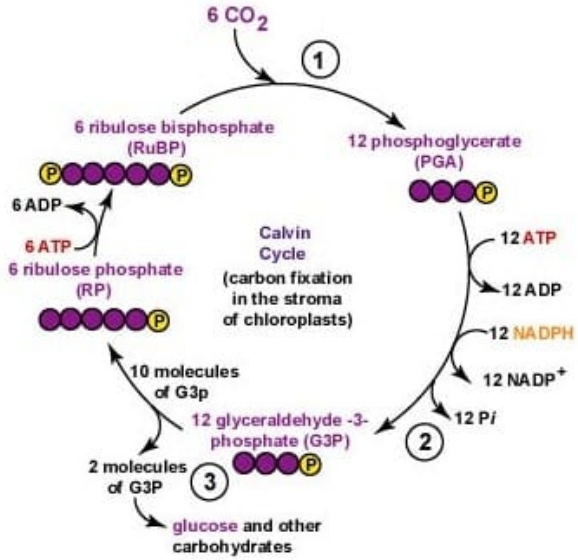


Figure 18.7C.18.7C.1). Ten molecules of the three-carbon compound G3P eventually form six molecules of the four-carbon compound ribulose phosphate (RP). Each molecule of RP then becomes phosphorylated by the hydrolysis of ATP to produce ribulose bisphosphate (RuBP), the starting compound for the Calvin cycle.

Summary

1. Photoautotrophs absorb and convert light energy into the stored energy of chemical bonds in organic molecules through a process called photosynthesis.
2. Plants, algae, and cyanobacteria are known as oxygenic photoautotrophs because they synthesize organic molecules from inorganic materials, convert light energy into chemical energy, use water as an electron source, and generate oxygen as an end product of photosynthesis.
3. Oxygenic photosynthesis is composed of two stages: the light-dependent reactions and the light-independent reactions.
4. The light-independent reactions use the ATP and NADPH from the light-dependent reactions to reduce carbon dioxide and convert the energy to the chemical bond energy in carbohydrates such as glucose.
5. The light-independent reactions can be summarized as follows: 12 NADPH + 18 ATP + 6 CO_2 yields $C_6H_{12}O_6$ (glucose) + 12 $NADP^+$ + 18 ADP + 18 P_i + 6 H_2O.
6. Most plants use the Calvin cycle to fix CO_2. To begin the Calvin cycle, a molecule of CO_2 reacts with a five-carbon compound called ribulose bisphosphate (RuBP) producing an unstable six-carbon intermediate which immediately breaks down into two molecules of the three-carbon compound phosphoglycerate (PGA).

7. The energy from ATP and the reducing power of NADPH (both produced during the light-dependent reactions) is now used to convert the molecules of PGA to glyceraldehyde-3-phosphate (G3P), another three-carbon compound.
8. Most of the G3P produced during the Calvin cycle are used to regenerate the RuBP so that the cycle may continue, however, some of the molecules of G3P, however, are used to synthesize glucose and other organic molecules.

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18.7D: C4 and CAM Pathways in Plants

Learning Objectives

1. Briefly describe the C_4 pathway and how it differs from the C_3 pathway.
2. Briefly describe the CAM pathway and how it differs from the C_4 pathway.

The entry and exit of gasses in plants is through small pores called stomata located on the underside of leaves. Carbon dioxide, the gas required for the Calvin cycle, is not a very abundant gas in nature. Under hot and dry environmental conditions the stomata close to reduce the loss of water vapor, but this also results in a greatly diminished supply of CO_2 for the plant. Plants that normally live in dry, hot climates have adapted different ways of initially fixing CO_2 prior to its entering the Calvin cycle. These pathways of carbon fixation, know as the C_4 and the CAM pathways, take place in the cytoplasm of the cell.

The C_4 pathway

The C_4 pathway is designed to efficiently fix CO_2 at low concentrations and plants that use this pathway are known as C_4 plants. These plants first fix CO_2 into a four carbon compound (C_4) called oxaloacetate (Figure $18.7D.1$). This occurs in cells called mesophyll cells. First, CO_2 is fixed to a three-carbon compound called phosphoenolpyruvate to produce the four-carbon compound oxaloacetate. The enzyme catalyzing this reaction, PEP carboxylase, fixes CO_2 very efficiently so the C_4 plants don't need to to have their stomata open as much.

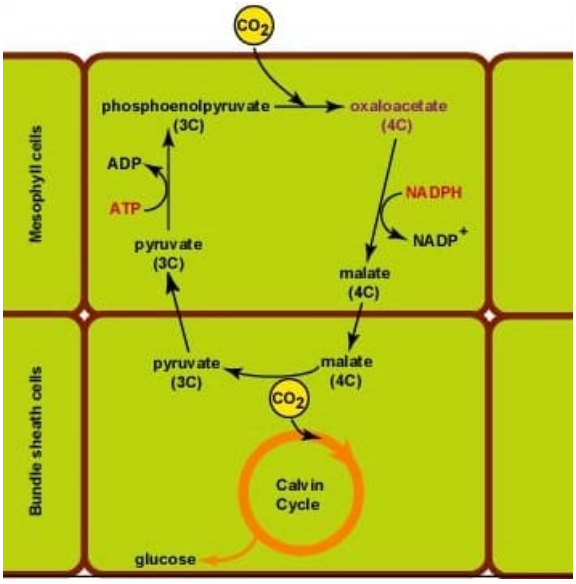


Figure $18.7D.1$: The C4 Pathway The C4 pathway is designed to efficiently fix CO2 at low concentrations and plants that use this pathway are known as C4 plants. These plants fix CO2 into a four carbon compound (C4) called oxaloacetate. This occurs in cells called mesophyll cells. (1) CO2 is fixed to a three-carbon compound called phosphoenolpyruvate to produce the four-carbon compound oxaloacetate. The enzyme catalyzing this reaction, PEP carboxylase, fixes CO_2 very efficiently so the C4 plants don't need to to have their stomata open as much. The oxaloacetate is then converted to another four-carbon compound called malate in a step requiring the reducing power of NADPH. (3). The malate then exits the mesophyll cells and enters the chloroplasts of specialized cells called bundle sheath cells. Here the four-carbon malate is decarboxylated to produce CO2, a three-carbon compound called pyruvate, and NADPH. The CO2 combines with ribulose bisphosphate and goes through the Calvin cycle. (4) The pyruvate re-enters the mesophyll cells, reacts with ATP, and is converted back to phosphoenolpyruvate, the starting compound of the C4 cycle.

The oxaloacetate is then converted to another four-carbon compound called malate in a step requiring the reducing power of NADPH. The malate then exits the mesophyll cells and enters the chloroplasts of specialized cells called bundle sheath cells. Here the four-carbon malate is decarboxylated to produce CO_2, a three-carbon compound called pyruvate, and NADPH. The CO_2

combines with ribulose bisphosphate and goes through the Calvin cycle while the pyruvate re-enters the mesophyll cells, reacts with ATP, and is converted back to phosphoenolpyruvate, the starting compound of the C_4 cycle. The C_4 cycle is summarized in Figure $18.7D.1$.

The CAM pathway

CAM plants live in very dry condition and, unlike other plants, open their stomata to fix CO_2 only at night. Like C_4 plants, the use PEP carboxylase to fix CO_2, forming oxaloacetate. The oxaloacetate is converted to malate which is stored in cell vacuoles. During the day when the stomata are closed, CO_2 is removed from the stored malate and enters the Calvin cycle.

Summary

1. Carbon dioxide, the gas required for the Calvin cycle, is not a very abundant gas in nature. Under hot and dry environmental conditions the stomata close to reduce the loss of water vapor, but this also results in a greatly diminished supply of CO_2 for the plant.
2. Plants that normally live in dry, hot climates have adapted different ways of initially fixing CO_2 prior to its entering the Calvin cycle. These pathways of carbon fixation, know as the C_4 and the CAM pathways, take place in the cytoplasm of the cell.
3. The C_4 pathway is designed to efficiently fix CO_2 at low concentrations and plants that use this pathway are known as C_4 plants.
4. CAM plants live in very dry condition and, unlike other plants, open their stomata to fix CO_2 only at night.

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18.E: Microbial Metabolism (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

18.2: Overview of Cellular Respiration

18.3: Aerobic Respiration

Study the material in this section and then **write out the answers** to these question. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe aerobic respiration.
2. Give the overall chemical reaction for aerobic respiration.
3. During aerobic respiration, glucose is _____ to carbon dioxide.
    a. oxidized
    b. reduced
4. During aerobic respiration, oxygen is _____ to water.
    a. oxidized
    b. reduced
5. Name the four stages of aerobic respiration.

18.3A: Glycolysis

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the function of glycolysis during aerobic respiration and indicate the reactants and products.
2. State the reactants in glycolysis.
3. State the products in glycolysis.
4. Does glycolysis require oxygen?
5. Is the following statement true or false?

    In eukaryotic cells, glycolysis takes place in the mitochondria.

6. Steps 1 and 3 of glycolysis are:
    a. exergonic
    b. endergonic
7. State why one molecule of glucose is able to produce two molecules of pyruvate during glycolysis.
8. The two net ATP produced in glycolysis are generated by:
    a. oxidative phosphorylation
    b. substrate-level phosphorylation
9. State the total number and the net number of ATP produced by substrate-level phosphorylation during glycolysis.
10. During aerobic respiration, state what happens to the 2 NADH produced during glycolysis.
11. During aerobic respiration, state what happens to the two molecules of pyruvate produced during glycolysis.

18.3B: Transition Reaction

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the function of transition reaction during aerobic respiration.
2. State the reactants in the transition reaction.
3. State the products in the transition reaction.
4. Is the following statement true or false?

    In eukaryotic cells, the transition reaction occurs inside the mitochondria.

5. During aerobic respiration, state what happens to the two molecules of Acetyl-CoA produced during the transition reaction.

18.3C: Citric Acid (Krebs) Cycle

Study the material in this section and then **write out the answers** to these question. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the function of the citric acid cycle during aerobic respiration.
2. State the reactants for the citric acid cycle.
3. State the products for the citric acid cycle.
4. Is the following statement true or false?

    In eukaryotic cells, the citric acid cycle occurs in the cytoplasm.

5. State the total number of ATP produced by substrate-level phosphorylation for each acetyl-CoA that enters the citric acid cycle.
6. State the total number of NADH and $FADH_2$ produced for each acetyl-CoA that enters the citric acid cycle.
7. During aerobic respiration, state what happens to the NADH and the $FADH_2$ produced during the citric acid cycle.

18.3D: Electron Transport Chain and Chemisomosis

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the function of the electron transport chain during aerobic respiration.
2. Describethe chemiosmotic theory of generation of ATP as a result of an electron transport chain. In the process, describe proton motive force and indicate the function of ATP synthase.
3. State whether the following statement is true or false.

    In eukaryotic cells, the electron transport chain is located in the inner membrane of the mitochondria.

4. State the final electron acceptor and the end product formed at the end of aerobic respiration.

18.3E: Theoretical ATP Yield

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Fill in the blanks.

    One molecule of glucose oxidized by aerobic respiration in prokaryotes yields the following:

    Glycolysis:

    _____ net ATP from substrate-level phosphorylation

    _____ NADH yields _____ ATP (assuming 3 ATP per NADH) by oxidative phosphorylation

    Transition Reaction:

_____ NADH yields _____ ATP (assuming 3 ATP per NADH) by oxidative phosphorylation

Citric Acid Cycle:

_____ ATP from substrate-level phosphorylation

____ NADH yields _____ ATP (assuming 3 ATP per NADH) by oxidative phosphorylation

_____ $FADH_2$ yields _____ ATP (assuming 2 ATP per $FADH_2$) by oxidative phosphorylation

Total Theoretical Maximum Number of ATP Generated per Glucose in Prokaryotes

_____ ATP : _____ from substrate-level phosphorylation ; _____ from oxidative phosphorylation .

In eukaryotic cells, the theoretical maximum yield of ATP generated per glucose is _____ to _____.

18.4: Anaerobic Respiration

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define anaerobic respiration.
2. State the pathways involved in anaerobic respiration.
3. State whether the following statement is true or false.

    All organisms are capable of anaerobic respiration.

18.5: Fermentation

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define fermentation.
2. All the ATP generated by fermentation are produced by:
    a. substrate-level phosphorylation
    b. oxidative phosphorylation
3. State the reactants for fermentation.
4. State the products for fermentation.
5. Compare the maximum yield of ATP from one molecule of glucose for aerobic respiration and for fermentation.

18.6: Precursor Metabolites: Linking Catabolic and Anabolic Pathways

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define precursor metabolites and indicate their importance in metabolism.

18.7: Photosynthesis

18.7A: Introduction to Photosynthesis

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Organisms that absorb and convert light energy into the stored energy of chemical bonds in organic molecules through a

process called photosynthesis best describes:
   a. anoxygenic photoautotrophs
   b. oxygenic photoautotrophs
2. Name the two stages of photosynthesis.
3. Define photon.
4. Describe what happens when photons of visible light energy strike certain atoms of pigments during photosynthesis and how this can lead to the generation of ATP.
5. Fill in the blank.

   The inner membrane of a chloroplast encloses a fluid-filled region called the _____ that contains enzymes for the light-independent reactions of photosynthesis. Infolding of this inner membrane forms interconnected stacks of disk-like sacs called _____ , often arranged in stacks called _____ .

6. Name three different types of pigments that play a role in photosynthesis by absorbing light energy.
7. State the reactants and the products for photosynthesis and indicate which are oxidized and which are reduced.

18.7B: Oxygenic Photosynthesis: Light-Dependent Reactions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the overall function of the light-dependent reactions in photosynthesis.
2. Where in the chloroplasts do the light-dependent reactions occur?
   a. In the thylakoids.
   b. In the stroma.
3. The parts of a photosystem that are able to trap light and transfer energy to a complex of chlorophyll molecules and proteins called the reaction center are called _____.
4. In Photosystem II, the electrons lost by chlorophyll P680 molecules are replaced by:
   a. the electrons traveling down the electron transport system of Photosystem I
   b. the electrons released by the splitting of water
5. The primary function of Photosystem II is to produce:
   a. ATP
   b. NADPH
6. Briefly describe how ATP is generated by chemiosmosis during the light-dependent reactions of photosynthesis.
7. In Photosystem I, the electrons lost by chlorophyll P700 molecules are replaced by:
   a. the electrons traveling down the electron transport system of Photosystem II
   b. the electrons released by the splitting of water
8. The primary function of Photosystem I is to produce:
   a. ATP
   b. NADPH
9. Involves only Photosystem I and generates ATP but not NADPH. This best describes:
   a. cyclic photophosphorylation
   b. noncyclic photophosphorylation

18.7C: Oxygenic Photosynthesis: Light-Independent Reactions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the overall function of the light-independent reactions in photosynthesis.
2. Where in the chloroplasts do the light-independent reactions occur?
   a. In the thylakoids.
   b. In the stroma.
3. State how the light-dependent and light-independent reactions are linked during photosynthesis.
4. Briefly describe the following stages of the Calvin cycle:
   a. CO_2 fixation
   b. production of G3P

c. regeneration of RuBP
5. State the significance of glyceraldehyde-3-phosphate (G3P) in the Calvin cycle.

18.7D: C4 and CAM Pathways in Plants

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Is the following statement true or false?

   During the C_4 pathway for fixing CO_2, CO_2 from the air combines with ribulose bisphosphate to begin the Calvin cycle.

2. Plants that live in very dry condition and, unlike other plants, open their stomata to fix CO_2 only at night best describes:
   a. C_4 plants
   b. C_3 plants
   c. CAM plants
3. C_4 and CAM pathways evolved for plants that live in _____ climates.
   a. hot, humid
   b. cold, dry
   c. hot, dry

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19.1: Polypeptides and Proteins

Learning Objectives

1. Define or describe the following:
   a. amino acid
   b. "R" group
   c. peptide bond
   d. peptide
   e. polypeptide
   f. primary protein structure
   g. secondary protein structure
   h. tertiary protein structure
   i. quaternary protein structure
   j. gene
2. Describe how the primary structure of a protein or polypeptide ultimately detemines its final three-dimensional shape.
3. Describe how the order of nucleotide bases in DNA ultimately determines the final three-dimensional shape of a protein or polypeptide.

Amino acids are the building blocks for proteins. All amino acids contain an amino or NH_2 group and a carboxyl (acid) or COOH group. There are 20 different amino acids commonly found in proteins and often 300 or more amino acids per protein molecule. Each amino acid differs in terms of its "R" group. The "R" group of an amino acid is the *r*emainder of the molecule, that is, the portion other than the amino group, the acid group, and the central carbon. Each different amino acid has a unique "R" group and the unique chemical properties of an amino acid depend on that of its "R" group (Figure 19.1.1).

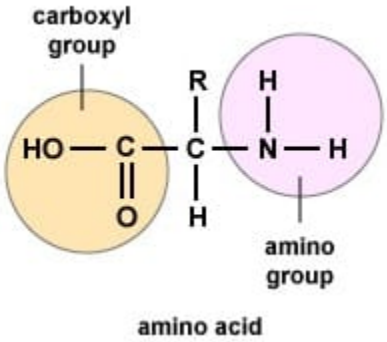


Figure 19.1.1: Amino Acids. Structure of an amino acid.

To form polypeptides and proteins, amino acids are joined together by peptide bonds, in which the amino or NH_2 of one amino acid bonds to the carboxyl (acid) or COOH group of another amino acid as shown in (Figure 19.1.2 and Figure 19.1.3).

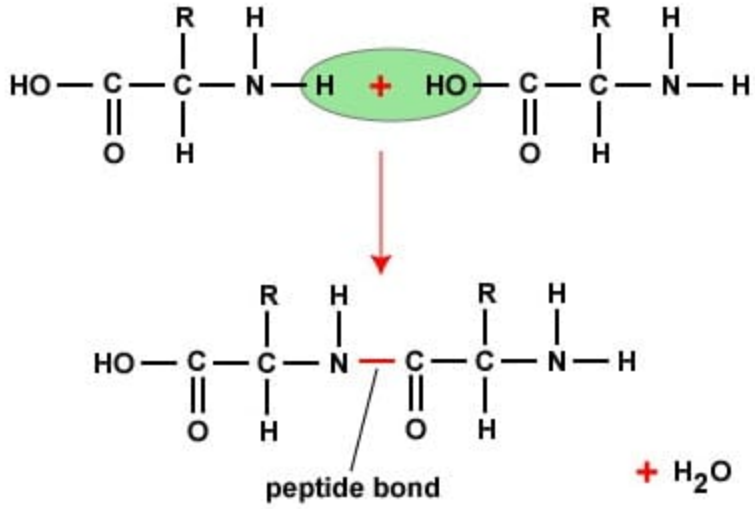


Figure 19.1.2: Peptide Bonds. A peptide bond forms when the amino group of one amino acid bonds to the carboxyl group of another amino acid.

A peptide is two or more amino acids joined together by peptide bonds, and a polypeptide is a chain of many amino acids. A protein contains one or more polypeptides. Therefore, proteins are long chains of amino acids held together by peptide bonds.

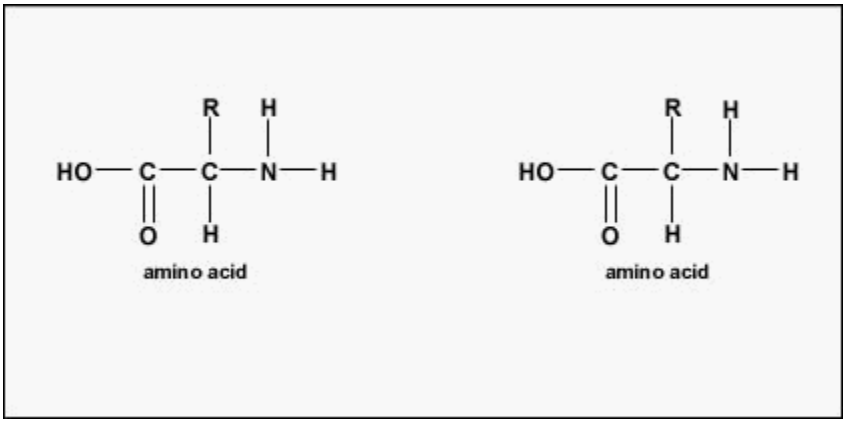


Figure 19.1.3: Formation of a Peptide Bond. A peptide bond forms when the amino group of one amino acid bonds to the carboxyl group of another amino acid.

The actual order of the amino acids in the protein is called its primary structure (Figure 19.1.4) and is determined by DNA. As will be seen later in this unit, DNA is divided into functional units called genes. A gene is a sequence of deoxyribonucleotide bases along one strand of DNA that codes for a functional product - a specific molecule of messenger RNA, transfer RNA, or ribosomal RNA. The product is usually messenger RNA (mRNA) and mRNA ultimately results in the synthesis of a polypeptide or a protein. Therefore, it is commonly said that the order of deoxyribonucleotide bases in a gene determines the amino acid sequence of a particular protein. Since certain amino acids can interact with other amino acids in the same protein, this primary structure ultimately determines the final shape and therefore the chemical and physical properties of the protein.



Figure 19.1.4: Primary Structure of a Protein or Polypeptide. The primary structure of a protein or polypeptide is the actual sequence of its amino acids. Primary structure is determined by the order of the deoxyribonucleotide bases in genes.

The secondary structure of the protein is due to hydrogen bonds that form between the oxygen atom of one amino acid and the nitrogen atom of another. This gives the protein or polypeptide the two-dimensional form of an alpha-helix or a beta-pleated

sheet (Figure 19.1.5).

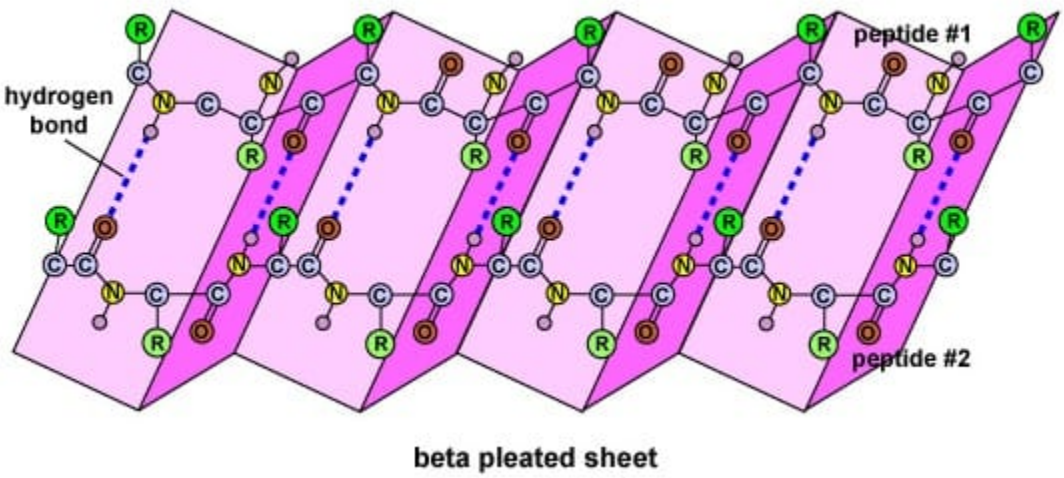


Figure 19.1.5: Secondary Structure of a Protein or Polypeptide. (left) The secondary structure of a protein or polypeptide is due to hydrogen bonds forming between an oxygen atom of one amino acid and a nitrogen atom of another. There are two possible types of secondary structure: an alpha helix and a beta sheet. In the case of an alpha helix, the hydrogen bonding causes the polypeptide to twist into a helix. With a beta sheet the hydrogen bonding enables the polypeptide to fold back and forth upon itself like a pleated sheet. (right) The secondary structure of a protein or polypeptide is due to hydrogen bonds forming between an oxygen atom of one amino acid and a nitrogen atom of another. There are two possible types of secondary structure: an alpha helix and a beta sheet. In the case of an alpha helix, the hydrogen bonding causes the polypeptide to twist into a helix. With a beta sheet the hydrogen bonding enables the polypeptide to fold back and forth upon itself like a pleated sheet.

In globular proteins such as enzymes, the long chain of amino acids becomes folded into a three-dimensional functional shape or tertiary structure. This is because certain amino acids with sulfhydryl or SH groups form disulfide (S-S) bonds with other amino acids in the same chain. Other interactions between R groups of amino acids such as hydrogen bonds, ionic bonds, covalent bonds, and hydrophobic interactions also contribute to the tertiary structure (Figure 19.1.6). In some proteins, such as antibody molecules and hemoglobin, several polypeptides may bond together to form a quaternary structure (Figure 19.1.7).

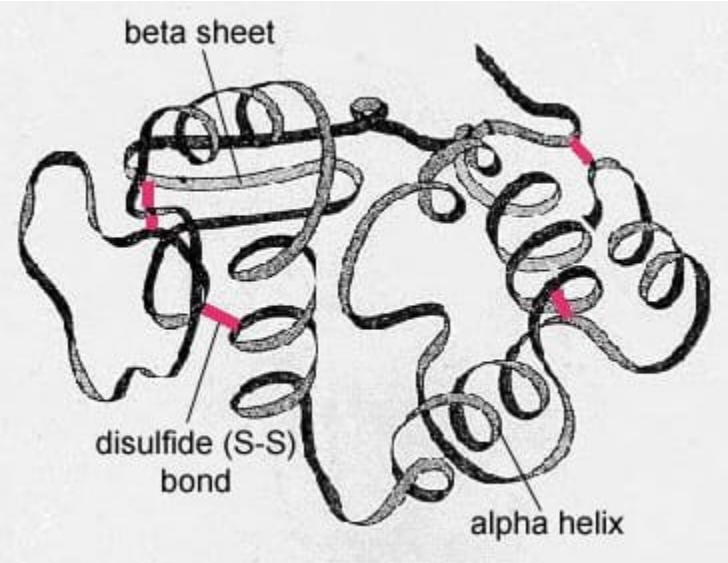


Figure 19.1.6: Tertiary Structure of a Protein or Polypeptide. In globular proteins such as enzymes, the long chain of amino acids becomes folded into a three-dimensional functional shape or tertiary structure. This is because certain amino acids with sulfhydryl or SH groups form disulfide (S-S) bonds with other amino acids in the same chain. Other interactions between R groups of amino acids such as hydrogen bonds, ionic bonds, covalent bonds, and hydrophobic interactions also contribute to the tertiary structure.

As will be seen later in this unit, during protein synthesis, the order of nucleotide bases along a gene gets transcribed into a complementary strand of mRNA which is then translated by tRNA into the correct order of amino acids for that polypeptide or

protein. Therefore, the order of deoxyribonucleotide bases along the DNA determines the order of amino acids in the proteins. Because certain amino acids can interact with other amino acids, the order of amino acids for each protein determines its final three-dimensional shape, which in turn determines the function of that protein (e.g., what substrate an enzyme will react with, what epitopes the Fab of an antibody will combine with, what receptors a cytokine will bind to).

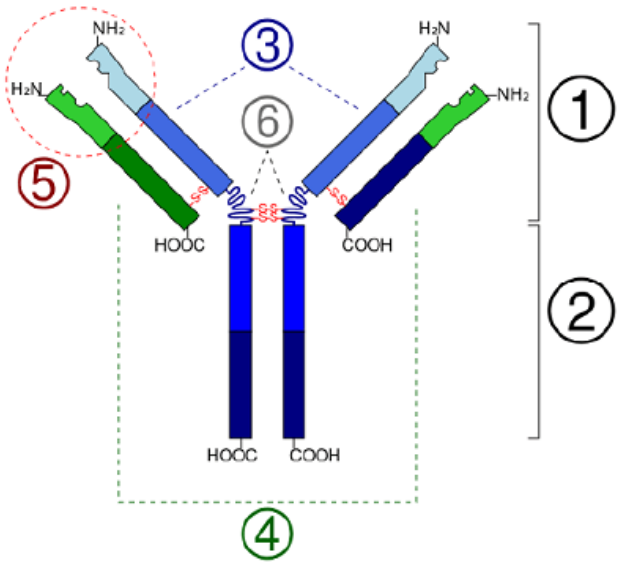


Figure 19.1.7: Quaternary Structure of a Protein. The quaternary structure of a protein is due to several polypeptides joining together, as in the case of antibody molecules. Schematic diagram of the basic unit of immunoglobulin (antibody) Fab Fc heavy chain (consist of VH, CH1, hinge, CH2 and CH3 regions: from N-term) light chain (consist of VL and CL regions: from N-term) antigen binding site hinge regions (*) -S-S- mean disulfide bonds. (CC-SA-BY 3.0; Y_tambe).

Summary

1. Amino acids are the building blocks for proteins. There are 20 different amino acids commonly found in proteins and often 300 or more amino acids per protein molecule.
2. All amino acids contain an amino or NH_2 group and a carboxyl (acid) or COOH group.
3. To form polypeptides and proteins, amino acids are joined together by peptide bonds, in which the amino or NH_2 of one amino acid bonds to the carboxyl (acid) or COOH group of another amino acid.
4. A peptide is two or more amino acids joined together by peptide bonds; a polypeptide is a chain of many amino acids; and a protein contains one or more polypeptides. Therefore, proteins are long chains of amino acids held together by peptide bonds.
5. The actual order of the amino acids in the protein is called its primary structure and is determined by DNA.
6. The order of deoxyribonucleotide bases in a gene determines the amino acid sequence of a particular protein. Since certain amino acids can interact with other amino acids in the same protein, this primary structure ultimately determines the final shape and therefore the chemical and physical properties of the protein.
7. The secondary structure of the protein is due to hydrogen bonds that form between the oxygen atom of one amino acid and the nitrogen atom of another and gives the protein or polypeptide the two-dimensional form of an alpha-helix or a beta-pleated sheet.
8. In globular proteins such as enzymes, the long chain of amino acids becomes folded into a three-dimensional functional shape or tertiary structure. This is because certain amino acids with sulfhydryl or SH groups form disulfide (S-S) bonds with other amino acids in the same chain. Other interactions between R groups of amino acids such as hydrogen bonds, ionic bonds, covalent bonds, and hydrophobic interactions also contribute to the tertiary structure.
9. In some proteins, such as antibody molecules, several polypeptides may bond together to form a quaternary structure.

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19: REVIEW OF MOLECULAR GENETICS

19.1: Polypeptides and Proteins

19.2: Enzymes

19.3: Deoxyribonucleic Acid (DNA)

19.4: DNA Replication in Prokaryotic Cells

19.5: DNA Replication in Eukaryotic Cells and the Eukaryotic Cell Cycle

19.6: Ribonucleic Acid (RNA)

19.7: Polypeptide and Protein Synthesis

19.7A: Transcription

19.7B: Translation

19.8: Enzyme Regulation

19.9: Mutation

19.E: Review of Molecular Genetics (Exercises)

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19.2: Enzymes

Learning Objectives

1. Define or describe the following:
   a. metabolism
   b. catabolic reaction
   c. anabolic reaction
   d. enzyme
   e. substrate
   f. apoenzyme
   g. haloenzyme
   h. cofactor (coenzyme)
2. State how enzymes are able to speed up the rate of chemical reactions.
3. Briefly describe a generalized enzyme-substrate reaction, state the function of an enzyme's active site, and describe how an enzyme is able to speed up chemical reactions.
4. State four characteristics of enzymes.
5. State how the following affect the rate of an enzyme reaction.
   a. enzyme concentration
   b. substrate concentration
   c. temperature
   d. pH
   e. salt concentration
6. State how chemicals such as chlorine, iodine, iodophores, mercurials, and ethylene oxide inhibit or kill bacteria.
7. State how high temperature and low temperature exert their effect on bacteria.

To live, grow, and reproduce, microorganisms undergo a variety of chemical changes. They alter nutrients so they can enter the cell and they change them once they enter in order to synthesize cell parts and obtain energy. Metabolism refers to all of the organized chemical reactions in a cell. Reactions in which chemical compounds are broken down are called catabolic reactions while reactions in which chemical compounds are synthesized are termed anabolic reactions. All of these reactions are under the control of enzymes.

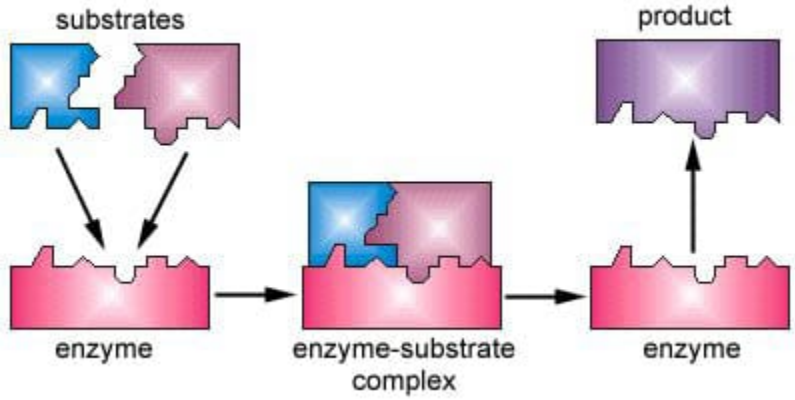


Figure 19.2.1: Enzymesare substances present in the cell in small amounts which speed up or catalyze chemical reactions. Enzymes speed up the rate of chemical reactions because they lower the energy of activation, the energy that must be supplied in order for molecules to react with one another. Enzymes lower the energy of activation by forming an enzyme-substrate complex.

Enzymes are substances present in the cell in small amounts that function to speed up or catalyze chemical reactions. On the surface of the enzyme is usually a small crevice that functions as an active site or catalytic site to which one or two specific substrates are able to bind. (Anything that an enzyme normally combines with is called a substrate.) The binding of the substrate to the enzyme causes the flexible enzyme to change its shape slightly through a process called induced fit to form a tempore

intermediate called an enzyme-substrate complex (Figure 19.2.1).

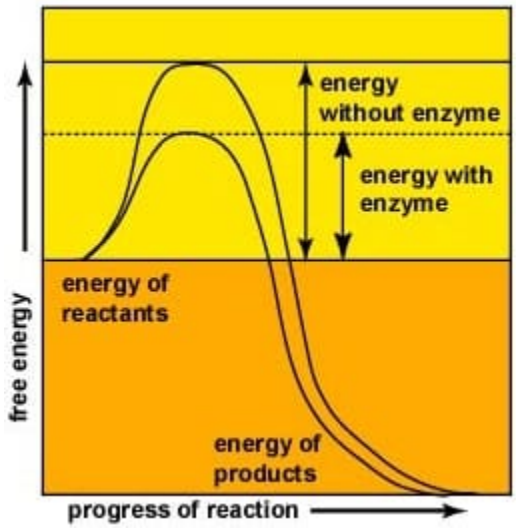


Figure 19.2.2: An enzyme speeds up a chemical reaction by lowering its energy of activation, the energy that must be supplied in order for molecules to react with one another.

Enzymes speed up the rate of chemical reactions because they lower the energy of activation, the energy that must be supplied in order for molecules to react with one another (Figure 19.2.2). Enzymes lower the energy of activation by forming an enzyme-substrate complex allowing products of the enzyme reaction to be formed and released (Figure 19.2.3).

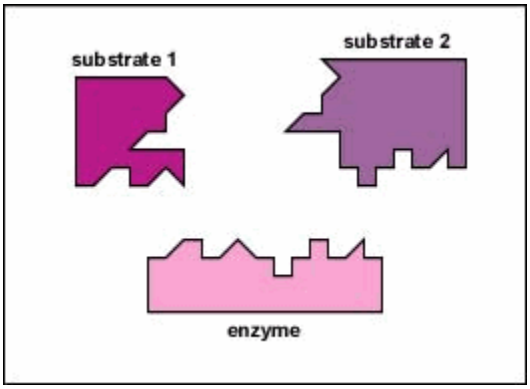


Figure 19.2.3: Enzyme-Substrate Reaction. Enzymesare substances present in the cell in small amounts which speed up or catalyze chemical reactions. Enzymes speed up the rate of chemical reactions because they lower the energy of activation, the energy that must be supplied in order for molecules to react with one another. Enzymes lower the energy of activation by forming an enzyme-substrate complex.

Many enzymes require a nonprotein cofactor to assist them in their reaction. In this case, the protein portion of the enzyme, called an apoenzyme, combines with the cofactor to form the whole enzyme or haloenzyme (Figure 19.2.3). Some cofactors are ions such as Ca^{++}, Mg^{++}, and K^{+}; other cofactors are organic molecules called coenzymes which serve as carriers for chemical groups or electrons. NAD^{+}, $NADP^{+}$, FAD, and coenzyme A (CoA) are examples of coenzymes.

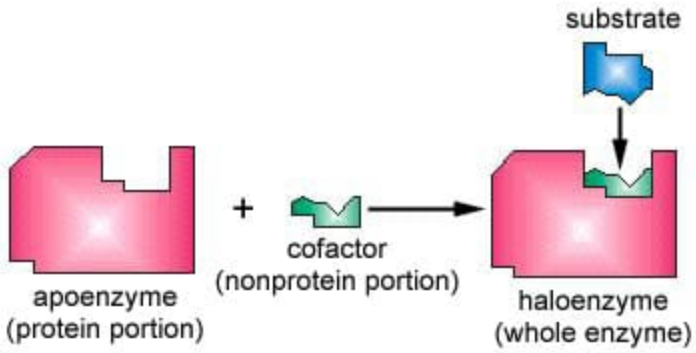


Figure 19.2.4: An apoenzyme and cofactor combine to form a haloenzyme. If the cofactor is an organic molecule, it is called a coenzyme.

Characteristics of Enzymes

Chemically, enzymes are generally globular proteins. (Some RNA molecules called ribozymes can also be enzymes. These are usually found in the nuclear region of cells and catalyze the splitting of RNA molecules). Enzymes are catalysts that breakdown or synthesize more complex chemical compounds. They allow chemical reactions to occur fast enough to support life. Enzymes speed up the rate of chemical reactions because they lower the energy of activation, the energy that must be supplied in order for molecules to react with one another. Anything that an enzyme normally combines with is called a substrate. Enzymes are very efficient. An enzyme generally can typically catalyze between 1 and 10,000 molecules of substrate per second. Enzymes are only present in small amounts in the cell since they are not altered during their reactions. and they are highly specific for their substrate. Generally there is one specific enzyme for each specific chemical reaction.

Enzyme Activity

Enzyme activity is affected by a number of factors including:

- **The concentration of enzyme**: Assuming a sufficient concentration of substrate is available, increasing enzyme concentration will increase the enzyme reaction rate.
- **The concentration of substrate**: At a constant enzyme concentration and at lower concentrations of substrates, the substrate concentration is the limiting factor. As the substrate concentration increases, the enzyme reaction rate increases. However, at very high substrate concentrations, the enzymes become saturated with substrate and a higher concentration of substrate does not increase the reaction rate.
- **The temperature**: Each enzyme has an optimum temperature at which it works best. A higher temperature generally results in an increase in enzyme activity. As the temperature increases, molecular motion increases resulting in more molecular collisions. If, however, the temperature rises above a certain point, the heat will denature the enzyme, causing it to lose its three-dimensional functional shape by denaturing its hydrogen bonds. Cold temperature, on the other hand, slows down enzyme activity by decreasing molecular motion.
- **The pH**: Each enzyme has an optimal pH that helps maintain its three-dimensional shape. Changes in pH may denature enzymes by altering the enzyme's charge. This alters the ionic bonds of the enzyme that contribute to its functional shape.
- **The salt concentration**: Each enzyme has an optimal salt concentration. Changes in the salt concentration may also denature enzymes.

Some relationships between bacterial enzymes and the use of disinfectants and extremes of temperature to control bacteria.

1. Many disinfectants, such as chlorine, iodine, iodophores, mercurials, silver nitrate, formaldehyde, and ethylene oxide, inactivate bacterial enzymes and thus block metabolism.
2. High temperatures, such as autoclaving, boiling, and pasteurization, denature proteins and enzymes.
3. Cold temperatures, such as refrigeration and freezing, slow down or stop enzyme reactions.

Summary

1. Enzymes are substances present in the cell in small amounts that function to speed up or catalyze chemical reactions so they occur fast enough to support life.
2. On the surface of the enzyme is typically a small crevice that functions as an active site or catalytic site to which one or two specific substrates are able to bind.
3. Anything that an enzyme normally combines with is called a substrate.
4. The binding of the substrate to the enzyme causes the flexible enzyme to change its shape slightly through a process called induced fit to form a temporary intermediate called an enzyme-substrate complex.
5. Enzymes speed up the rate of chemical reactions because they lower the energy of activation, the energy that must be supplied in order for molecules to react with one another.
6. Many enzymes require a nonprotein cofactor to assist them in their reaction. In this case, the protein portion of the enzyme, called an apoenzyme, combines with the cofactor to form the whole enzyme or haloenzyme.
7. Some cofactors are ions such as Ca^{++}, Mg^{++}, and K^{+}; other cofactors are organic molecules called coenzymes which serve as carriers for chemical groups or electrons. NAD^{+}, $NADP^{+}$, FAD, and coenzyme A (CoA) are examples of coenzymes.
8. Chemically, enzymes are generally globular proteins. Some RNA molecules called ribozymes can also be enzymes, usually functioning to cleave RNA molecules.
9. Enzymes are only present in small amounts in the cell since they are not altered during their reactions and are highly specific for their substrate.
10. Enzyme activity is affected by a number of factors including the concentration of the enzyme, the concentration of the substrate, the temperature, the pH, and the salt concentration.

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19.3: Deoxyribonucleic Acid (DNA)

Learning Objectives

1. State the three basic parts of a deoxyribonucleotide.
2. State which nitrogenous bases are purines and which are pyrimidines.
3. Define complementary base pairing.
4. State why DNA can only be synthesized in a 5' to 3' direction.
5. Compare the prokaryotic nucleoid with the eukaryotic nucleus in terms of the following:
   a. number of chromosomes
   b. linear or circular chromosomes
   c. presence or absence of a nuclear membrane
   d. presence or absence of nucleosomes
   e. presence or absence of mitosis
   f. presence or absence of meiosis

DNA is a long, double-stranded, helical molecule composed of building blocks called deoxyribonucleotides. Each deoxyribonucleotide is composed of three parts: a molecule of the 5-carbon sugar deoxyribose, a nitrogenous base, and a phosphate group (Figure 19.3.1).

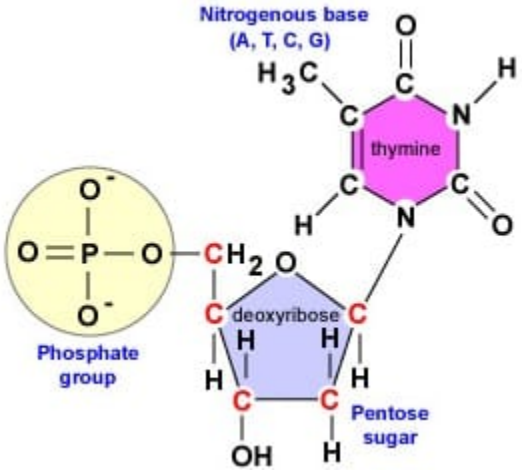


Figure 19.3.1: A Deoxyribonucleotide. Note the phosphate group attached to the 5' carbon of the deoxyribose and the nitrogenous base, in this case thymine, attached to the 1' carbon.

- **Deoxyribose**. Deoxyribose is a ringed 5-carbon sugar (Figure 19.3.2). The 5 carbons are numbered sequentially clockwise around the sugar. The first 4 carbons actually form the ring of the sugar with the 5' carbon coming off of the 4' carbon in the ring. The nitrogenous base of the nucleotide is attached to the 1' carbon of the sugar and the phosphate group is bound to the 5' carbon. During DNA synthesis, the phosphate group of a new deoxyribonucleotide is covalently attached by the enzyme DNA polymerase to the 3' carbon of a nucleotide already in the chain.

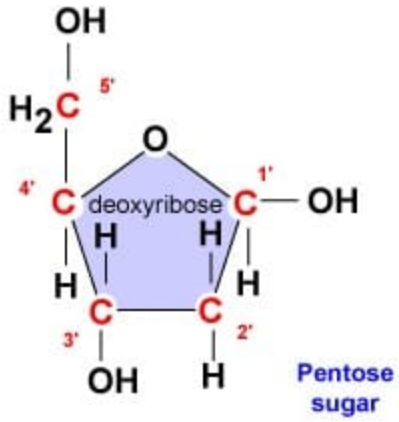


Figure 19.3.2: The 5-Carbon Sugar Deoxyribose. During nucleotide production, the nitrogenous base will attach to the 1' carbon and the phosphate group will attach to the 5' carbon. The first 4 carbons shown form the actual ring of the sugar. The 5' carbon comes off of the ring.

- **A nitrogenous base**. There are four nitrogenous bases found in DNA: adenine, guanine, cytosine, or thymine. Adenine and guanine are known as purine bases while cytosine and thymine are known as pyrimidine bases (Figure 19.3.3).

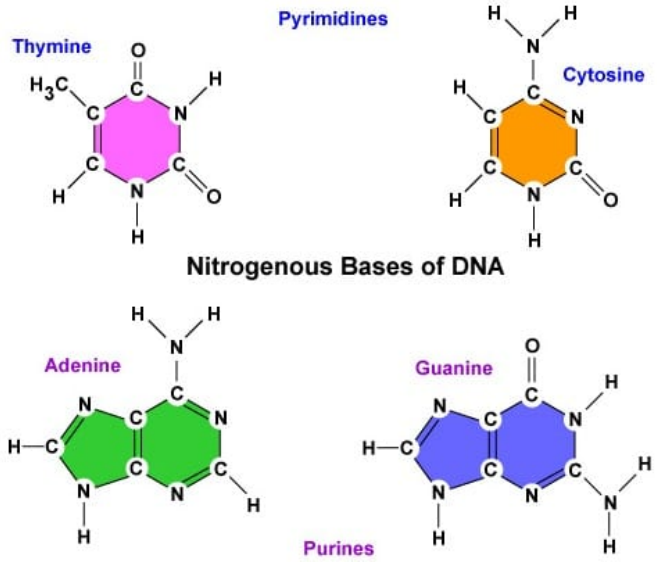


Figure 19.3.3: The Four Nitrogenous Bases in DNA: Adenine, Guanine, Cytosine, and Thymine. The phosphate of one deoxyribonucleotide binding to the 3' carbon of the deoxyribose of another forms the sugar-phosphate backbone of the DNA (the sides of the "ladder"). The hydrogen bonds between the complementary nucleotide bases (adenine-thymine; guanine-cytosine) form the rungs. Note the antiparallel nature of the DNA. One strand ends in a 5' phosphate and the other ends in a 3' hydroxyl.

- **A phosphate group** (Figure 19.3.4).

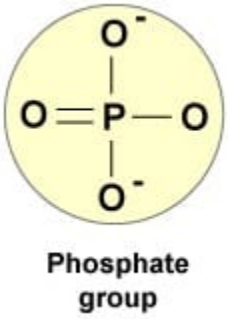


Figure 19.3.4: A Phosphate Group

To synthesize the two chains of deoxyribonucleotides during DNA replication, the DNA polymerase enzymes involved are only able to join the phosphate group at the 5' carbon of a new nucleotide to the hydroxyl (OH) group of the 3' carbon of a nucleotide (Figure 19.3.2) already in the chain. The covalent bond that joins the nucleotides is called a phosphodiester bond. Each DNA strand has what is called a 5' end and a 3' end. This means that one end of each DNA strand, called the 5' end , will always have a phosphate group attached to the 5' carbon of its terminal deoxyribonucleotide (Figure 19.3.5). The other end of that strand, called the 3' end, will always have a hydroxyl (OH) on the 3' carbon of its terminal deoxyribonulceotide.

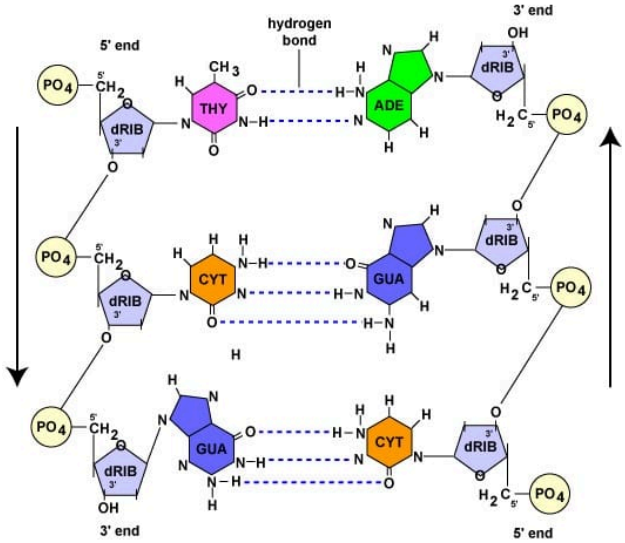


Figure 19.3.5: Chemical Structure of DNA. The phosphate of one deoxyribonucleotide binding to the 3' carbon of the deoxyribose of another forms the sugar-phosphate backbone of the DNA (the sides of the "ladder"). The hydrogen bonds between the complementary nucleotide bases (adenine-thymine; guanine-cytosine) form the rungs. Note the antiparallel nature of the DNA. One strand ends in a 5' phosphate and the other ends in a 3' hydroxyl.

As will be seen in the next section, each parent strand, during DNA replication, acts as a template for the synthesis of the other strand by way of complementary base pairing. Complementary base pairing refers to DNA nucleotides with the base adenine only forming hydrogen bonds with nucleotides having the base thymine (A-T). Likewise, nucleotides with the base guanine can hydrogen bond only with nucleotides having the base cytosine (G-C). (In the case of RNA nucleotides, as will be seen later, adenine nucleotides form hydrogen bonds with nucleotides having the base uracil since thymine is not found in RNA.) As a result of this bonding, the DNA assumes its helical shape. Therefore, the two strands of DNA are said to be complementary. Wherever one strand has an adenine-containing nucleotide, the opposite strand will always have a thymine nucleotide; wherever there is a guanine-containing nucleotide, the opposite strand will always have a cytosine nucleotide (Figure 19.3.1).

While the two strands of DNA are complementary, they are oriented in opposite directions to each other. One strand is said to run 5' to 3'; the opposite DNA strand runs antiparallel, or 3' to 5' (Figure 19.3.1).

We will now briefly compare the genome of prokaryotic cells with that of eukaryotic cells.

The Prokaryotic (Bacterial) Genome

The area within a bacterium where the chromosome can be seen with an electron microscope is called a **nucleoid**. The chromosome of most prokaryotes is typically one long, single molecule of double stranded, helical, supercoiled DNA which forms a physical and genetic circle. The chromosome is generally around 1000 µm long and frequently contains around 4000 genes (Figure 19.3.8). *Escherichia coli*, which is 2-3 µm in length has a chromosome approximately 1400 µm long. To enable a macromolecule this large to fit within the bacterium, histone-like proteins bind to the DNA, segregating the DNA molecule into around 50 chromosomal domains and making it more compact. A DNA topoisomerase enzyme called DNA gyrase then supercoils the chromosome into a tight bundle forming a compacted, supercoiled mass of DNA approximately 0.2 µm in diameter.

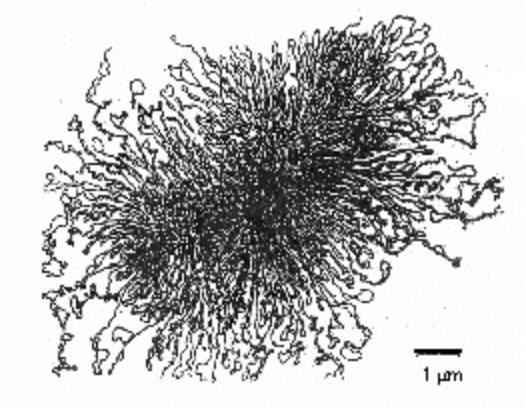


Figure 19.3.6: Electron Micrograph of Nucleoid DNA

Bacterial enzymes called DNA topoisomerases are essential in the unwinding, replication, and rewinding of the circular, supercoiled bacterial DNA (Figure 19.3.7). They are also essential in transcription of DNA into RNA, in DNA repair, and in genetic recombination in bacteria.

***Figure** 19.3.7**:** Circular, Supercoiled Prokaryotic DNA. To enable the large DNA molecyle to fit within the bacterium, a DNA topoisomerase enzyme called DNA gyrase supercoils the chromosome into a tight bundle forming a compacted, supercoiled mass of DNA approximately 0.2 µm in diameter.*

The prokaryotic nucleoid has no nuclear membrane surrounding the DNA and the nuclear body does not divide by mitosis. The cytoplasmic membrane plays a role in DNA separation during bacterial replication. Since bacteria are haploid (have only one chromosome), there is also no meiosis.

The Eukaryotic Genome

Prokaryotic and eukaryotic cells differ a great detail in both the amount and the organization of their molecules of DNA. Eukaryotic cells contain much more DNA than do bacteria, and this DNA is organized as multiple chromosomes located within a nucleus.

The nucleus in eukaryotic cells is surrounded by a nuclear membrane (Figure 19.3.7) and contains linear chromosomes composed of negatively charged DNA associated with positively charged basic proteins called histones to form structures known as nucleosomes. The nucleosomes are part of what is called chromatin, the DNA and proteins that make up the chromosomes. The nucleus divides my mitosis and haploid sex cells are produced from diploid cells by meiosis.

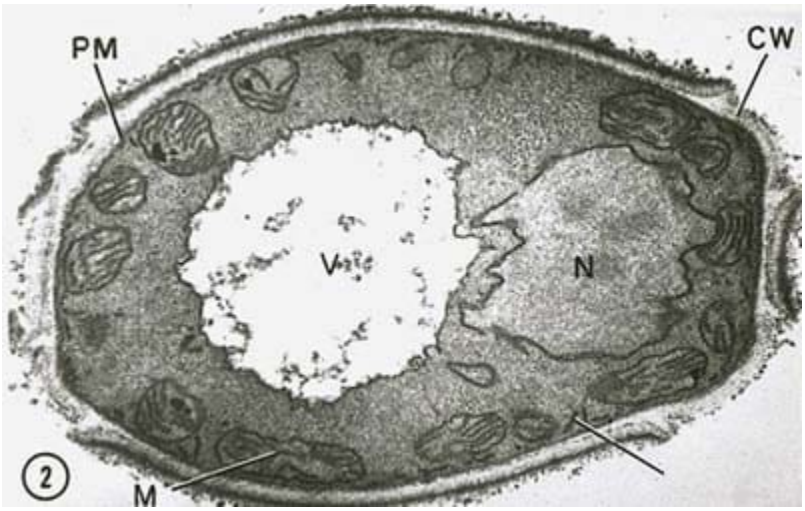


Figure 19.3.8: Transmission Electron Micrograph of *Candida albicans*, A Eukaryotic Cell. PM = plasma membrane; M = mitochondria; N = nucleus; V = vacuole; CW = cell wall. (Centers for Disease Control and Prevention).

The DNA in eukaryotic cells is packaged in a highly organized way. It consists of a basic unit called a nucleosome, a beadlike

structure 11 nm in diameter that consists of 146 base pairs of DNA wrapped around eight histone molecules. The nucleosomes are linked to one another by a segment of DNA approximately 60 base pairs long called linker DNA (Figure 19.3.9). Another histone associated with the linker DNA then packages adjacent nucleotides together to form a nucleosome thread 30nm in diameter. Finally, these packaged nucleosome threads form large coiled loops that are held together by nonhistone scaffolding proteins. These coiled loops on the scaffolding proteins interact to form the condensed chromatin seen in chromosomes during mitosis (Figure 19.3.10).

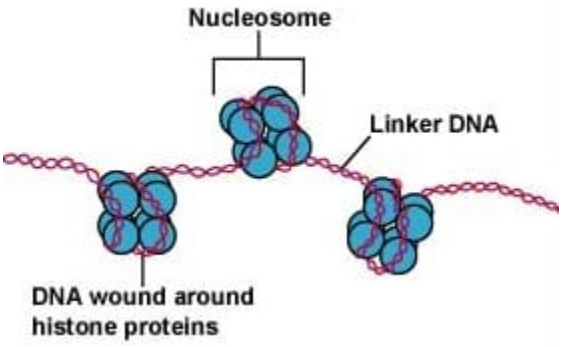


Figure 19.3.9: Nucleosomes. The DNA in eukaryotic cells is packaged in a highly organized way. It consists of a basic unit called a nucleosome, a beadlike structure with 146 base pairs of DNA wrapped around eight histone molecules. The nucleosomes are linked to one another by a segment of DNA approximately 60 DNA base pairs long.

In recent years its been found that the structural nature of the deoxyribonucleoprotein contributes to whether or not DNA is transcribed into RNA. For example, chemical changes to the chromatin can enable portions of it to condense or relax. When a region is condensed, genes cannot be transcribed. In addition, chemical can attach to or be removed from the histone proteins around which the DNA wraps. The attachment or removal of these chemical groups to the histone determines whether nearby gene expression is amplified or repressed.

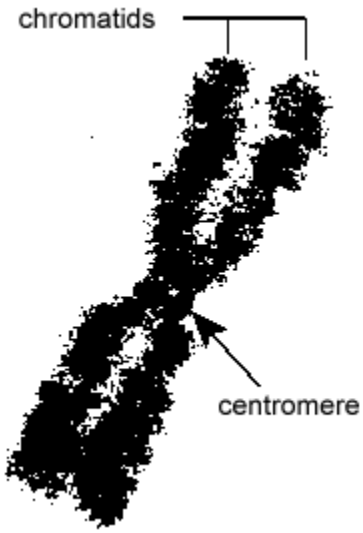


Figure 19.3.10: Replicating Eukaryotic Chromosome

The epigenome refers to a variety of chemical compounds that modify the genome typically by adding a methyl (CH_3) group to the nucleotide base adenine at specific locations along the DNA molecule. This methylation can, in turn, either repress or activate transcription of specific genes. By basically turning genes on or off, the epigenome enables the genome to interact with and respond to the cell's environment. The epigenome can be inherited just like the genome.

Summary

1. Deoxyribonucleic acid (DNA) is a long, double-stranded, helical molecule composed of building blocks called

deoxyribonucleotides.

2. A deoxyribonucleotide is composed of 3 parts: a molecule of the 5-carbon sugar deoxyribose, a nitrogenous base, and a phosphate group.
3. There are four nitrogenous bases found in DNA: adenine, guanine, cytosine, or thymine. Adenine and guanine are known as purine bases while cytosine and thymine are known as pyrimidine bases.
4. Deoxyribose is a ringed 5-carbon sugar. The 5 carbons are numbered sequentially clockwise around the sugar. The first 4 carbons actually form the ring of the sugar with the 5' carbon coming off of the 4' carbon in the ring. The nitrogenous base of the nucleotide is attached to the 1' carbon of the sugar and the phosphate group is bound to the 5' carbon.
5. During DNA synthesis, the enzyme DNA polymerase can only attach the phosphate group of a new deoxyribonucleotide to the 3' carbon of a nucleotide already in the chain.
6. During DNA replication, each parent strand acts as a template for the synthesis of the other strand by way of complementary base pairing.
7. Complementary base pairing refers to DNA nucleotides with the base adenine only forming hydrogen bonds with nucleotides having the base thymine (A-T). Likewise, nucleotides with the base guanine can hydrogen bond only with nucleotides having the base cytosine (G-C).
8. While the two strands of DNA are complementary, they are oriented in opposite directions to each other. One strand is said to run 5' to 3'; the opposite DNA strand runs antiparallel, or 3' to 5'.
9. In prokaryotic cells there is no nuclear membrane surrounding the DNA. Prokaryotic cells lack mitosis and meiosis.
10. To enable a macromolecule this large to fit within the bacterium, histone-like proteins bind to the DNA, segregating the DNA molecule into around 50 chromosomal domains and making it more compact. Then an enzyme called DNA gyrase supercoils each domain around itself forming a compacted, supercoiled mass of DNA. A topoisomerase called DNA gyrase catalyzes the negative supercoiling of the circular DNA found in bacteria. Topoisomerase IV, on the other hand, is involved in the relaxation of the supercoiled circular DNA, enabling the separation of the interlinked daughter chromosomes at the end of bacterial DNA replication.
11. The DNA in eukaryotic cells is packaged in basic units called a nucleosomes, a beadlike structure consisting of DNA wrapped around eight histone molecules. The DNA is organized as multiple chromosomes located within a nucleus surrounded by a nuclear membrane. The nucleus divides by mitosis and gametes are produced by meiosis in eukaryotes reproducing sexually.
12. The structural nature of the deoxyribonucleoprtein contributes to whether or not DNA is transcribed into RNA. For example, chemical changes to the chromatin can enable portions of it to condense or relax. When a region is condensed, genes cannot be transcribed. In addition, chemical can attach to or be removed from the histone proteins around which the DNA wraps. The attachment or removal of these chemical groups to the histone determines whether nearby gene expression is amplified or repressed.

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19.4: DNA Replication in Prokaryotic Cells

Learning Objectives

1. Briefly describe the process of DNA replication.
2. State why DNA can only be synthesized in a 5' to 3' direction.
3. State the function of the following enzymes in bacterial DNA replication:
   a. DNA polymeraseIII
   b. DNA polymerase II
   c. DNA helicase
   d. primase
   e. DNA ligase

In general, DNA is replicated by uncoiling of the helix, strand separation by breaking of the hydrogen bonds between the complementary strands, and synthesis of two new strands by complementary base pairing. Replication begins at a specific site in the DNA called the **origin of replication** (*ori*C). DNA replication is bidirectional from the origin of replication. To begin DNA replication, unwinding enzymes called DNA helicases cause short segments of the two parent DNA strands to unwind and separate from one another at the origin of replication to form two "Y"-shaped replication forks. These replication forks are the actual site of DNA copying (Figure 19.4.1).

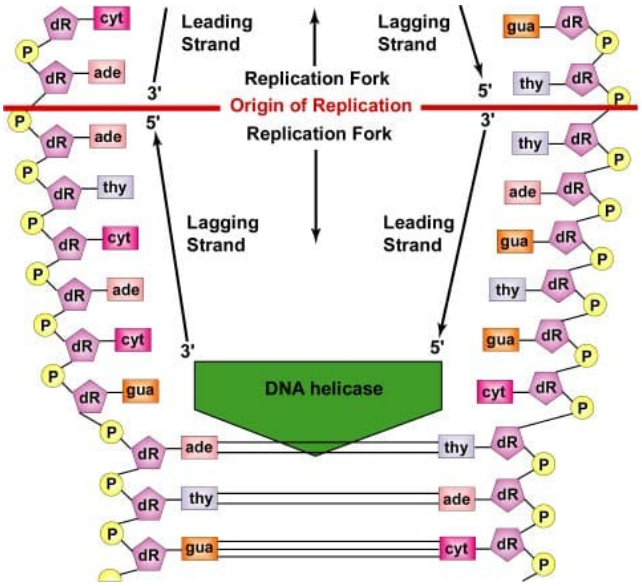


Figure 19.4.1: DNA Replication by Complementary Base Pairing: Unwinding by DNA Helicase. Replication begins at a specific site in the DNA called the origin of replication. Unwinding enzymes called DNA helicases cause the two parent DNA strands to unwind and separate from one another in both directions at this site to form two Y-shaped replication forks. These replication forks are the actual site of DNA copying. During replication within the fork, helix destabilizing proteins (not shown here) bind to the single-stranded regions preventing the strands from rejoining.

All the proteins involved in DNA replication aggregate at the replication forks to form a replication complex called a *replisome* (Figure 19.4.2).

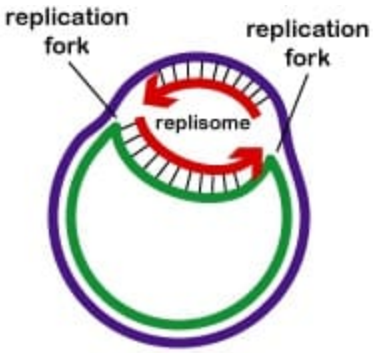


Figure 19.4.2: Bidirectional Circular DNA Replication in Bacteria. DNA replication (arrows) occurs in both directions from the origin of replication in the circular DNA found in most bacteria. All the proteins involved in DNA replication aggregate at the replication forks to form a replication complex called a replisome. The lagging DNA strand loops out from the leading strand and this enables the replisome to move along both strands pulling the DNA through as replication occurs. It is the actual DNA, not the DNA polymerase that moves during bacterial DNA replication.

Single-strand binding proteins bind to the single-stranded regions so the two strands do not rejoin. Unwinding of the double-stranded helix generates positive supercoils ahead of the replication fork. Enzymes called *topoisomerases* counteract this by producing breaks in the DNA and then rejoin them to form negative supercoils in order to relieve this stress in the helical molecule during replication.

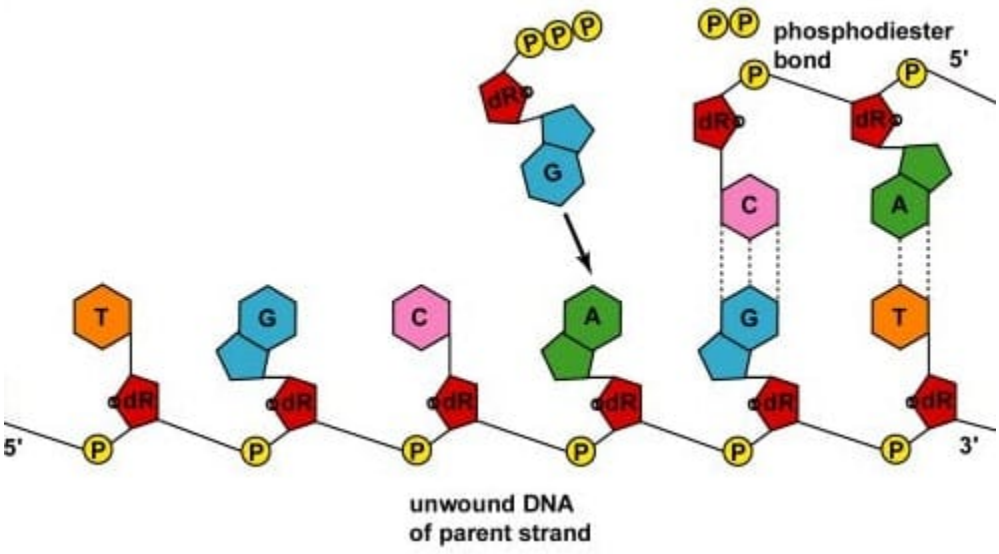


Figure 19.4.3: DNA Replication by Complementary Base Pairing. As the two strands of DNA unwind and separate in both directions, the hydrogen bonding of free DNA nucleotides with those on each parent strand produces new complementary strands. As the new nucleotides line up opposite each parent strand by hydrogen bonding, enzymes called DNA polymerases join the nucleotides by way of phosphodiester bonds. Actually, the nucleotides lining up by complementary base pairing are deoxynucleoside triphosphates, composed of a nitrogenous base, deoxyribose, and three phosphates. As the phosphodiester bond forms between the 5' phosphate group of the new nucleotide and the 3' OH of the last nucleotide in the DNA strand, two of the phosphates are removed providing energy for bonding.

As the strands continue to unwind and separate in both directions around the entire DNA molecule, new complementary strands are produced by the hydrogen bonding of free DNA nucleotides with those on each parent strand. As the new nucleotides line up opposite each parent strand by hydrogen bonding, enzymes called DNA polymerases join the nucleotides by way of phosphodiester bonds. Actually, the nucleotides lining up by complementary base pairing are deoxynucleotide triphosphates, composed of a nitrogenous base, deoxyribose, and three phosphates. As the phosphodiester bond forms between the 5' phosphate group of the new nucleotide and the 3' OH of the last nucleotide in the DNA strand, two of the phosphates are removed providing energy for bonding (Figure 19.4.3). In the end, each parent strand serves as a template to synthesize a complementary copy of itself, resulting in the formation of two identical DNA molecules (Figure 19.4.4).

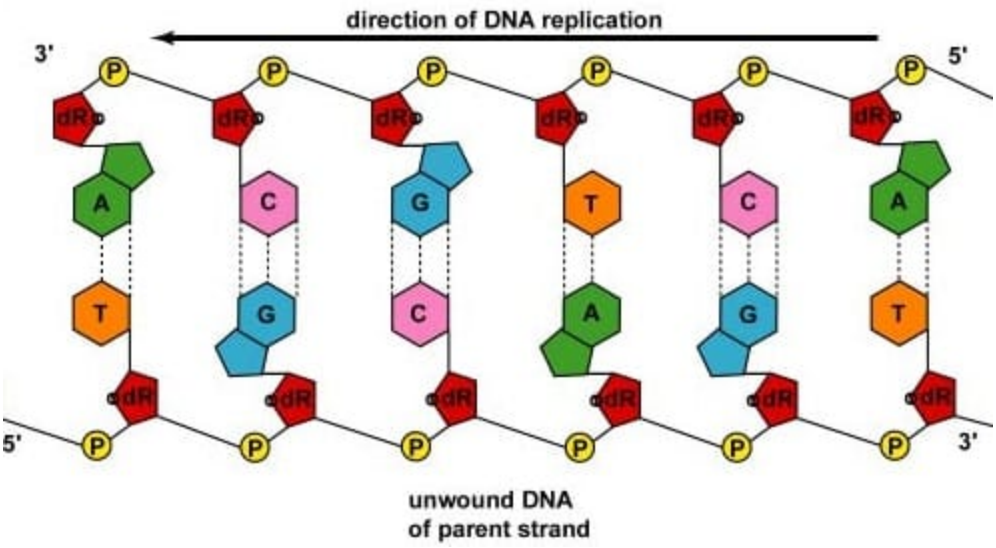
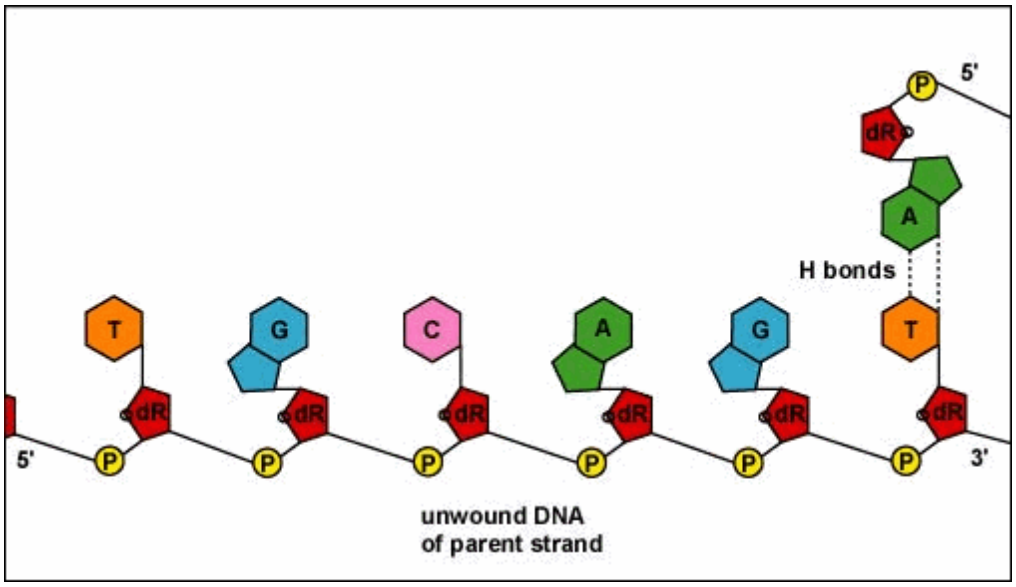


Figure 19.4.4: DNA Replication by Complementary Base Pairing

In bacteria, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells. Fts proteins, such as FtsK in the divisome, also help in separating the replicated bacterial chromosome.



***Animation**: Replication of DNA by Complementary Base Pairing. As the DNA strands unwind and separate, new complementary strands are produced by the hydrogen bonding of free DNA nucleotides with those on each parent strand. As the new nucleotides line up opposite each parent strand by hydrogen bonding, enzymes called DNA polymerases join the nucleotides by way of phosphodiester bonds. The DNA polymerase responsible for these events is not shown here.*

In reality, DNA replication is more complicated than this because of the nature of the DNA polmerases. DNA polymerase enzymes are only able to join the phosphate group at the 5' carbon of a new nucleotide to the hydroxyl (OH) group of the 3' carbon of a nucleotide already in the chain. As a result, DNA can only be synthesized in a 5' to 3' direction while copying a parent strand running in a 3' to 5' direction.

Remember, as mentioned above, each DNA strand has two ends. The 5' end of the DNA is the one with the terminal phosphate group on the 5' carbon of the deoxyribose; the 3' end is the one with a terminal hydroxyl (OH) group on the deoxyribose of the 3' carbon of the deoxyribose. The two strands are antiparallel, that is they run in opposite directions. Therefore, one parent strand - the one running 3' to 5' and called the leading strand - can be copied directly down its entire length (Figure 19.4.5).

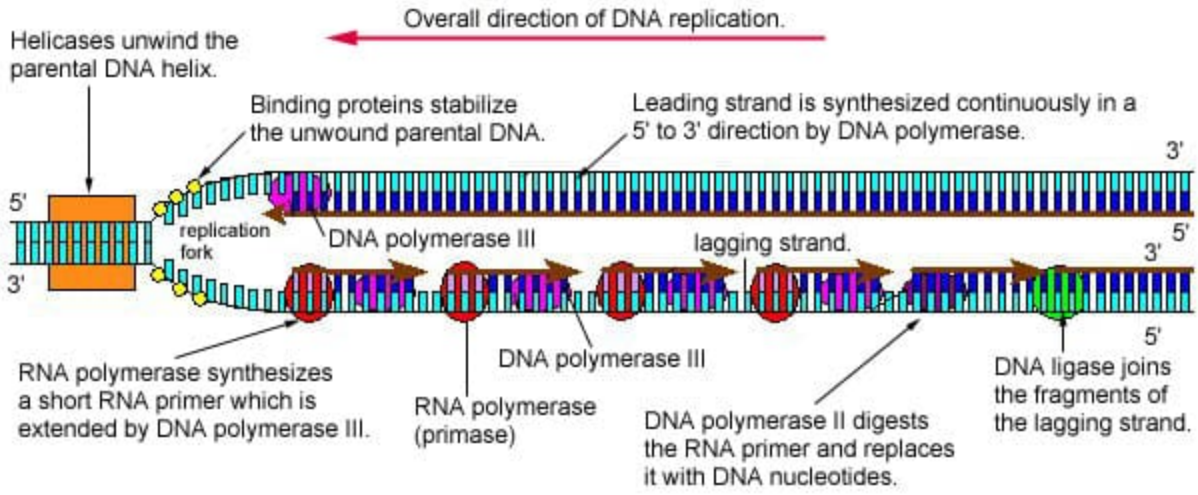


Figure 19.4.5: Replication of Leading and Lagging DNA Strands. The leading strand is made continuously in a 5' to 3' direction by DNA polymerase III as the DNA helicase unwinds the parental DNA helix. However, because the parental DNA strands are antiparallel, the lagging strand must be made in short fragments. RNA polymerase (primase) synthesizes a short RNA primer which is extended by DNA polymerase III. DNA polymerase II then digests the RNA primer and replaces it with DNA. Finally, DNA ligase joins the fragments of the lagging strand together.

However, the other parent strand - the one running 5' to 3' and called the lagging strand - must be copied discontinuously in short fragments (Okazaki fragments) of around 100-1000 nucleotides each as the DNA unwinds. This occurs, as mentioned above, at the replisome. The lagging DNA strand loops out from the leading strand and this enables the replisome to move along both strands pulling the DNA through as replication occurs. It is the actual DNA, not the DNA polymerase that moves during bacterial DNA replication (Figure 19.4.2).

In addition, DNA polymerase enzymes cannot begin a new DNA chain from scratch. They can only attach new nucleotides onto 3' OH group of a nucleotide in a preexisting strand. Therefore, to start the synthesis of the leading strand and each DNA fragment of the lagging strand, an RNA polymerase complex called a *primase* is required. The primase, which is capable of joining RNA nucleotides without requiring a preexisting strand of nucleic acid, first adds several complementary RNA nucleotides opposite the DNA nucleotides on the parent strand. This forms what is called an RNA primer (Figure 19.4.6).

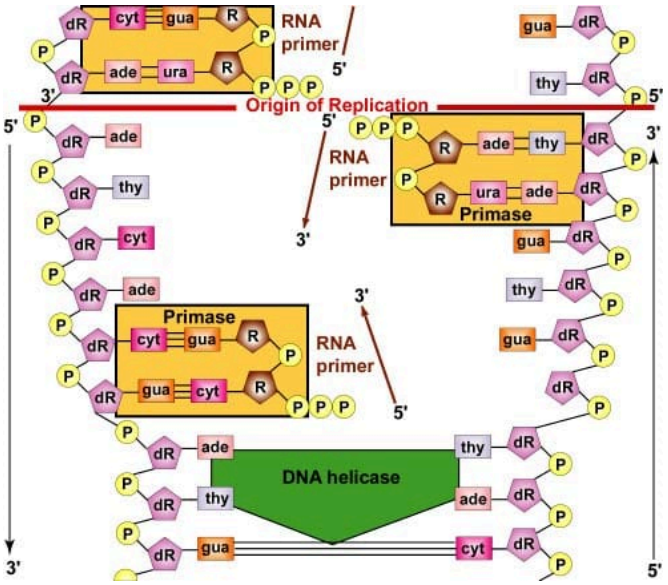


Figure 19.4.6: DNA Replication by Complementary Base Pairing: Producing an RNA Primer. DNA polymerases cannot begin a new DNA chain from scratch. They can only attach new nucleotides onto 3' OH group of a nucleotide in a preexisting strand. Therefore, to start the synthesis of the leading strand and each DNA fragment of the lagging strand, an RNA polymerase complex called a primosome or primase (not shown here) is required. The primase, which is capable of joining RNA nucleotides without requiring a preexisting strand of nucleic acid, first adds several comlementary RNA nucleotides opposite the DNA nucleotides on the parent strand. This forms what is called an RNA primer. The free ribonucleoside triphosphates line up by complementary base pairing with the nucleotides on each parent strand of the unwound DNA in the replication fork and are then joined together by the primase.

DNA polymerase III then replaces the primase and is able to add DNA nucleotides to the RNA primer (Figure 19.4.7).

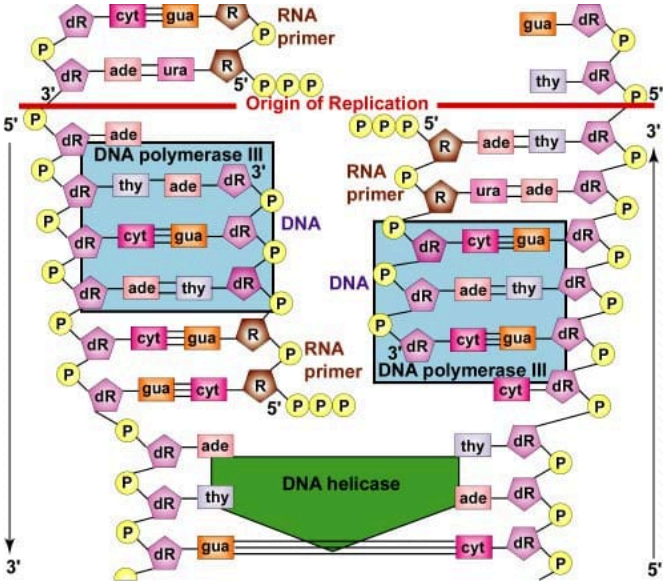


Figure 19.4.7: DNA Replication by Complementary Base Pairing: Adding DNA Nucleotides to the RNA Primer. DNA polymerase III replaces the primase and is able to add DNA nucleotides to the RNA primer. As the free deoxyribonucleoside triphosphates line up by complementary base pairing with the nucleotides on each parent strand of the unwound DNA in the replication fork, the phosphate on the 5' carbon of the newest building block lining up then forms a phosphodiester bond with the 3' carbon of the last nucleotide in the growing strand. During the process, two phosphates are lost . Because the parent strands are antiparallel and DNA can only be replicated in a 5' to 3' direction, the the two new strands must be synthesized in opposite directions.

Later, DNA polymerase II digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides to fill the gap (Figure 19.4.8).

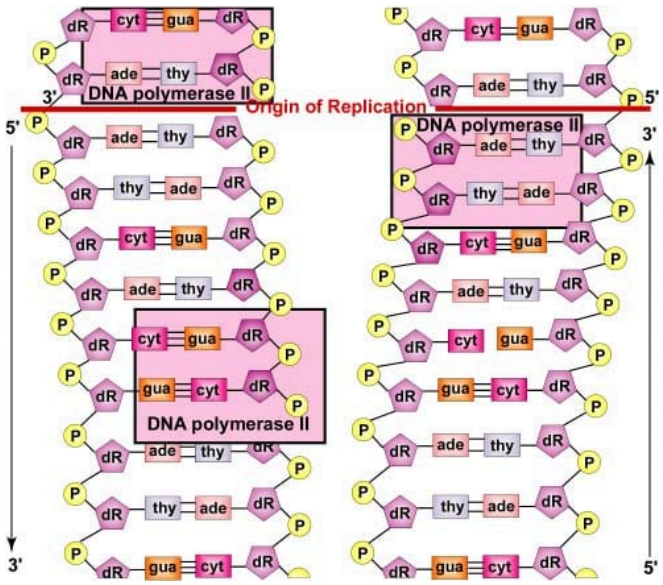
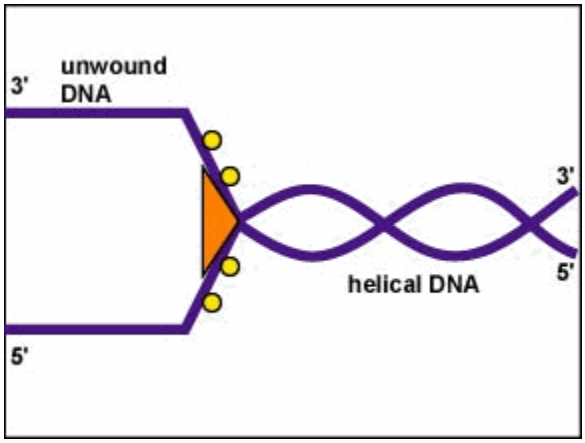


Figure 19.4.8: DNA Replication by Complementary Base Pairing: Replacing RNA Primer with DNA. Eventually, DNA polymerase II digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides to fill the gap. Finally, the DNA fragments on the lagging strand are hooked together by the enzyme DNA ligase.

Finally, the DNA fragments themselves are hooked together by the enzyme DNA ligase (Figure 19.4.6). Yet even with this complicated procedure, a 1000 micrometer-long macromolecule of tightly-packed, supercoiled DNA can make an exact copy of itself in only about 10 minutes time under optimum conditions, inserting nucleotides at a rate of about 1000 nucleotides per second!



Animation: *Replication of Leading and Lagging DNA Strands. The leading strand is made continuously in a 5' to 3' direction by DNA polymerase III as the DNA helicase unwinds the parental DNA helix. However, because the parental DNA strands are antiparallel, the lagging strand must be made in short fragments. RNA polymerase (primase) synthesizes a short RNA primer which is extended by DNA polymerase III. DNA polymerase II then digests the RNA primer and replaces it with DNA. Finally, DNA ligase joins the fragments of the lagging strand together.*

There is a great deal of genetic information in the bacterial chromosome. For example *Escherichia coli*, the most studied of all bacteria, has a genome containing 4,639,221 base pairs, which code for at least 4288 proteins.

Summary

1. During DNA replication, each parent strand acts as a template for the synthesis of the other strand by way of complementary base pairing.
2. Complementary base pairing refers to DNA nucleotides with the base adenine only forming hydrogen bonds with nucleotides having the base thymine (A-T). Likewise, nucleotides with the base guanine can hydrogen bond only with nucleotides having

the base cytosine (G-C).

3. Each DNA strand has two ends. The 5' end of the DNA is the one with the terminal phosphate group on the 5' carbon of the deoxyribose; the 3' end is the one with a terminal hydroxyl (OH) group on the deoxyribose of the 3' carbon of the deoxyribose.
4. To synthesize the two chains of deoxyribonucleotides during DNA replication, the DNA polymerase enzymes involved are only able to join the phosphate group at the 5' carbon of a new nucleotide to the hydroxyl (OH) group of the 3' carbon of a nucleotide already in the chain.
5. While the two strands of DNA are complementary, they are oriented in opposite directions to each other. One strand is said to run 5' to 3'; the opposite DNA strand runs antiparallel, or 3' to 5'.
6. To begin DNA replication, unwinding enzymes called DNA helicases cause short segments of the two parent DNA strands to unwind and separate from one another at the origin of replication to form two "Y"-shaped replication forks.
7. Single-strand binding proteins bind to the now unpaired single-stranded regions so the two strands do not rejoin.
8. As the strands continue to unwind and separate in both directions around the entire DNA molecule, new complementary strands are produced by the hydrogen bonding of free DNA nucleotides with those on each parent strand.
9. As the new nucleotides line up opposite each parent strand by hydrogen bonding, enzymes called DNA polymerases join the nucleotides by way of phosphodiester bonds.
10. The two strands are antiparallel, that is they run in opposite directions. Therefore, one parent strand - the one running 3' to 5' and called the leading strand- can be copied directly down its entire length. However, the other parent strand - the one running 5' to 3' and called the lagging strand- must be copied discontinuously in short fragments (Okazaki fragments) of around 100-1000 nucleotides each as the DNA unwinds.
11. Furthermore, DNA polymerase enzymes cannot begin a new DNA chain from scratch. They can only attach new nucleotides onto 3' OH group of a nucleotide in a preexisting strand. Therefore, to start the synthesis of the leading strand and each DNA fragment of the lagging strand, an RNA polymerase complex called a primase is required. The primase, which is capable of joining RNA nucleotides without requiring a preexisting strand of nucleic acid, first adds several comlementary RNA nucleotides opposite the DNA nucleotides on the parent strand forming what is called an RNA primer.
12. DNA polymerase III then replaces the primase and is able to add DNA nucleotides to the RNA primer. Later, DNA polymerase II digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides to fill the gap.
13. The DNA fragments themselves are hooked together by the enzyme DNA ligase to complete the process.

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19.5: DNA Replication in Eukaryotic Cells and the Eukaryotic Cell Cycle

Learning Objectives

1. Briefly describe the process of DNA replication.
2. Compare prokaryotic and eukaryotic DNA replication in terms of origins of replication.
3. Define telomeres and state whether they are found in prokaryotic or eukaryotic DNA.
4. Name the stages of mitosis and state what happens during each.

As in prokaryotes, the linear chromosomes of eukaryotes replicate by strand separation and complementary base pairing of free deoxyribonucleotides with those on each parent DNA strand. As with prokaryotes, DNA replication in eukaryotic cells is bidirectional. However, unlike the circular DNA in prokaryotic cells that usually has a single origin of replication, the linear DNA of a eukaryotic cell contains multiple origins of replication (Figure 19.5.11).

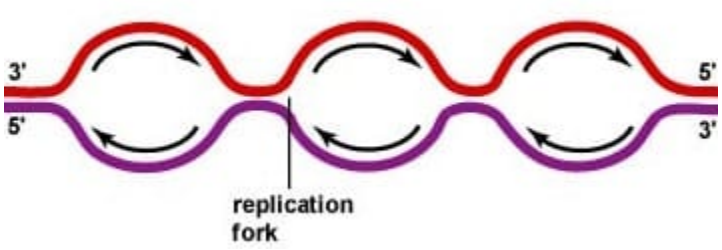
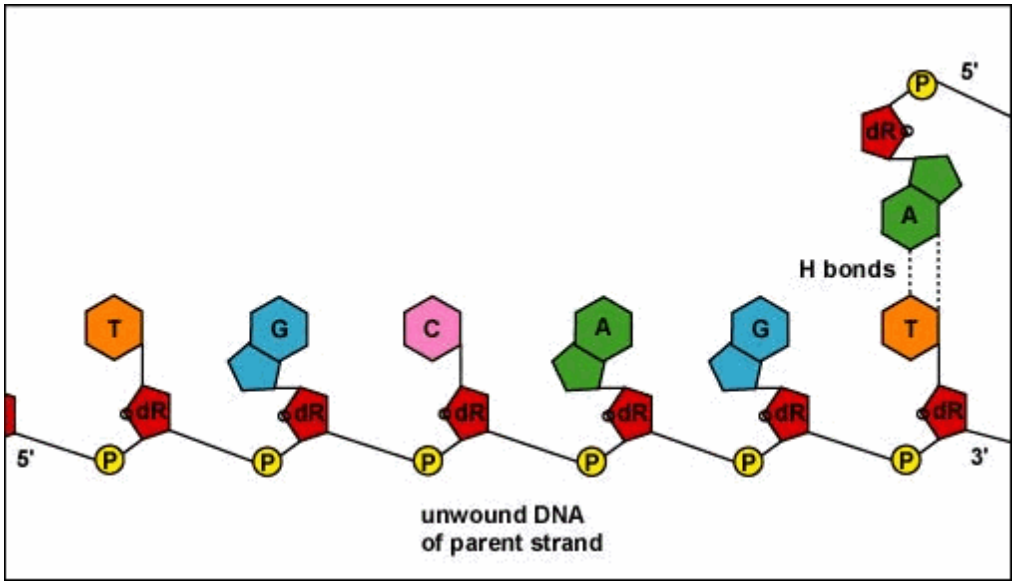


Figure 19.5.11: Bidirectional DNA Replication in Eukaryotic Cells. DNA replication (arrows) occurs in both directions from multiple origins of replication in the linear DNA found in eukaryotic cells.

As discussed earlier under prokaryotic DNA replication, DNA can only be synthesized in a 5' to 3' direction and all DNA polymerase requires a primer. To solve this problem, the ends of the linear eukaryotic DNA strands, called *telomeres* , have short, repetitive, noncoding DNA base sequences. A unique enzyme called *telomerase* binds to the telomeric DNA at the 3' end. The telomerase contains a small RNA template as a cofactor which is copied by DNA nucleotides to extend the 3' end. Once the extension is long enough, primase can assemble a short RNA primer on the lagging strand and DNA replication can proceed in a manner similar to the lagging strand of prokaryotic DNA.



***Animation**: Replication of DNA by Complementary Base Pairing. As the DNA strands unwind and separate, new complementary strands are produced by the hydrogen bonding of free DNA nucleotides with those on each parent strand. As the new nucleotides line up opposite each parent strand by hydrogen bonding, enzymes called DNA polymerases join the nucleotides by way of phosphodiester bonds. The DNA polymerase responsible for these events is not shown here.*

Once the chromosomes have replicated, the nucleus divides by mitosis (see Figure 19.5.12 through 16). The eukaryotic cell cycle is divided into two major phases: interphase and cell division.

Interphase

Ninety percent or more of the cell cycle is spent in interphase. During interphase, cellular organelles double in number, the DNA replicates, and protein synthesis occurs. The chromosomes are not visible and the DNA appears as uncoiled chromatin.

Interphase in a plant cell: see Figure 19.5.17

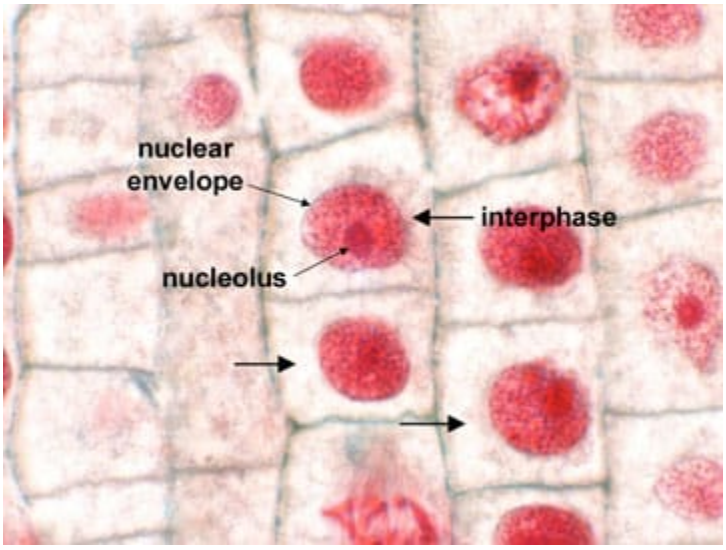


Figure 19.5.17: Interphase in a Plant Cell. Ninety percent or more of the cell cycle is spent in interphase. During interphase, cellular organelles double in number, the DNA replicates, and protein synthesis occurs. The chromosomes are not visible and the DNA appears as uncoiled chromatin.These are cells found in the roor tip of an onion plant.

Interphase in an animal cell: see Figure 19.5.18



Figure 19.5.18: Interphase in an Animal Cell. Ninety percent or more of the cell cycle is spent in interphase. During interphase, cellular organelles double in number, the DNA replicates, and protein synthesis occurs. The chromosomes are not visible and the DNA appears as uncoiled chromatin. These are cells from a whitefish.

Interphase is divided into the following stages: G_1, S, and G_2.

1. G_1 phase: During G_1 phase, the period that immediately follows cell division, the cell grows and differentiates. New organelles are made but the chromosomes have not yet replicated in preparation for cell division.
2. S phase: DNA synthesis occurs during S phase. The chromosomes replicate in preparation for cell division.
3. G_2 phase: During G_2 phase, molecules that will be required for cell replication are synthesized.

Cell Division

Cell division consists of nuclear division and cytoplasmic division. Nuclear division is referred to as mitosis while cytoplasmic division is called cytokenesis.

1. Mitosis (nuclear division)

Mitosis is the nuclear division process in eukaryotic cells and ensures that each daughter cell receives the same number of chromosomes as the original parent cell. Mitosis can be divided into the following phases: prophase, metaphase, anaphase, and telophase.

a. Prophase: During prophase, the chromatin condenses and the chromosomes become visible. Also the nucleolus disappears, the nuclear membrane fragments, and the spindle apparatus forms and attaches to the centromeres of the chromosomes.

Prophase in a plant cell: see Figure 19.5.19 and Figure 19.5.20

Prophase in an animal cell: see Figure 19.5.21 and Figure 19.5.22

b. Metaphase: During metaphase, the nuclear membrane fragmentation is complete and the duplicated chromosomes line up along the cell's equator.

Metaphase in a plant cell: see Figure 19.5.23

Metaphase in an animal cell: see Figure 19.5.24

c. Anaphase: During anaphase, diploid sets of daughter chromosomes separate and are pushed and pulled toward opposite poles of the cell. This is accomplished by the polymerization and depolymerization of the microtubules that help to form the spindle apparatus.

Anaphase in a plant cell: see Figure 19.5.25 and Figure 19.5.26

d. Telophase: During telophase, the nuclear membrane and nucleoli reform, cytokinesis is nearly complete, and the chromosomes eventually uncoil to chromatin. Usually cytokinesis occurs during telophase.

Telophase in a plant cell: see Figure 19.5.28 and Figure 19.5.29

Telophase in an animal cell: see Figure 19.5.30

YouTube movie illustrating mitosis.

2. Cytokinesis (cytoplasmic division)

During cytokinesis, the dividing cell separates into two diploid daughter cells. In animal cells, which lack a cell wall and are surrounded only by a cytoplasmic membrane, microfilaments of actin and myosin attached to the membrane form constricting rings around the central portion of the dividing cell and eventually divide the cytoplasm into two daughter cells. In the case of plant cells , which are surrounded by a cell wall in addition to the cytoplasmic membrane, carbohydrate-filled vesicles accumulate and fuse along the equator of the cell forming a cell plate that separates the cytoplasm into two daughter cells.

Summary

1. During DNA replication, each parent strand acts as a template for the synthesis of the other strand by way of complementary base pairing.
2. Complementary base pairing refers to DNA nucleotides with the base adenine only forming hydrogen bonds with nucleotides having the base thymine (A-T). Likewise, nucleotides with the base guanine can hydrogen bond only with nucleotides having the base cytosine (G-C).
3. Each DNA strand has two ends. The 5' end of the DNA is the one with the terminal phosphate group on the 5' carbon of the deoxyribose; the 3' end is the one with a terminal hydroxyl (OH) group on the deoxyribose of the 3' carbon of the deoxyribose.
4. To synthesize the two chains of deoxyribonucleotides during DNA replication, the DNA polymerase enzymes involved are only able to join the phosphate group at the 5' carbon of a new nucleotide to the hydroxyl (OH) group of the 3' carbon of a nucleotide already in the chain.
5. While the two strands of DNA are complementary, they are oriented in opposite directions to each other. One strand is said to run 5' to 3'; the opposite DNA strand runs antiparallel, or 3' to 5'.
6. Unlike the circular DNA in prokaryotic cells that usually has a single origin of replication, the linear DNA of a eukaryotic cell contains multiple origins of replication.
7. Because DNA can only be synthesized in a 5' to 3' direction and all DNA polymerase requires a primer, the ends of the linear eukaryotic DNA strands, called telomeres, have short, repetitive, noncoding DNA base sequences. A unique enzyme called telomerase binds to the telomeric DNA at the 3' end. The telomerase contains a small RNA template as a cofactor which is copied by DNA nucleotides to extend the 3' end. Once the extension is long enough, primase can assemble a short RNA primer on the lagging strand and DNA replication can proceed in a manner similar to the lagging strand of prokaryotic DNA.
8. Once the chromosomes have replicated, the nucleus divides by mitosis.
9. During interphase, cellular organelles double in number, the DNA replicates, and protein synthesis occurs. The chromosomes are not visible and the DNA appears as uncoiled chromatin.
10. During G_1 phase, the period that immediately follows cell division, the cell grows and differentiates and new organelles are made.
11. DNA synthesis (chromosome replication) occurs during S phase.
12. During G_2 phase, molecules that will be required for cell replication are synthesized.
13. Nuclear division is referred to as mitosis while cytoplasmic division is called cytokenesis.
14. During prophase, the chromatin condenses and the chromosomes become visible, the nucleolus disappears, the nuclear membrane fragments, and the spindle apparatus forms and attaches to the centromeres of the chromosomes.
15. During metaphase, the nuclear membrane fragmentation is complete and the duplicated chromosomes line up along the cell's equator.
16. During anaphase, diploid sets of daughter chromosomes separate and are pushed and pulled toward opposite poles of the cell.
17. During telophase, the nuclear membrane and nucleoli reform, cytokinesis is nearly complete, and the chromosomes eventually uncoil to chromatin.
18. During cytokinesis, the dividing cell separates into two diploid daughter cells.

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19.6: Ribonucleic Acid (RNA)

Learning Objectives

1. State the 3 basic parts of a ribonucleotide.
2. State 3 ways RNA differs from DNA.
3. State the function of each of the following:
   a. tRNA
   b. mRNA
   c. rRNA

RNA is a single-stranded molecule composed of building blocks called ribonucleotides. A ribonucleotide is composed of three parts: a molecule of the sugar ribose, a nitrogenous base, and a phosphate group (Figure 19.6.1).

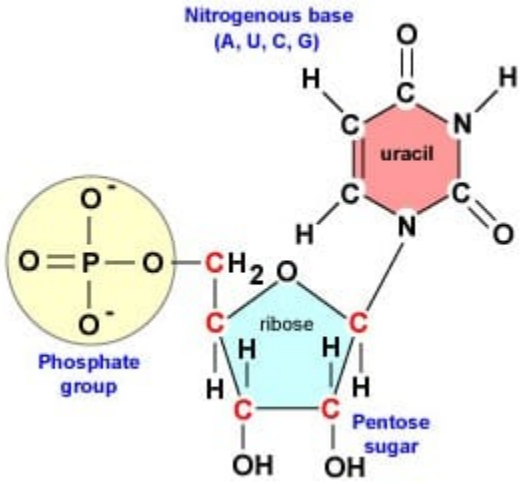


Figure 19.6.1: A Ribonucleotide.Note the phosphate group attached to the 5' carbon of the ribose and the nitrogenous base, in this case uracil, attached to the 1' carbon.

Ribose is a ringed 5-carbon sugar (Figure 19.6.2) similar to deoxyribose except it has a hydroxyl (OH) group) on its 2' carbon. The nitrogenous base is attached to the 1' carbon of the sugar and the phosphate group is bound to the 5' carbon. During RNA synthesis, the phosphate group of a new ribonucleotide is attached by the enzyme RNA polymerase to the 3' carbon of a ribonucleotide.

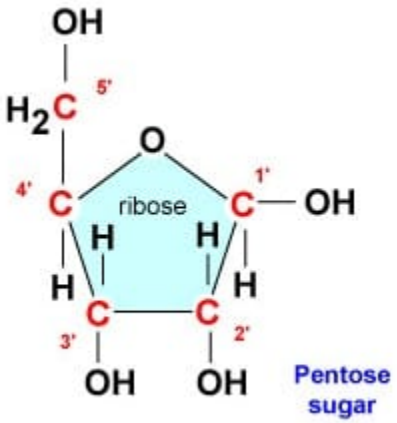


Figure 19.6.2: The 5-Carbon Sugar Ribose. During nucleotide production, the nitrogenous base will attach to the 1' carbon and the phosphate group will attach to the 5' carbon. The first 4 carbons shown form the actual ring of the sugar. The 5' carbon comes off of the ring.

There are four nitrogenous bases found in RNA: adenine, guanine, cytosine, or uracil. Adenine and guanine are known as purine bases while cytosine and uracil are known as pyrimidine bases (Figure 19.6.3).

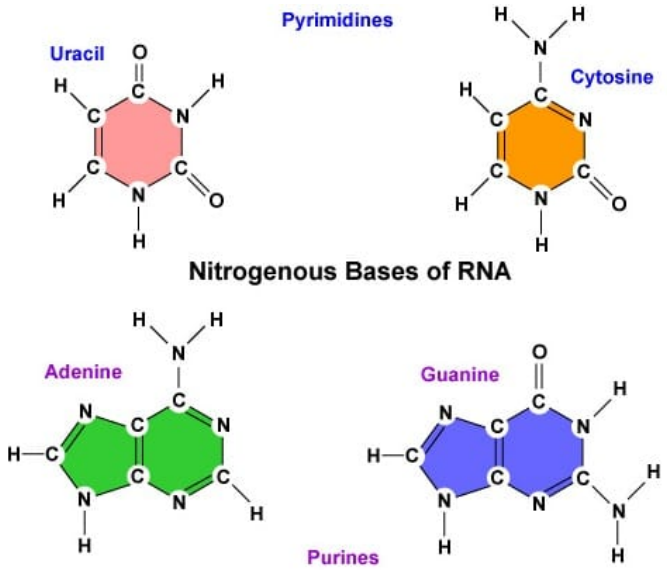


Figure 19.6.3: The Four Nitrogenous Bases in RNA: Adenine, Guanine, Cytosine, and Uracil. Adenine and guanine are also known as purine bases; cytosine and uracil are also called pyrimidine bases. Each ribonucleotide will contain one of these four bases.

A phosphate group (Figure 19.6.4).

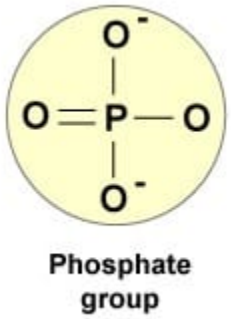


Figure 19.6.4: A Phosphate Group

RNA differs from DNA in several ways. First of all, RNA is single-stranded, not double-stranded. Unlike DNA polymerases, RNA polymerases are able to join RNA nucleotides together without requiring a preexisting strand of RNA. In addition, RNA has the base uracil in place of thymine. Uracil, like thymine, can form hydrogen bond with adenine. Also, RNA and has the sugar ribose instead of deoxyribose. Finally, there are three functionally different types of RNA:

- **Messenger RNA (mRNA)**: Messenger RNA copies the genetic information in the DNA by complementary base pairing and carries this "message" to the ribosomes where the proteins are assembled.
- **Transfer RNA (tRNA)**: Transfer RNAs picks up specific amino acids, transfers the amino acids to the ribosomes, and insert the correct amino acids in the proper place according to the mRNA message.
- **Ribosomal RNA (rRNA)**: Ribosomal RNA and ribosomal proteins form the ribosomal subunits.
- **Other RNA transcripts**: A variety of other RNA molecules transcribed off of DNA have also been found. These RNA molecules are not translated into proteins, but rather perform a wide range of direct genetic regulatory functions. Examples include antisense RNAs, microRNAs, and riboswitch RNAs.

RNA has the base uracil in place of thymine in DNA.

Summary

1. RNA is a single-stranded molecule composed of building blocks called ribonucleotides.
2. A ribonucleotide is composed of 3 parts: a molecule of the sugar ribose, a nitrogenous base, and a phosphate group.
3. RNA differs from DNA in several ways: RNA is single-stranded, not double-stranded; unlike DNA polymerases, RNA polymerases are able to join RNA nucleotides together without requiring a preexisting strand of RNA; RNA has the base uracil in place of thymine, but like thymine, uracil can form hydrogen bond with adenine; and RNA and has the sugar ribose instead of deoxyribose.
4. There are three functionally different types of RNA: messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA).
5. Messenger RNA copies the genetic information in the DNA by complementary base pairing and carries this "message" to the ribosomes where the proteins are assembled.
6. Transfer RNAs picks up specific amino acids, transfers the amino acids to the ribosomes, and insert the correct amino acids in the proper place according to the mRNA message.
7. Ribosomal RNA and ribosomal proteins form the ribosomal subunits.
8. A variety of other RNA molecules transcribed off of DNA have also been found, including antisense RNAs, microRNAs, and riboswitch RNAs. These RNA molecules are not translated into proteins but rather perform a wide range of direct genetic regulatory functions

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19.7: POLYPEPTIDE AND PROTEIN SYNTHESIS

DNA is divided into functional units called genes. A gene is a segment of DNA that codes for a functional product (mRNA, tRNA, or rRNA). Since the vast majority of genes are transcribed into mRNA and mRNA is subsequently translated into polypeptides or proteins, most genes code for protein synthesis. The term polypeptide refers to many amino acids connected by peptide bonds. While all proteins are polypeptides, not all polypeptides are proteins. In some cases, smaller polypeptides coded for by two or more genes must be joined together to produce a functional protein. In other cases, as will be mentioned below, mRNA carries a transcript of several genes resulting in the synthesis of a large polypeptide that must subsequently be cleaved by enzymes called proteases into two or more smaller functional proteins. For simplicity, we will use the term protein when referring to the end product of transcription and translation. In this section we will see how the sequence of deoxyribonucleotide bases along one strand of DNA ultimately codes for the amino acid sequence of a particular polypeptide or protein.

During protein synthesis, the order of nucleotide bases along a gene gets transcribed into a complementary strand of mRNA which is then translated by tRNA into the correct order of amino acids for that polypeptide or protein. Therefore, the order of deoxyribonucleotide bases along the DNA determines the order of amino acids in the proteins, that is, its primary structure. Because certain amino acids can interact with other amino acids, the order of amino acids for each protein determines its final three-dimensional shape, which in turn determines the function of that protein. Protein synthesis can be divided into two stages: transcription and translation. In the next two sections we will look at these stages in greater detail.

- Topic hierarchy

19.7A: Transcription

19.7B: Translation

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19.7A: Transcription

Learning Objectives

1. Define the following:
   a. gene
   b. transcription
2. Briefly describethe function of the following in terms of transcription:
   a. mRNA
   b. 3' end
   c. 5' end
   d. RNA polymerase
   e. phosphodiester bond
   f. promoter
   g. leader sequence
   h. coding sequence
   i. transcription terminator
   j. codon
3. Define the following in terms of transcription in eukaryotic cells:
   a. introns
   b. exons
   c. precurser mRNA
   d. cap
   e. poly-A tail
   f. mature mRNA

Transcription in Prokaryotic Cells

Description: Messenger RNA (mRNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene. Although genes are present on both strands of DNA, only one strand is transcribed for any given gene. Following transcription, 30S and 50S ribosomal subunits attach to the mRNA and tRNA inserts the correct amino acids which are subsequently joined to form a polypeptide or a protein through a process called translation.

The enzyme RNA polymerase transcribes DNA. This enzyme initiates transcription, joins the RNA nucleotides together, and terminates transcription. To initiate transcription in bacteria, a variety of proteins called sigma factors bind to RNA polymerases. This complex can then bind to a specific sequence of usually about 40 deoxyribonucleotide bases called the promoter located along the DNA prior to the coding region of the gene. The promotor determines what region of the DNA and which strand of DNA will be transcribed into RNA.

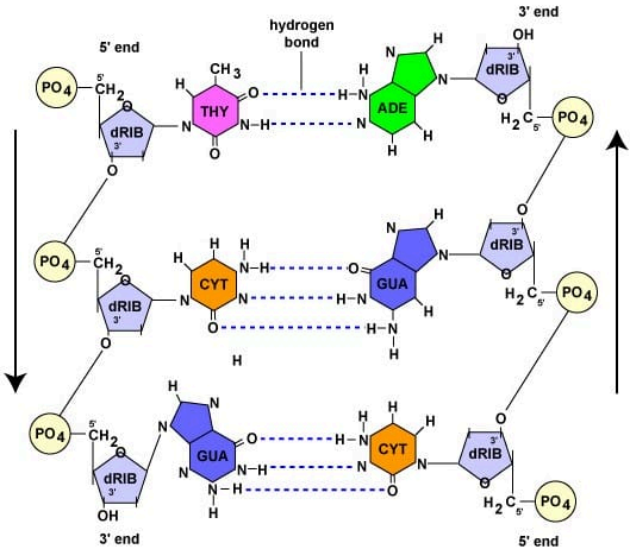
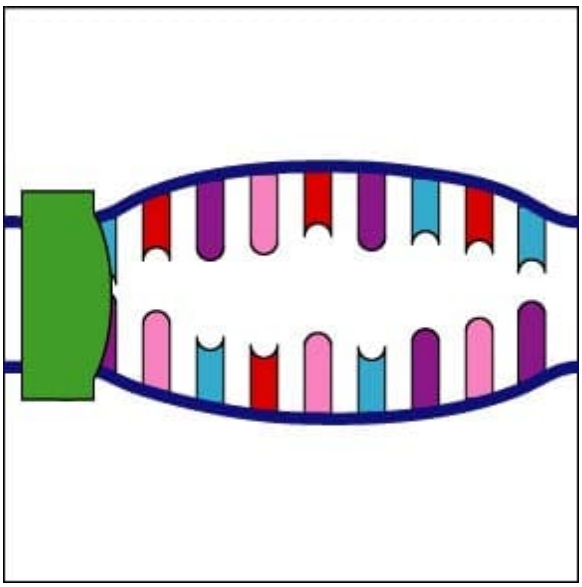


Figure 19.7A.1: Chemical Structure of DNA. The phosphate of one deoxyribonucleotide binding to the 3' carbon of the deoxyribose of another forms the sugar-phosphate backbone of the DNA (the sides of the "ladder"). The hydrogen bonds between the complementary nucleotide bases (adenine-thymine; guanine-cytosine) form the rungs. Note the antiparallel nature of the DNA. One strand ends in a 5' phosphate and the other ends in a 3' hydroxyl.

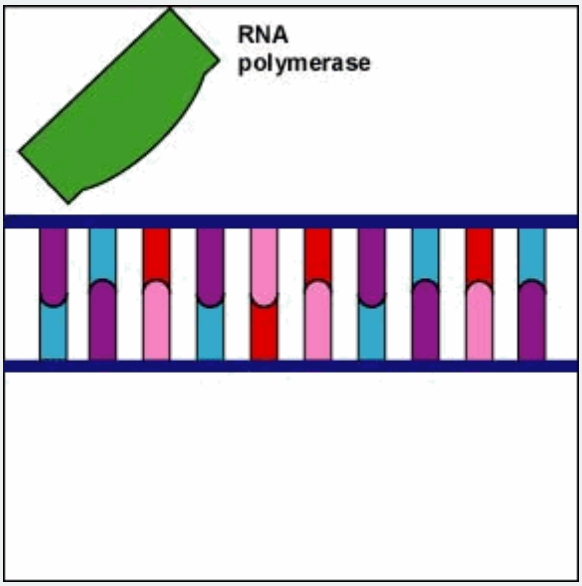
Like DNA polymerase, RNA polymerase can only synthesize nucleic acid in a 5' to 3' direction while "reading" a DNA template in the 3' to 5' direction. As mentioned earlier in this unit, the 3' end of a strand of nucleic acid has a hydroxyl (OH) group on the 3' carbon of the deoxyribose or ribose and is not linked to another nucleotide. The 5' end of that strand has a phosphate group attached to the 5' carbon of the sugar and is not linked to another nucleotide (Figure 19.7A.1).

Once the RNA polymerase/sigma factor complex recognizes the correct promoter, the sigma factor dissociate from the RNA polymerase and the enzyme begins to unwind the helix of the DNA creating a region of nonpaired deoxyribonucleotides that serve as a template for RNA synthesis (Figures 2 and 3).



Figures 2 and 3: Unwinding of the DNA Helix by RNA Polymerase, Step-1. Once the RNA polymerase/sigma factor complex recognizes the correct promoter, the sigma factor dissociate from the RNA polymerase and the enzyme begins to unwind the helix of the DNA creating a region of nonpaired deoxyribonucleotides that serve as a template for RNA synthesis.

Unwinding of the DNA Helix by RNA Polymerase



Once the RNA polymerase/sigma factor complex recognizes the correct promoter, the sigma factor dissociate from the RNA polymerase and the enzyme begins to unwind the helix of the DNA creating a region of nonpaired deoxyribonucleotides that serve as a template for RNA synthesis

While the RNA polymerase does not transcribe the promoter itself, it does transcribe a short noncoding leader sequence just prior to the coding sequence of the gene. The leader sequence is the portion of DNA that is transcribed into the ribosome-binding site of the mRNA (below under translation.) The coding sequence contains the actual message for protein synthesis.

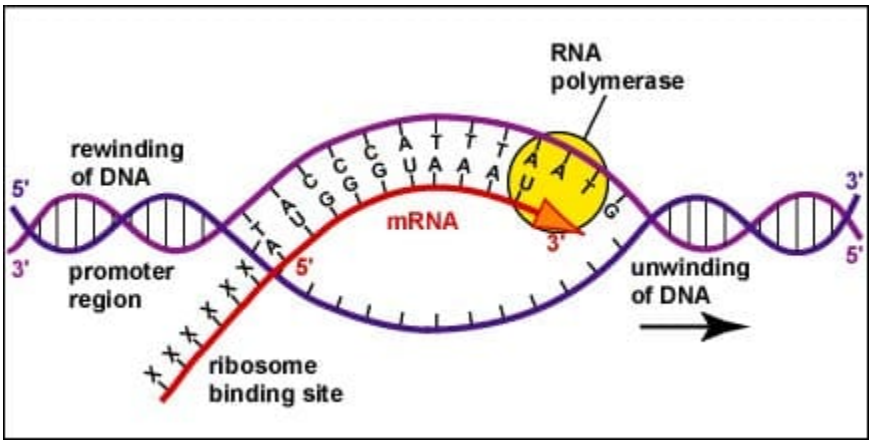


Figure $19.7A.4$: Transcription of mRNA Complementary to a Gene. RNA is synthesized by complementary base pairing of free ribonucleotides with the deoxyribonucleotides of a gene. The enzyme responsible for transcription is RNA polymerase. (Xs represent the ribonucleotides for the ribosome binding site prior to the Start codon AUG.)

Once the actual transcription begins, ribonucleotides containing 3 phosphate groups hydrogen bond through the process of complementary base pairing with the exposed deoxyribonucleotides on the unwound strand that is to be transcribed (Figure $19.7A.4$). The ribonucleotides are then covalently bonded together by phosphodiester bonds, the energy being supplied by the cleavage of two phosphate groups from the ribonucleotide triphosphate (Figure $19.7A.5$). (The phosphodiester bond refers to the phosphate on the 5'C of the newly inserted nucleotide covalently bonding to the 3'C of the last ribonucleotide in the mRNA chain.) The mRNA polymerizes at a rate of about 30 nucleotides per second.

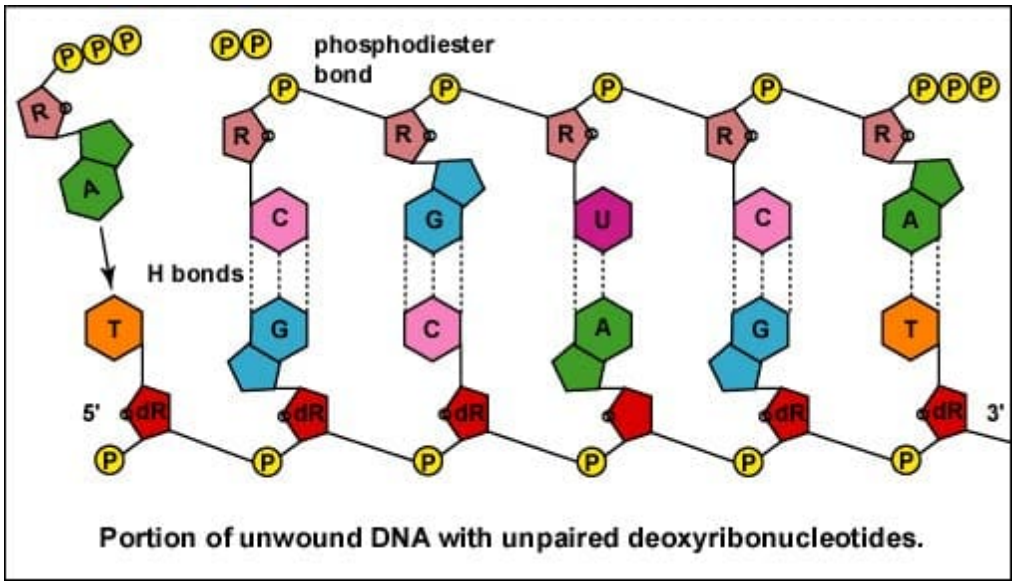
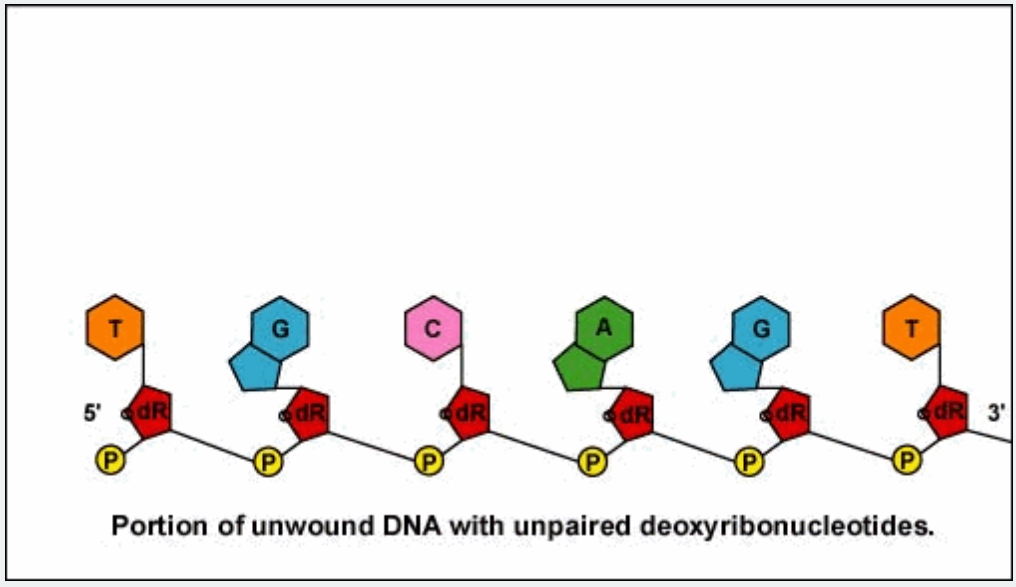


Figure 19.7A.5: Transcription of mRNA Complementary to DNA. RNA is synthesized by complementary base pairing of free ribonucleotides with the deoxyribonucleotides of a gene. The ribonucleotides are then covalently bonded together by phosphodiester bonds, the energy being supplied by the cleavage of two phosphate groups from the ribonucleotide triphosphate.The enzyme responsible for transcription is RNA polymerase (not shown here)

As the RNA polymerase moves down the DNA, the previous stretch of DNA again pairs with its complementary strand. This process continues until the RNA polymerase encounters a "stop" signal or transcription terminator at the end of the gene. This causes the completed mRNA to drop off the gene.

Transcription of mRNA Complementary to DNA



Once the RNA polymerase/sigma factor complex recognizes the correct promoter, the sigma factor dissociate from the RNA polymerase and the enzyme begins to unwind the helix of the DNA creating a region of nonpaired deoxyribonucleotides that serve as a template for RNA synthesis. Transcription is under control of the enzyme RNA polymerase which is not shown here.

Once the RNA polymerase moves beyond the promotor region, a new molecule of RNA polymerase can bind to the promotor and start a new round of transcription. In this way, a single gene can be transcribed multiple times.

YouTube movie illustrating DNA replication, transcription, and translation.

YouTube movie illustrating transcription.

YouTube movie illustrating complementary base pairing during transcription.

YouTube movie illustrating transcription and translation.

YouTube movie illustrating transcription and protein assembly.

YouTube movie illustrating transcription in bacteria

Transcription is summarized in Figs. 6 and 7.

There are 22 amino acids that can be encoded by the genetic information carried on mRNA. The mRNA molecule is divided up into codons. A codon is a series of three consecutive mRNA bases coding for one specific amino acid. The various codons and the amino acids for which they code are shown in Table 19.7A.16.8.1. There are 64 codons. One codon, AUG, also serves as a start codon to initiate translation, and three codons, UAG, UAA, and UGA, function as stop or nonsense codons to terminate translation. (Alternative start codons are different from the standard AUG codon and are found occasionally in both prokaryotes and eukaryotes.)

Table 19.7A.16.8.1: The Genetic Code - Codons

	U	C	A	G	
U	UUU = Phe UUC = Phe UUA = Leu UUG = Leu	UCU = Ser UCC = Ser UCA = Ser UCG = Ser	UAU = Tyr UAC = Tyr UAA = Stop UAG = Stop	UGU = Cys UGC = Cys UGA = Stop UGG = Trp	**U** **C** **A** **G**
C	CUU = Leu CUC = Leu CUA = Leu CUG = Leu	CCU = Pro CCC = Pro CCA = Pro CCG = Pro	CAU = His CAC = His CAA = Gln CAG = Gln	CGU = Arg CGC = Arg CGA = Arg CGG = Arg	**U** **C** **A** **G**
A	AUU = Ile AUC = Ile AUA = Ile AUG = Met	ACU = Thr ACC = Thr ACA = Thr ACG = Thr	AAU = Asn AAC = Asn AAA = Lys AAG = Lys	AGU = Ser AGC = Ser AGA = Arg AGG = Arg	**U** **C** **A** **G**
G	GUU = Val CUC = Val GUA = Val GUG = Val	GCU = Ala GCC = Ala GCA = Ala GCG = Ala	GAU = Asp GAC = Asp GAA = Glu GAG = Glu	GGU = Gly GGC = Gly GGA = Gly GGG = Gly	**U** **C** **A** **G**
	Phe = phenylalanine *Leu = leucine* *Ile = isoleucine* *Met = methionine* *Val = valine*	*Ser = serine* *Pro = proline* *Thr = threonine* *Ala = alanine* *Tyr = tyrosine*	*His = histidine* *Gln = glutamine* *Asn = asparagine* *Lys = lysine* *Asp = aspartic acid*	*Glu = glutamic acid* *Cys = cysteine* *Trp = tryptophan* *Arg = arginine* *Gly = glycine*	
AUG = start codon, UAA, UAG, and UGA = stop (nonsense) codons					

In bacteria, a mRNA can be monocistronic or polycistronic. A monocistronic mRNA is a transcript of a single gene. A polycistronic mRNA carries a transcript of multiple genes, often involved in a single biochemical pathway. Groups of related genes that are transcribed together to form a polycistronic mRNA are known as operons. There are also specific genes along the DNA from which each of the different transfer RNAs (tRNAs) and the ribosomal RNAs (rRNAs) are transcribed.

Most mRNAs in prokaryotes have a half-life on the order of a few minutes. Molecules of rRNA and tRNA, on the other hand,

are much more stabile. Because rRNA and tRNA are highly folded molecules, unlike mRNA, they are much more resistant to degradation by ribonucleases. Once transcribed, the mRNA can be translated into protein.

Transcription in Eukaryotic Cells

Transcription is more complex in eukaryotic cells than in those that are prokaryotic. Activator proteins bind to genes known as enhancers which help determine which genes are switched on and speed up transcription. Repressor proteins bind to genes called silencers which interfere with activator proteins and slow down transcription. Coactivators, adapter molecules which coordinate signals from activator and repressor proteins, relay this information to basal factors which then position RNA polymerase at the start of the coding region of the gene to begin transcription.

Once the actual transcription begins, ribonucleotides containing 3 phosphate groups form hydrogen bonds through the process of complementary base pairing with the exposed deoxyribonucleotides on the unwound strand that is to be transcribed. The ribonucleotides are then covalently bonded together by phosphodiester bonds, the energy being supplied by the cleavage of two phosphate groups from the ribonucleotide triphosphate (Figure $19.7A.16$.8B.5). (The phosphodiester bond refers to the phosphate on the 5'C of the newly inserted nucleotide covalently bonding to the 3'C of the last ribonucleotide in the mRNA chain.)

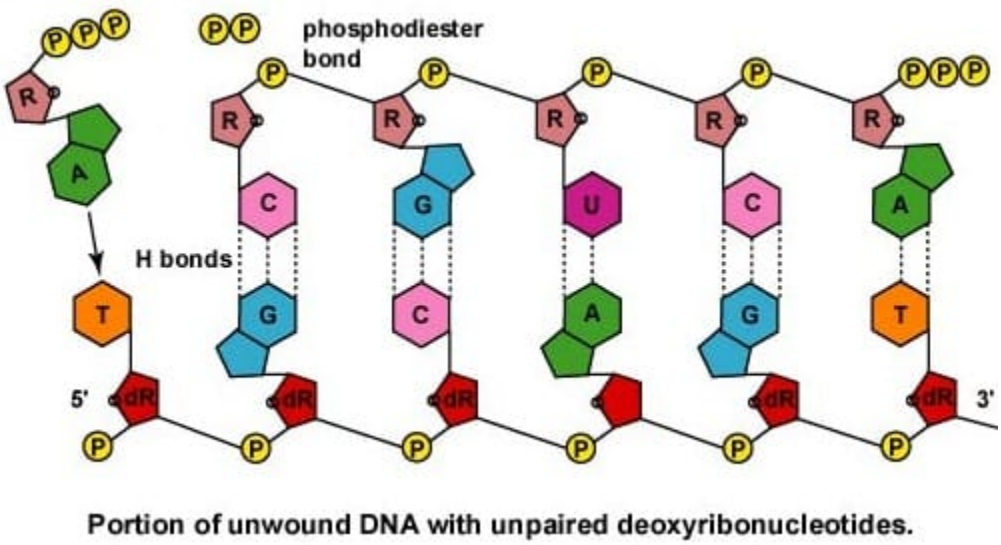


Figure $19.7A.18$.6B.5: Transcription of mRNA Complementary to DNA. RNA is synthesized by complementary base pairing of free ribonucleotides with the deoxyribonucleotides of a gene. The ribonucleotides are then covalently bonded together by phosphodiester bonds, the energy being supplied by the cleavage of two phosphate groups from the ribonucleotide triphosphate.The enzyme responsible for transcription is RNA polymerase (not shown here)

Unlike prokaryotes, most genes in higher eukaryotic cells contain large amounts - as much as 98% in the human genome - of regionscalled introns that are not part of the code for the final protein. These are interspersed among the coding regions or exons that actually code for the final protein.

RNA polymerase copies both the exons and the introns to form what is called precursor mRNA or pre-mRNA. Early in transcription, a cap in the form of an unusual nucleotide, 7-methylguanylate, is added to the 5' end of the pre-mRNA. This cap helps ribosomes attach for translation. As transcription is nearly completed, a series of 100-250 adenine ribonucleotides called a poly-A tail is added to the 3' end of the pre-mRNA. This poly-A tail is thought to help transport the mRNA out of the nucleus and may stabilize the mRNA against degradation in the cytoplasm. After transcription of the precursor mRNA, non-protein coding regions (introns) are excised and coding regions (exons) are joined together by complexes of ribonucleoproteins called spliceosomes to produce what is termed mature mRNA as shown in Figure $19.7A.9$. This process is called RNA processing.

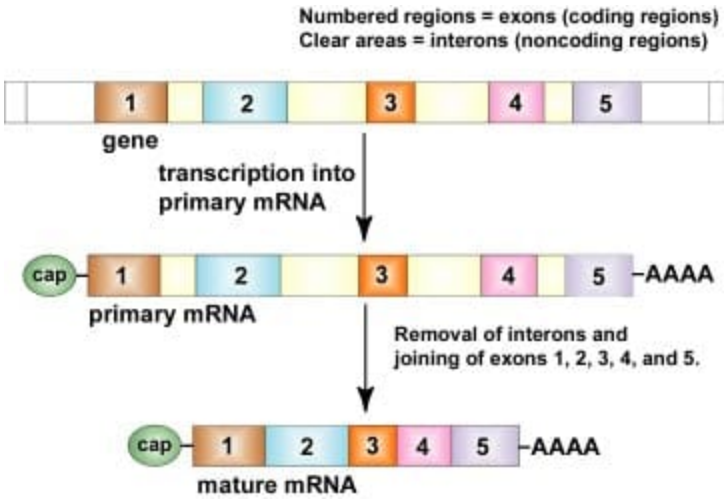


Figure 19.7A.9: mRNA Processing in Eukaryotic Cells (Excision of Interons and Joining of Exons). During processing of the precursor mRNA, interons are excised and exons are joined together to produce a mature mRNA that can be translated into protein.

GIF animation illustrating RNA processing.

YouTube movie illustrating DNA replication, transcription, and translation.

YouTube movie illustrating transcription.

YouTube movie illustrating complementary base pairing during transcription.

YouTube movie illustrating transcription and translation.

YouTube movie illustrating transcription and protein assembly.

YouTube movie illustrating RNA processing in eukaryotic cells #1.

YouTube movie illustrating RNA processing in eukaryotic cells #2.

The mature mRNA then passes through the pores in the nuclear membrane to be translated into protein by tRNA on eukaryotic 80S ribosomes (composed of 60S and 40S subunits) in a manner similar to prokaryotes.

The mRNA molecule is divided up into codons. A codon is a series of three consecutive mRNA bases coding for one specific amino acid. The various codons and the amino acids for which they code are shown in Figure 19.7A.8. There are 64 codons. One codon, AUG, also serves as a start codon to initiate translation, and three codons, UAG, UAA, and UGA, function as stop or nonsense codons to terminate translation. (Alternative start codons are different from the standard AUG codon and are found occasionally in both prokaryotes and eukaryotes.)

In addition to the genes that are transcribed into mRNA to be translated into polypeptides and proteins, there are also specific genes in the DNA from which each of the different transfer RNAs (tRNAs) and the ribosomal RNAs (rRNAs) are transcribed.

Once transcribed, the mRNA can be translated into protein.

As mentioned above, introns make up the majority of DNA in higher eukaryotic cells and for decades was considered to be "junk DNA" accumulated over millions of years of evolution. Over recent years however, it has been discovered that much of this intergenic DNA, although it does not code for protein synthesis, is transcribed into functional molecules of RNA with names such as antisense RNA microRNA, and riboswitch RNA that play important roles in whether or not a protein is actually made.

Antisense RNA is RNA transcribed off of the strand of DNA complementary to the one being transcribed into mRNA. In other

words, it is an RNA molecule complementary to a mRNA and as such may complementary base pair with the mRNA and prevents it from being translated into protein.

MicroRNA, often transcribed from intron DNA, folds over upon itself to resemble double-stranded RNA, a form of RNA produced by many viruses during their life cycle. Viral double-stranded RNA activates a host defense mechanism that degrades that viral RNA. The MicroRNA frequently binds to mRNA and tricks this defense mechanism into degrading that mRNA so it can not be translated into protein.

Riboswitch RNA, often transcribed from introns, exists in an inactive form until a specific target chemical binds. The binding of the target chemical turns the riboswitch RNA to an active form that can be translated into a specific protein.

Summary

1. During protein synthesis, the order of nucleotide bases along a gene gets transcribed into a complementary strand of mRNA which is then translated by tRNA into the correct order of amino acids for that polypeptide or protein.
2. The order of deoxyribonucleotide bases along the DNA determines the order of amino acids in the proteins, that is, its primary structure.
3. Because certain amino acids can interact with other amino acids, the order of amino acids for each protein determines its final three-dimensional shape, which in turn determines the function of that protein.
4. Messenger RNA (mRNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene.
5. Although genes are present on both strands of DNA, only one strand is transcribed for any given gene.
6. The enzyme RNA polymerase transcribes DNA.
7. To initiate transcription in bacteria, a variety of proteins called sigma factors bind to RNA polymerases. This complex can then bind to a specific DNA sequence called the promoter located along the DNA prior to the coding region of the gene. The promotor determines what region of the DNA and which strand of DNA will be transcribed into RNA.
8. Like DNA polymerase, RNA polymerase can only synthesize nucleic acid in a 5' to 3' direction while "reading" a DNA template in the 3' to 5' direction.
9. Once the RNA polymerase/sigma factor complex recognizes the correct promoter, the sigma factor dissociate from the RNA polymerase and the enzyme begins to unwind the helix of the DNA creating a region of nonpaired deoxyribonucleotides that serve as a template for RNA synthesis.
10. During transcription, ribonucleotides hydrogen bond through the process of complementary base pairing with the exposed deoxyribonucleotides on the unwound strand that is to be transcribed. The ribonucleotides are then covalently bonded together by phosphodiester bonds.
11. This process continues until the RNA polymerase encounters a "stop" signal or transcription terminator at the end of the gene.
12. A single gene can be transcribed multiple times.
13. The mRNA molecule is divided up into codons. A codon is a series of three consecutive mRNA bases coding for one specific amino acid.
14. Three codons, UAG, UAA, and UGA, function as stop or nonsense codons to terminate translation.
15. In bacteria, a mRNA can be monocistronic or polycistronic. A monocistronic mRNA is a transcript of a single gene; a polycistronic mRNA carries a transcript of multiple genes, often involved in a single biochemical pathway. Once transcribed, the mRNA can be translated into protein by tRNA on 70S ribosomes (composed of 50S and 30S subunits).
16. Transcription is more complex in eukaryotic cells than in those that are prokaryotic. Activator proteins bind to genes known as enhancers which help determine which genes are switched on and speed up transcription. Repressor proteins bind to genes called silencers which interfere with activator proteins and slow down transcription. Coactivators, adapter molecules which coordinate signals from activator and repressor proteins, relay this information to basal factors which then position RNA polymerase at the start of the coding region of the gene to begin transcription.
17. Most genes in higher eukaryotic cells contain regions called introns that are not part of the code for the final protein. These are interspersed among the coding regions or exons that actually code for the final protein.
18. After transcription of the precursor mRNA, non-protein coding regions (introns) are excised and coding regions (exons) are joined together by complexes of ribonucleoproteins called spliceosomes to produce what is termed mature mRNA.
19. The mature mRNA then passes through the pores in the nuclear membrane to be translated into protein by tRNA on 80S ribosomes (composed of 60S and 40S subunits) in a manner similar to prokaryotes.

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19.7B: Translation

Define translation.

- Briefly describethe function of the following in terms of translation:

a. 30S ribosomal subunit
b. ribosome binding site
c. start codon
d. initiation complex
e. 50S ribosomal subunit
f. tRNA
g. aminoacyl-tRNA
h. anticodon
i. P-site of ribosome
j. A-site of ribosome
k. E-site of ribosome
l. peptidyl transferase
m. nonsense (stop) codon
n. release factors

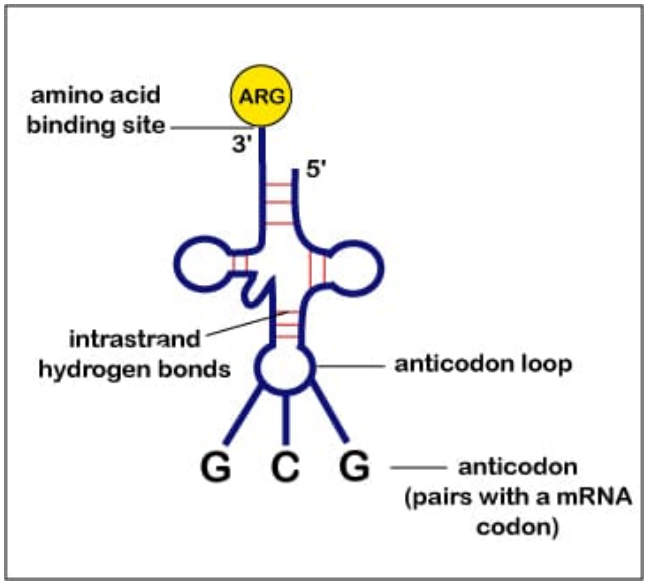


Figure $19.7B.3$).

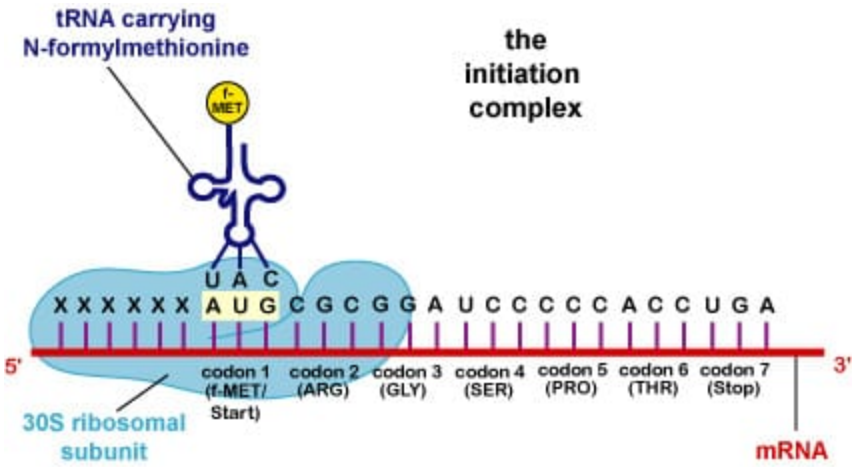


Figure $19.7B.3$: Translation of mRNA by tRNA: Formation of the Initiation Complex. To initiate translation, a 30S ribosomal subunitbinds to a short nucleotide sequence on the mRNA called the ribosome binding site. However, translation doesn't usually begin until the 30S ribosomal subunit reaches the first AUG sequence in the mRNA. For this reason, **AUG is known as the start codon**. At this point, an initiation complex composed of the 30S subunit, a tRNA having the anticodon UAC and carrying an altered form of the amino acid methionine (N-formylmethionine or f-Met), and proteins called initiation factors is formed.

Flash Animation illustrating the formation of the initiation complex during translation

html5 version of animation for iPad illustrating the formation of the initiation complex during translation

A 50S ribosomal subunit then attaches to the initiation complex and the initiation factors leave. This forms the 70S ribosome. (see Figure $19.7B.4$).

Flash Animation illustrating the joining of the 50S ribosomal subunit to the initiation complex during translation

html5 version of animation for iPad illustrating the joining of the 50S ribosomal subunit to the initiation complex during translation

The joining of individual amino acids to form a protein or polypeptide is known as the elongation phase of translation. There are three sites on the 70S ribosome. The A or acceptor or aminoacyl site is where an aminoacyl-tRNA first attaches. The P or peptide site is where a tRNA is temporarily holding the growing amino acid chain as the next codon in the mRNA is being read. The E or exit site is where the uncharged tRNA that has released its amino acid exits the ribosome. During peptide bond formation, the amino acid chain or peptide moves from the tRNA at the P-site and forms a peptide bond with the new amino acid attached to the tRNA at the A-site. The peptide bond is formed by a ribozyme , an enzyme composed of the 23S rRNA itself, called peptidyl transferase. The now uncharged tRNA at the P-site leaves the ribosome through the E-site to eventually pick up a new amino acid and be recycled. Meanwhile, the 70S ribosome moves a distance of one codon down the mRNA through a process called translocation to allow decoding of the next codon in the message (see Figure $19.7B.5$A - 5F). The growing polypeptide chain actually passes through a tunnel in the 50S ribosomal subunit.

Flash Animation illustrating the insertion of amino acids into a growing protein during translation

html5 version of animation for iPad illustrating the insertion of amino acids into a growing protein during translation

This process continues over and over again in the 5' to 3' direction until the ribosome hits a stop codon. A stop codon is a series of three mRNA bases coding for no amino acid and thus terminates the protein chain. UAA, UAG, UGA are the three stop codons

in the genetic code. Stop codons do not code for an amino acid because a tRNA cannot recognize them.

Proteins called release factors free the protein from the tRNA and the two ribosomal subunits come apart to be recycled (see Figure $19.7B.5$F). During this elongation process, the protein has assumed its three-dimensional functional shape. Proteins called chaperonins assist in the protein folding.

Flash Animation illustrating the termination of translation

html5 version of animation for iPad illustrating the termination of translation

Flash Animation summarizing translation.

html5 version of animation for iPad summarizing translation.

YouTube movie illustrating DNA replication, transcription, and translation.

YouTube movie illustrating transcription and translation.

YouTube movie illustrating translation (1)

YouTube movie illustrating translation (2)

Once the ribosome is clear of the ribosome binding site and the AUG start codon, another 30S ribosomal subunit attaches to the ribosome binding site of the mRNA to initiate another round of translation. In this way, multiple copies of a protein can be produced from a single molecule of mRNA. A mRNA with multiple ribosomes attached is known as a polyribosome or polysome .

Summary

1. During translation, specific tRNAs pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA genetic "message."
2. This is done by the anticodon portion of the tRNA molecules complementary base pairing with the codons along the mRNA.
3. Transfer RNA (tRNA) is a three-dimensional, inverted cloverleaf-shaped molecule of RNA.
4. At the top, or 3' end, a specific amino acid can be attached to a specific tRNA by means of specific enzymes called aminoacyl-tRNA synthetases.
5. At the bottom loop of the cloverleaf is a series of three unpaired tRNA bases called the anticodon. An anticodon is a series of three tRNA bases complementary to a mRNA codon.
6. The anticodons of some tRNAs are able to recognize more than one codon because the tRNA's recognition of the third nucleotide of the codon is not always precise, however, the right amino acid is still inserted because there are 61 codons that code for the 22 different amino acids.
7. To initiate translation in prokaryotic cells, a 30S ribosomal subunit binds to a short nucleotide sequence on the mRNA called the ribosome binding site.
8. AUG is known as the start codon. At this point, an initiation complex composed of the 30S subunit, a tRNA having the anticodon UAC and carrying an altered form of the amino acid methionine (N-formylmethionine or f-Met), and proteins called initiation factors is formed. A 50S ribosomal subunit then attaches to the initiation complex and the initiation factors leave.

This forms the 70S ribosome.

9. The A or acceptor or aminoacyl site of the ribosome is where an aminoacyl-tRNA first attaches.
10. The P or peptide site of the ribosome is where a tRNA is temporarily holding the growing amino acid chain as the next codon in the mRNA is being read.
11. The E or exit site of the ribosome is where the uncharged tRNA that has released its amino acid exits the ribosome.
12. During peptide bond formation, the amino acid chain or peptide moves from the tRNA at the P-site and forms a peptide bond with the new amino acid attached to the tRNA at the A-site.
13. A stop codon is a series of three mRNA bases coding for no amino acid and thus terminates the protein chain. UAA, UAG, UGA are the three stop codons in the genetic code. (Stop codons do not code for an amino acid because a tRNA cannot recognize them.)
14. A mRNA with multiple ribosomes attached is known as a polyribosome or polysome.

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19.8: Enzyme Regulation

Briefly compare the genetic control of enzyme activity in bacteria with control of enzyme activity through feedback inhibition.

- Briefly compare an inducible operon with a repressible operon.
- Briefly compare competitive inhibition with noncompetitive inhibition.

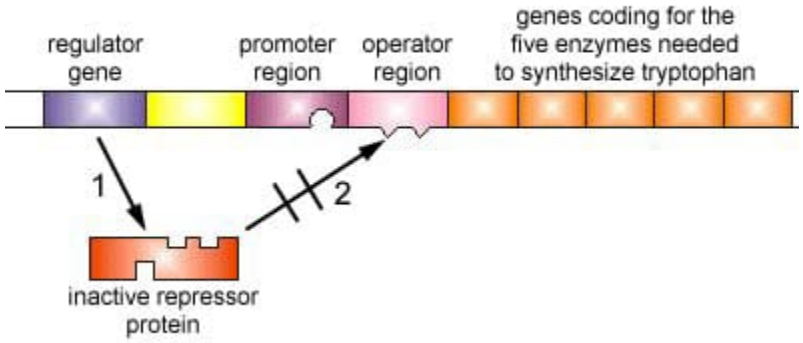


Figure 19.8.6).

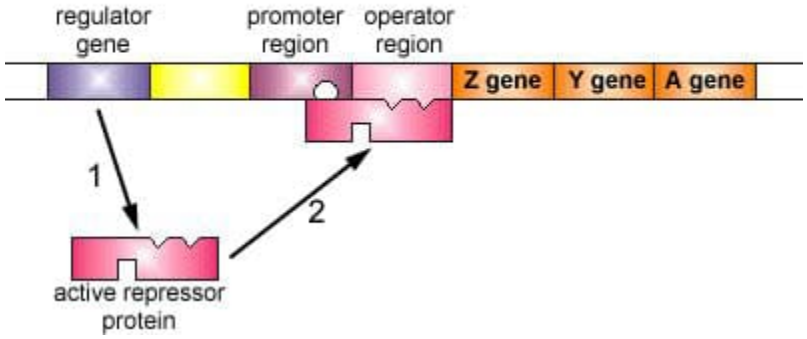


Figure 19.8.5***:*** *An Inducible Operon in the Absence of an Inducer (The Lactose Operon). Step 1: The regulator gene codes for an active repressor protein.*
Step 2: The repressor protein then binds to the operator region of the operon.

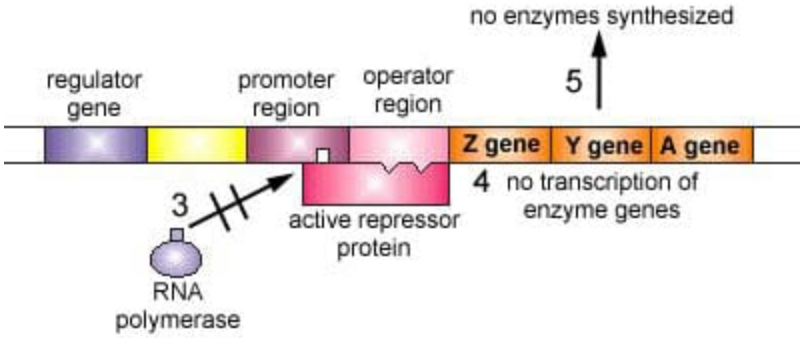
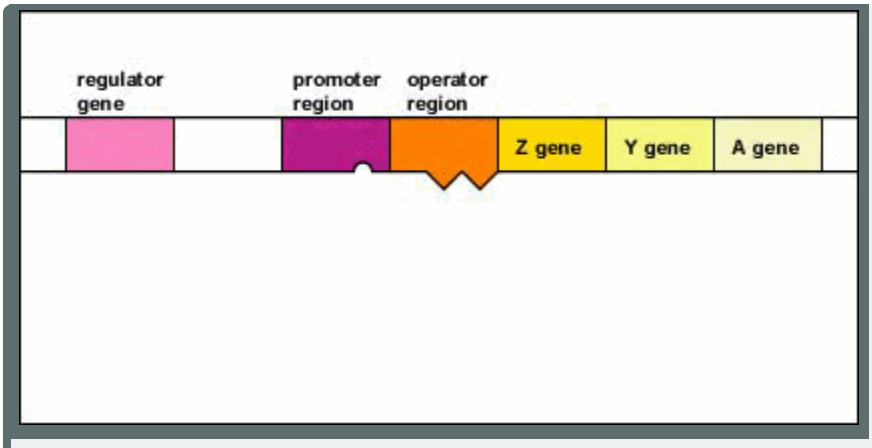


Figure 19.8.8: An Inducible Operon in the Presence of an Inducer (The Lactose Operon)Step 5: Since the inactive repressor protein is unable to bind to the operator region, RNA polymerase (the enzyme responsible for the transcription of genes) is now able to bind to the promoter region of the operon. Step 6: RNA polymerase is now able to transcribe the three enzyme genes (Z, Y, and A) into mRNA. Step 7: With the transcription of these genes, the three enzymes needed for the bacterium to utilize the sugar lactose are now synthesized. (The Z gene codes for beta-galactosidase, an enzyme that breaks down lactose into glucose and galactose. The Y gene codes for permease, an enzyme which transports lactose into the bacterium. The A gene codes for transacetylase, an enzyme which is thought to aid in the release of galactosides.)

The regulator gene codes for an active repressor protein.

- The repressor protein then binds to the operator region of the operon.
- With the active repressor protein bound to the operator region, RNA polymerase (the enzyme responsible for the transcription of genes) is unable to bind to the promoter region of the operon.
- If RNA polymerase does not bind to the promoter region, the three enzyme genes (Z, Y, and A) are not transcribed into mRNA.
- Without the transcription of the three enzyme genes, the three enzymes needed for the utilization of the sugar lactose by the bacterium are not synthesized.



- The regulator gene codes for an active repressor protein.
- Lactose, the inducer molecule binds to the active repressor protein.
- The binding of the inducer alters the shape of the allosteric repressor causing it to become inactivated.
- The inactivated repressor protein is then unable to bind to the operator region of the operon.
- Since the inactive repressor protein is unable to bind to the operator region, RNA polymerase (the enzyme responsible for the transcription of genes) is now able to bind to the promoter region of the operon.
- RNA polymerase is now able to transcribe the three enzyme genes (Z, Y, and A) into mRNA.
- With the transcription of these genes, the three enzymes needed for the bacterium to utilize the sugar lactose are now synthesized. (The Z gene codes for beta-galactosidase, an enzyme that breaks down lactose into glucose and galactose. The Y gene codes for permease, an enzyme which transports lactose into the bacterium. The A gene codes for transacetylase, an enzyme which is thought to aid in the release of galactosides.)

Genetic Control: Activators

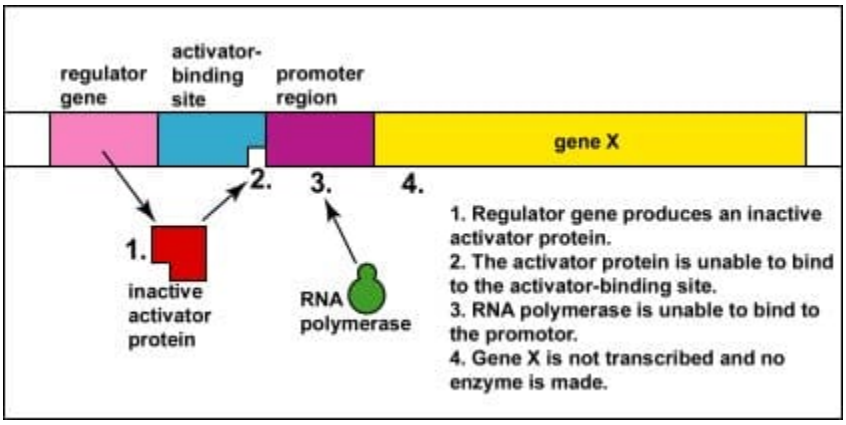
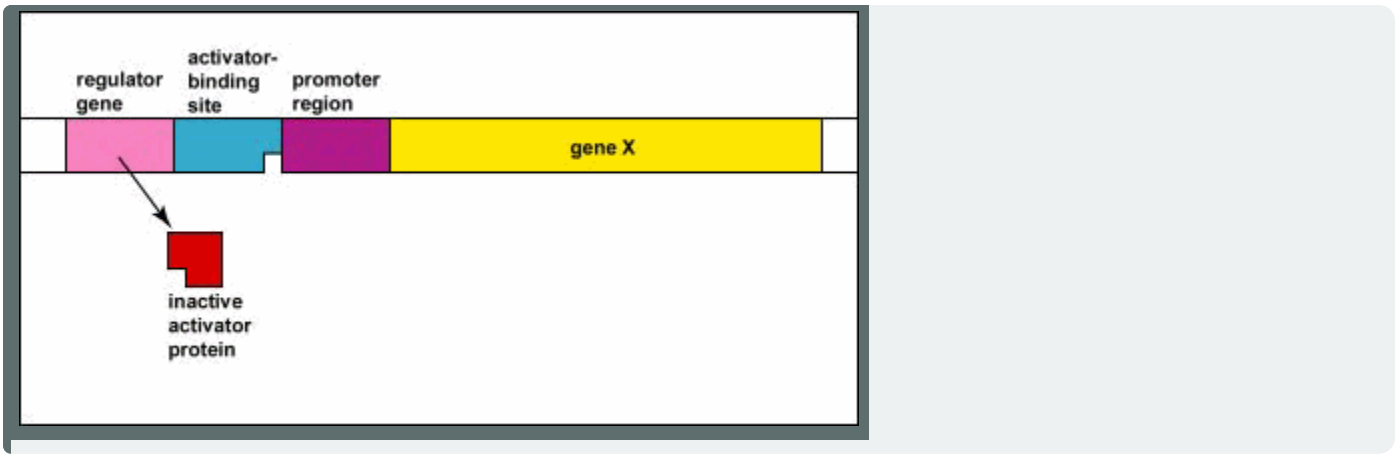
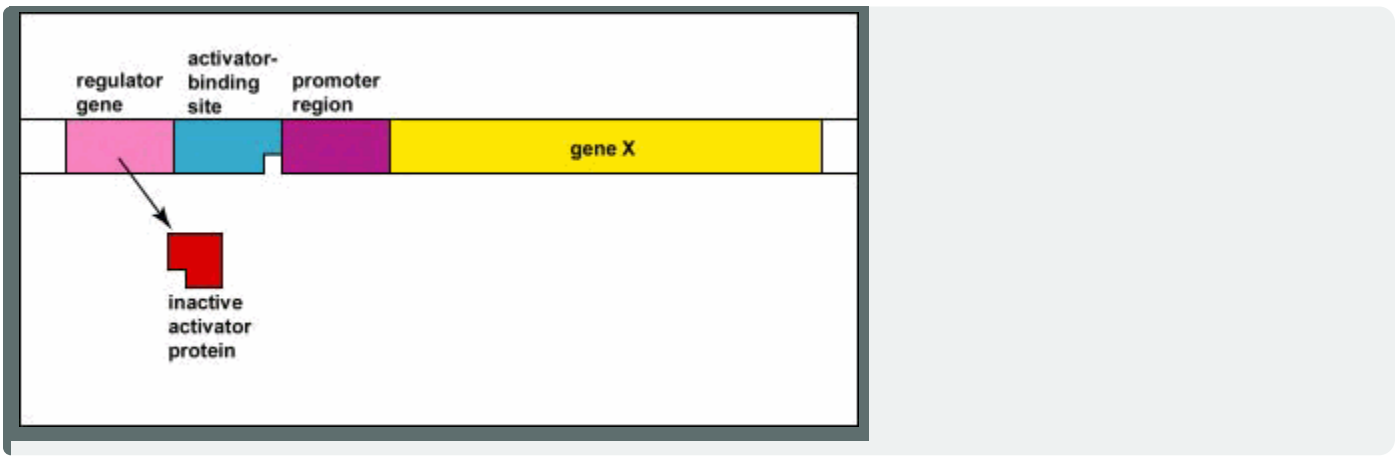


Figure 19.8.11: An Activator Protein in the Presence of an Inducer, Step-2





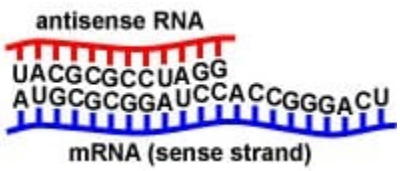
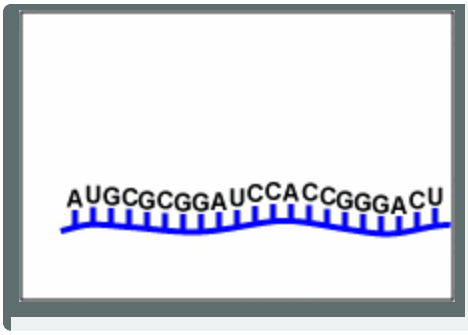


Figure 19.8.12: Antisense RNA. During translational control of enzyme synthesis, bacteria produce antisense RNA that is complementary to the mRNA coding for the enzyme. When the antisense RNA binds to the mRNA by complementary base pairing, the mRNA cannot be translated into protein and the enzyme is not made.



Feedback Inhibition

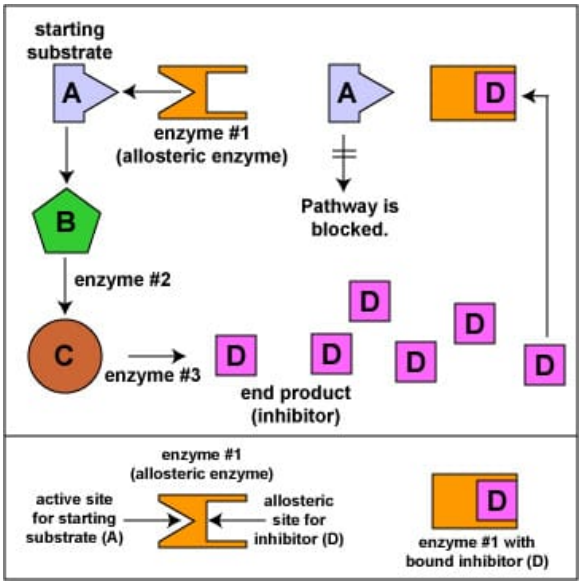


Figure 19.8.13: Noncompetitive Inhibition with Allosteric Enzymes. When the end product (inhibitor) of a pathway combines with the allosteric site of the enzyme, this alters the enzyme's active site so it can no longer bind to the starting substrate of the pathway. This blocks production of the end product.

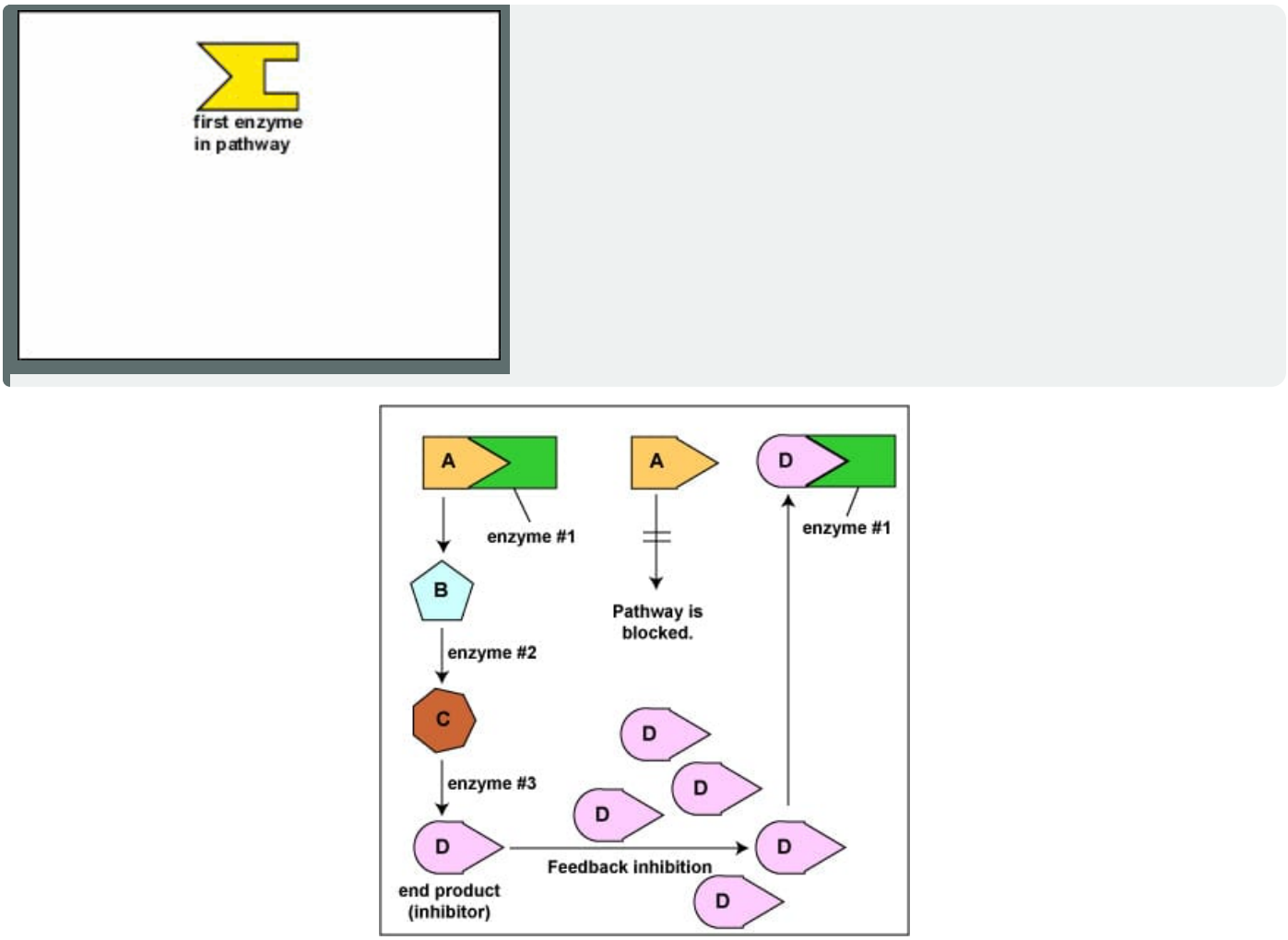


Figure 19.8.14: Competitive Inhibition of Enzyme Activity. The end product (inhibitor) of a pathway binds to the active site of the first enzyme in the pathway. As a result, the enzyme can no longer bind to the starting substrate of the pathway.

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19.9: Mutation

Define the following:

a. genotype
b. phenotype
c. allele
d. mutation
e. spontaneous mutation
f. induced mutation

- Describe two different mechanisms of spontaneous mutation and, in terms of protein synthesis, describe the four possible results that may occur as a result of these mutations.
- Briefly describe three ways chemical mutagens work.
- Compare ultraviolet radiation and gamma radiation in terms of how they induce mutation.

As we learned earlier, the sequence of deoxyribonucleotide bases in the genes that make up a bacterium's DNA determines the order of amino acids in the proteins and polypeptides made by that organism. This order of DNA bases constitutes the organism's genotype. A particular organism may possess alternate forms of some genes. Such alternate forms of genes are referred to as alleles. The physical characteristics an organism possesses, based on its genotype and the interaction with its environment, make up its phenotype.

Mutation is an error during DNA replication that results in a change in the sequence of deoxyribonucleotide bases in the DNA. Spontaneous mutation occurs naturally (a normal mistake rate) about one in every million to one in every billion divisions and is probably due to low level natural mutagens normally present in the environment. Induced mutation is caused by mutagens, substances that cause a much higher rate of mutation.

Mechanisms of Mutation

There are two general mechanisms of mutation.

1. Substitution of a nucleotide (point mutations): substitution of one deoxyribonucleotide for another during DNA replication (see Figure 19.9.1). This is the most common mechanism of mutation. Substitution of one nucleotide for another is a result of tautomeric shift, a rare process by which the hydrogen atoms of a deoxyribonucleotide base move in a way that changes the properties of its hydrogen bonding. For example, a shift in the hydrogen atom of adenine enables it to form hydrogen bonds with cytosine rather than thymine. Likewise, a shift in the hydrogen atom in thymine allows it to bind with guanine rather than adenine.
2. Deletion or addition of a nucleotide (frameshift mutations): deletion or addition of a deoxyribonucleotide during DNA replication (see Figure 19.9.2 and Figure 19.9.3).

Results of Mutation

One of four things can happen as a result of these mechanisms of mutation and the resulting change in the deoxyribonucleotide base sequence mentioned above:

- A missense mutation occurs. This is usually seen with a single substitution mutation and results in one wrong codon and one wrong amino acid (Figure 19.9.4).

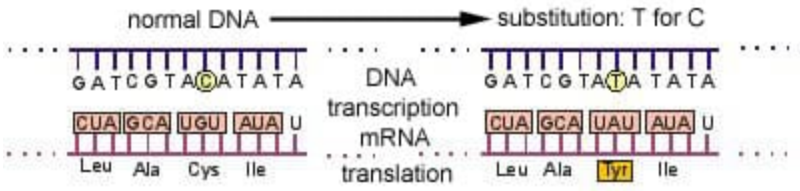


Figure 19.9.4***:*** *Results in one wrong codon and one wrong amino acid.*

- A nonsense mutation occurs. If the change in the deoxyribonucleotide base sequence results in transcription of a stop or nonsense codon, the protein would be terminated at that point in the message (Figure 19.9.5).

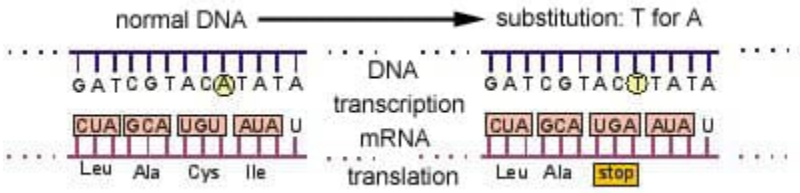


Figure 19.9.5***:*** *Results in a "stop" codon and premature termination of the protein.*

- A sense mutation occurs. This is sometimes seen with a single substitution mutation when the change in the DNA base sequence results in a new codon still coding for the same amino acid (Figure 19.9.6). (With the exception of methionine, all amino acids are coded for by more than one codon.)

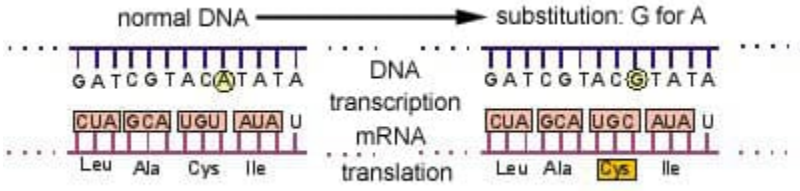


Figure 19.9.6***:*** *Results in a new codon which still codes for the same amino acid.*

- A frameshift mutation occurs. This is seen when a number of DNA nucleotides not divisible by three is added or deleted. Remember, the genetic code is a triplet code where three consecutive nucleotides code for a specific amino acid. This causes a reading frame shift and all of the codons and all of the amino acids after that mutation are usually wrong (Figure 19.9.7); frequently one of the wrong codons turns out to be a stop or nonsense codon and the protein is terminated at that point.

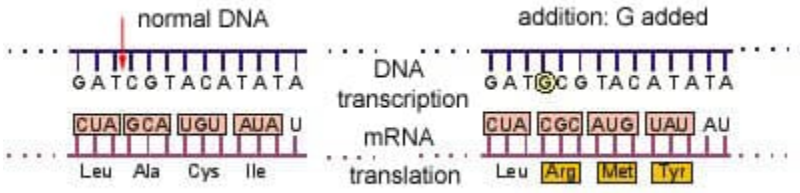


Figure 19.9.7***:*** *Results in a reading frame shift. All codons and all amino acid after the shift are usually wrong.*

YouTube Video

This interactive element is not available in this format. Visit the link or scan the QR code to access it online.

View this YouTube Video online

YouTube movie illustrating frameshift mutations (www.youtube.com/v/o-otJTJ3N_E)

Induced mutation is caused by mutagens, substances that cause a much higher rate of mutation. Chemical mutagens generally work in one of three ways.

1. Some chemical mutagens, such as nitrous acid and nitrosoguanidine work by causing chemical modifications of purine and pyrimidine bases that alter their hydrogen-bonding properties. For example, nitrous acid converts cytosine to uracil which then forms hydrogen bonds with adenine rather than guanine.

2. Other chemical mutagens function as base analogs. They are compounds that chemically resemble a nucleotide base closely enough that during DNA replication, they can be incorporated into the DNA in place of the natural base. Examples include 2-amino purine, a compound that resembles adenine, and 5-bromouracil, a compound that resembles thymine. The base analogs, however, do not have the hydrogen-bonding properties of the natural base.

3. Still other chemical mutagens function as intercalating agents. Intercalating agents are planar three-ringed molecules that are about the same size as a nucleotide base pair. During DNA replication, these compounds can insert or intercalate between adjacent base pairs thus pushing the nucleotides far enough apart that an extra nucleotide is often added to the growing chain during DNA replication. An example is ethidium bromide.

When under stress from antibiotics or other harmful chemicals, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium 10,000 times as fast as the mutation rate that occurs during normal binary fission. This causes a sort of hyperevolution where mutation acts as a self defense mechanism for the bacterial population by increasing the chance of forming an antibiotic-resistant mutant that is able to survive at the expense of the majority of the population. (Remember that most mutations are harmful to a cell; see SOS repair below.)

Certain types of radiation can also function as mutagens.

1. Ultraviolet Radiation. The ultraviolet portion of the light spectrum includes all radiations with wavelengths from 100 nm to 400 nm. It has low wave length and low energy. The microbicidal activity of ultraviolet (UV) light depends on the length of exposure: the longer the exposure the greater the cidal activity. It also depends on the wavelength of UV used. The most cidal wavelengths of UV light lie in the 260 nm - 270 nm range where it is absorbed by nucleic acid.

In terms of its mode of action, UV light is absorbed by microbial DNA and causes adjacent thymine bases on the same DNA strand to covalently bond together, forming what are called thymine-thymine dimers (see Figure 19.9.8). As the DNA replicates, nucleotides do not complementary base pair with the thymine dimers and this terminates the replication of that DNA strand. However, most of the damage from UV radiation actually comes from the cell trying to repair the damage to the DNA by a process called SOS repair. In very heavily damaged DNA containing large numbers of thymine dimers, a process called SOS repair is activated as kind of a last ditch effort to repair the DNA. In this process, a gene product of the SOS system binds to DNA polymerase allowing it to synthesize new DNA across the damaged DNA. However, this altered DNA polymerase loses its proofreading ability resulting in the synthesis of DNA that itself now contains many misincorporated bases. (Most of the chemical mutagens mentioned above also activate SOS repair.)

YouTube Video

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View this YouTube Video online

Video illustrating frameshift mutations (www.youtube.com/v/azszodOhXqk)

2. Ionizing Radiation. Ionizing radiation, such as X-rays and gamma rays, has much more energy and penetrating power than ultraviolet radiation. It ionizes water and other molecules to form radicals (molecular fragments with unpaired electrons) that can break DNA strands and alter purine and pyrimidine bases.

Summary

1. The sequence of deoxyribonucleotide bases in the genes that make up an organism's DNA determines the order of amino acids in the proteins and polypeptides made by that organism. This order of DNA bases constitutes the bacterium's genotype.
2. A particular organism may possess alternate forms of some genes referred to as alleles.
3. The physical characteristics an organism possesses, based on its genotype and the interaction with its environment, make up an organism's phenotype.
4. Mutation is an error during DNA replication that results in a change in the sequence of deoxyribonucleotide bases in the DNA.
5. Spontaneous mutation occurs naturally (a normal mistake rate) about one in every million to one in every billion divisions and is probably due to low level natural mutagens normally present in the environment; induced mutation is caused by mutagens, substances that cause a much higher rate of mutation.
6. There are two primary mechanisms of mutation: substitution of a deoxyribonucleotide (point mutations) whereby one deoxyribonucleotide is substituted for another during DNA replication; and deletion or addition of a nucleotide (frameshift mutations) where deoxyribonucleotides are either added or deleted during DNA replication. Point mutations are most common.
7. There are four possible results from a mutation: missense, nonsense, sense, or frameshift.
8. A missense mutation usually seen with a single substitution mutation and results in one wrong codon and one wrong amino acid.
9. A nonsense mutation occurs when the change in the deoxyribonucleotide base sequence results in transcription of a stop or nonsense codon. The protein would be terminated at that point in the message.
10. A sense mutation occurs is sometimes seen with a single substitution mutation when the change in the DNA base sequence results in a new codon still coding for the same amino acid.
11. A frameshift mutation occurs when a number of DNA nucleotides not divisible by three is added or deleted. This causes a reading frame shift and all of the codons and all of the amino acids after that mutation are usually wrong; frequently one of the wrong codons turns out to be a stop or nonsense codon and the protein is terminated at that point.
12. When under stress from harmful chemicals, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium 10,000 times as fast as the mutation rate that occurs during normal binary fission. This causes a hyperevolution where mutation acts as a self defense mechanism for the bacterial population by increasing the chance of forming an antibiotic-resistant mutant that is able to survive at the expense of the majority of the population.

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19.E: Review of Molecular Genetics (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

19.1: Polypeptides and Proteins

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe an amino acid and state what all amino acids have in common.
2. State what makes one amino acid different from another.
3. Describe how amino acids are joined by peptide bonds.
4. Compare the terms peptide, polypeptide, and protein.
5. Due to hydrogen bonds that form between the oxygen atom of one amino acid and the nitrogen atom of another, this gives the protein or polypeptide the two-dimensional form of an alpha-helix or a beta-pleated sheet. This best describes:
   a. the primary structure of a protein
   b. the secondary structure of a protein
   c. the tertiary structure of a protein
   d. the quaternary structure of a protein
6. In some cases, such as with antibody molecules and hemoglobin, several polypeptides may bond together to form a quaternary structure. This best describes:
   a. the primary structure of a protein
   b. the secondary structure of a protein
   c. the tertiary structure of a protein
   d. the quaternary structure of a protein
7. The actual order of the amino acids in the protein that is determined by DNA. This best describes:
   a. the primary structure of a protein
   b. the secondary structure of a protein
   c. the tertiary structure of a protein
   d. the quaternary structure of a protein
8. In globular proteins such as enzymes, the long chain of amino acids becomes folded into a three-dimensional functional shape. This is because certain amino acids with sulfhydryl or SH groups form disulfide (S-S) bonds with other amino acids in the same chain. Other interactions between R groups of amino acids such as hydrogen bonds, ionic bonds, covalent bonds, and hydrophobic interactions also contribute to this structure. This best describes:
   a. the primary structure of a protein
   b. the secondary structure of a protein
   c. the tertiary structure of a protein
   d. the quaternary structure of a protein
9. Define gene.
10. Describe how the order of nucleotide bases in DNA ultimately determines the final three-dimensional shape of a protein or polypeptide.

19.2: Enzymes

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define enzyme and state how enzymes are able to speed up the rate of chemical reactions.
2. Fill in the blanks.

   Many enzymes require a nonprotein cofactor to assist them in their reaction. In this case, the protein portion of the

enzyme, called an _____ , combines with the cofactor to form the whole enzyme or _____ . Some cofactors are ions such as Ca^{++}, Mg^{++}, and K^{+}; other cofactors are organic molecules called _____ which serve as carriers for chemical groups or electrons. Anything that an enzyme normally combines with is called a _____ .

3. Briefly describe a generalized enzyme-substrate reaction, state the function of an enzyme's active site, and describe how an enzyme is able to speed up chemical reactions.
4. State four characteristics of enzymes.
5. State how the following will affect the rate of an enzyme reaction.
   a. increasing temperature
   b. decreasing temperature
   c. pH
   d. salt concentration

19.3: Deoxyribonucleic Acid (DNA)

Questions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State the 3 basic parts of a deoxyribonucleotide.
2. State which nitrogenous bases are purines.
   a. cytosine and thymine
   b. adenine and guanine
3. In the complement base pairing of nucleotides, adenine can form hydrogen bonds with _____ and guanine can form hydrogen bonds with _____ .
4. State what is meant by the 3' (3-prime) and 5' (5-prime) ends of a DNA strand.
5. State why DNA can only be synthesized in a 5' to 3' direction.
6. What is a nucleosome?
7. State whether the following characteristics are seen in prokaryotic or eukaryotic DNA.
   a. linear chromosomes
   b. no nuclear membrane
   c. presence of nucleosomes
   d. no mitosis
   e. produce gametes through meiosis

19.4: DNA Replication in Prokaryotic Cells

Questions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the process of DNA replication.
2. State what enzyme carries out the following functions during DNA replication.
   a. Unwinds the helical DNA by breaking the hydrogen bonds between complementary bases.
   b. Synthesizes a short RNA primer at the beginning of each origin of replication.
   c. Adds DNA nucleotides to the RNA primer.
   d. Digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides.
   e. Links the DNA fragments of the lagging strand together.
3. The DNA strand replicated in short fragments called Okazaki fragments is called the:
   a. lagging strand
   b. leading strand

19.5: DNA Replication in Eukaryotic Cells and the Eukaryotic Cell Cycle

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the process of DNA replication.
2. State which cell type has multiple origins of replication in its genome.
   a. prokaryotic
   b. eukaryotic
3. Identify the following stages of mitosis.
   a. During this final stage of mitosis, the nuclear membrane and nucleoli reform, cytokinesis is nearly complete, and the chromosomes eventually uncoil to chromatin.
   b. Refers to all stages of the cell cycle other than mitosis. During this phase, cellular organelles double in number, the DNA replicates, and protein synthesis occurs. The chromosomes are not visible and the DNA appears as uncoiled chromatin.
   c. During this phase of mitosis, the nuclear membrane fragmention is complete and the duplicated chromosomes line up along the cell's equator.
   d. During the first stage of mitosis, the chromatin condenses and the chromosomes become visible. Also the nucleolus disappears, the nuclear membrane fragments, and spindle fibers are assembled.
   e. During this phase of mitosis, diploid sets of daughter chromosomes move toward opposite poles of the cell and cytokinesis (cytoplasmic cleavage) begins.

19.6: Ribonucleic Acid (RNA)

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State the 3 basic parts of a ribonucleotide.
2. State 3 ways RNA differs from DNA.
3. Copies the genetic information in the DNA by complementary base pairing and carries this "message" to the ribosomes where the proteins are assembled. This best describes:
   a. tRNA
   b. mRNA
   c. rRNA
4. Picks up specific amino acids, transfers the amino acids to the ribosomes, and insert the correct amino acids in the proper place according to the mRNA message. This best describes:
   a. tRNA
   b. mRNA
   c. rRNA

19.7: Polypeptide and Protein Synthesis

Questions: Transcription

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define transcription.
2. Match the following with their role in transcription.

_____ The end of a strand of nucleic acid that has a hydroxyl (OH) group on the number 3 carbon of the deoxyribose or ribose and is not linked to another nucleotide.
_____ The covalent bond that links ribonucleotides together to form RNA.
_____ The portion of DNA that contains the actual message for protein synthesis.
_____ A molecule synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA coding for a polypeptide or protein.
_____ A series of three consecutive mRNA bases coding for one specific amino acid.

_____ A segment of DNA that determines what region of the DNA and which strand of DNA will be transcribed into RNA.
_____ The enzyme that initiates transcription, joins the RNA nucleotides together, and terminates transcription.
_____ A "stop" signal at the end of a gene that causes the completed mRNA to drop off the gene.

a. mRNA
b. 3' end
c. 5' end
d. RNA polymerase
e. phosphodiester bond
f. promoter
g. leader sequence
h. coding sequence
i. transcription terminator
j. codon

3. Match the following with their role in transcription in eukaryotic cells.

_____ The RNA synthesized after RNA polymerase copies both the exons and the interons of a gene.
_____ The RNA produced after non-protein coding regions (introns) are excised and coding regions (exons) are joined together by complexes of ribonucleoproteins called spliceosomes.
_____ An unusual nucleotide, 7-methylguanylate, that is added to the 5' end of the pre-mRNA early in transcription. It helps ribosomes attach for translation.
_____ Non-protein coding regions of DNA that are not part of the code for the final protein that are interspersed among the coding regions of DNA in most genes of higher eukaryotic cells.
_____ The coding regions of DNA in most genes of higher eukaryotic cells that actually code for the final protein.
_____ A series of 100-250 adenine ribonucleotides that is added to the 3' end of the pre-mRNA. This series of nucleotides is thought to help transport the mRNA out of the nucleus and may stabilize the mRNA against degradation in the cytoplasm.

a. introns
b. exons
c. precurser mRNA
d. cap
e. poly-A tail
f. mature mRNA

4. What amino acid sequence would the DNA base sequence 5' ATAGCCACC 3'code for? Hint: see Figure 8.

Questions: Translation

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define translation.
2. Match the following with their role in translation.

_____ A series of three tRNA bases complementary to a mRNA codon.
_____ The ribozyme that forms peptide bonds between amino acids during translation.
_____ The ribosomal subunit that binds to mRNA to form the initiation complex.
_____ The ribosomal site where an aminoacyl-tRNA first attaches during translation.
_____ The ribosomal site where the growing amino acid chain is temporarily being held by a tRNA as the next codon in the mRNA is being read.
_____ A complex of an amino acid and a tRNA molecule.
_____ The sequence of bases on mRNA to which a 30S or 40S ribosomal subunit first attaches.
_____ A series of three mRNA bases coding for no amino acid and thus terminates the protein chain: UAA, UAG, UGA.
_____ A complex consisting of a 30S or 40S ribosomal subunit, a tRNA having the anticodon UAC and carrying an altered form of the amino acid methionine (N-formylmethionine or f-Met), and proteins called initiation factors.
_____ A three-dimensional, inverted cloverleaf-shaped molecule about 70 nucleotides long to which a specific amino acid can be attached; transports amino acids to the ribosome during translation.

a. 30S or 40S ribosomal subunit

b. ribosome binding site
c. initiation complex
d. 50S or 60S ribosomal subunit
e. tRNA
f. aminoacyl-tRNA
g. anticodon
h. P-site of ribosome
i. A-site of ribosome
j. peptidyl transferase
k. nonsense (stop) codon
l. release factors
m. start cocon

3. What amino acid sequence would the DNA base sequence AAAGAGCCT code for? Hint: see Fig. 2.

19.8: Enzyme Regulation

Questions

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Matching

_____ Regulatory proteins that block transcription of mRNA by binding to a portion of DNA called the operator that lies downstream of a promoter.

_____ A molecule that alters the shape of the regulatory protein in a way that blocks its binding to the operator and thus permits transcription.

_____ Regulatory proteins that promote transcription of mRNA.

_____ A molecule that alters the shape of the regulatory protein to a form that can bind to the operator and block transcription.

_____ Producing antisense RNA that is complementary to the mRNA coding for the enzyme. When the antisense RNA binds to the mRNA by complementary base pairing, the mRNA cannot be translated into protein and the enzyme is not made.

_____ The induction or repression of enzyme synthesis by regulatory proteins that can bind to DNA and either block or enhance the function of RNA polymerase.

_____ The inhibitor is the end product of a metabolic pathway that is able to bind to a second site (the allosteric site) on an enzyme. Binding of the inhibitor to the allosteric site alters the shape of the enzyme's active site thus preventing binding of the first substrate in the metabolic pathway.

_____ The inhibitor is the end product of an enzymatic reaction. That end product is also capable of reacting with the enzyme's active site and prevents the enzyme from binding its normal substrate.

A. activators
B. competitive inhibition
C. corepressors
D. genetic control
E. inducer
F. noncompetitive inhibition
G. repressors
H. translational control

2. Describe how the *lac* operon in *E. coli* functions as an inducible operon.

19.9: Mutation

Study the material in this section and then write out the answers to these question. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

   _____The sequence of deoxyribonucleotide bases in the genes that make up a organism's DNA.
   _____ An error during DNA replication that results in a change in the sequence of deoxyribonucleotide bases in the DNA.
   _____ Alternate forms of a gene.
   _____ Mutations caused by mutagens, substances that cause a high rate of mutation.
   _____ The physical characteristics of an organism.

   a. genotype
   b. phenotype
   c. allele
   d. mutation
   e. spontaneous mutation
   f. induced mutation
2. Describe 2 different mechanisms of spontaneous mutation.
3. Match the following:

   _____ This is usually seen with a single substitution mutation and results in one wrong codon and one wrong amino acid
   _____ If the change in the deoxyribonucleotide base sequence results in transcription of a stop, the protein is terminated at that point in the message.
   _____ This is sometimes seen with a single substitution mutation when the change in the DNA base sequence results in a new codon still coding for the same amino acid.
   _____ This is seen when a number of DNA nucleotides not divisible by three is added or deleted and all of the codons and all of the amino acids after that addition or deletion are usually wrong.

   a. sense mutation
   b. nonsense mutation
   c. frameshift mutation
   d. missense mutation
4. Briefly describe 3 ways chemical mutagens work.
5. Compare ultraviolet radiation and gamma radiation in terms of how they induce mutation.
6. As a result of a substitution mutation, a DNA base triplet AGA is changed to AGG. State specifically what effect this would have on the resulting protein (see Figure 9).
7. A third triplet in a bacterial gene is TTT. A substitution mutation changes it to ATT. State specifically what effect this would have on the resulting protein (see Figure 9).

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BACTERIA

Clostridium tetani

Escherichia coli

Haemophilus influenzae

Helicobacter pylori

Neisseria gonorrhoeae

Neisseria meningitidis

Staphylococcus aureus

Streptococcus pneumoniae

Streptococcus pyogenes

Vibrio cholerae

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Clostridium tetani

Organism

- *Clostridium tetani* is a moderately-sized Gram-positive, endospore-producing bacillus.
- Motile with a peritrichous arrangement of flagella.
- Produce round, terminal endospores that give the bacterium a "tennis-racquet" appearance.
- An obligate anaerobe*(def)*.

Habitat

- Colonizes the intestinal tract in humans and animals.

Source

- Endospores found in fertile soil or feces.

Epidemiology

- Endospores are found in most soils and in the intestinal tract of many animals and humans.
- Although exposure to endospores is commom, disease is uncommon except in countries with poor medical care and vaccination compliance.
- Fewer than 50 cases per year in the U.S.; most in elderly individuals with waning immunity.
- It is estimated that there is more than one million cases a year worldwide, with a mortality rate of 20% to 50%.
- Most deaths occur in neonates and originates from infection of umbilical stumps in mothers that have no immunity.

Clinical Disease

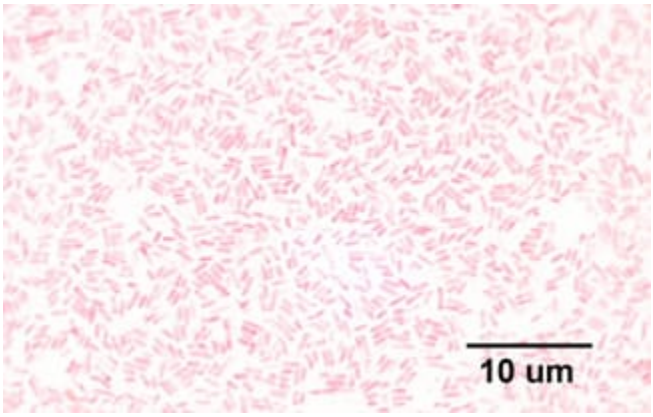
- Generalized tetanus is most common. Typical presenting symptoms include lockjaw and sardonic smile, arrising as a result of spastic paralysis of the masseter muscles and other facial muscles. Difficulty in swallowing, drooling, irritability, and persistent back spasms are other early symptoms. When the autonomic nervous system is involved, symptoms include perfuse sweating, hyperthermia , cardiac arrhythmias , and fluctuations in blood pressure.
- Cephalic infection primarily infects the head and involves cranial nerves.
- Localized infection involves the muscles in the area of primary injury.
- Neonatal tetanus is in newborns and originates from infection of umbilical stumps in mothers that have no immunity.
- The infection begins when endospores of *C. tetani* enter an anaerobic wound . Since the bacterium is an obligate anaerobe, an anaerobic environment is needed for the endospores to germinate and the vegetative bacteria to grow. Vegetative bacteria eventually produce tetanospasmin, the toxin responsible for symptoms of tetanus.

** CDC Recommendations for tetanus prophylaxis.

From Tetanus, by Daniel J Dire, MD, FACEP, FAAEM, Associate Professor, Department of Emergency Medicine, University of Alabama at Birmingham and Daniel J Dire, MD, FACEP, FAAEM, is a member of the following medical societies: American Academy of Clinical Toxicology, American Academy of Emergency Medicine, Association of Military Surgeons of the US, and Society for Academic Emergency Medicine

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Escherichia coli



Gram Stain of *Escherichia coli*. Note gram-negative (pink) bacilli.

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Haemophilus influenzae

Organism

- *Haemophilus influenzae* is a small Gram-negative bacillus.
- It is nonmotile.
- Facultative anaerobe *(def)*.
- Fastideous growth needs. Requires enrichments for growth.

Habitat

- Mucous membranes of the respiratory tract in humans.

Source

- The patient's own mucous membranes or transmitted patient-to-patient.

Epidemiology

- *Haemophilus parainfluenzae* and nonencapsulated *H. influenzae* typically colonize the upper respiratory tract in humans within the first few months of life. These bacteria typically cause sinusitis, otitis media *(def)*, bronchitis*(def)*, and pneumonia *(def)*.
- Encapsulated *H. influenzae*, primarily *H. influenzae* type b, is uncommon as normal flora of the upper respiratory tract but can be a common cause of serious infection in children.
- Until immunization of children against *H. influenzae* type b became routine in developed countries, this bacterium was the most common cause of pneumonia, septicemia*(def)*, meningitis *(def)*, and epiglottitis *(def)* in children under the age of four. Immunization has reduced the incidence of systemic infection by this bacterium 95%.

Clinical Disease

- *Haemophilus influenzae* does not cause influenza. Influenza is a viral infection.
- *Haemophilus parainfluenzae* and nonencapsulated *H. influenzae* typically cause sinusitis, otitis media *(def)*, bronchitis *(def)*, and pneumonia *(def)*.
- *H. influenzae* type b is the most common cause of pneumonia, septicemia *(def)*, meningitis *(def)*, epiglottitis *(def)*, and cellulitis in children under the age of four who are not immunized.

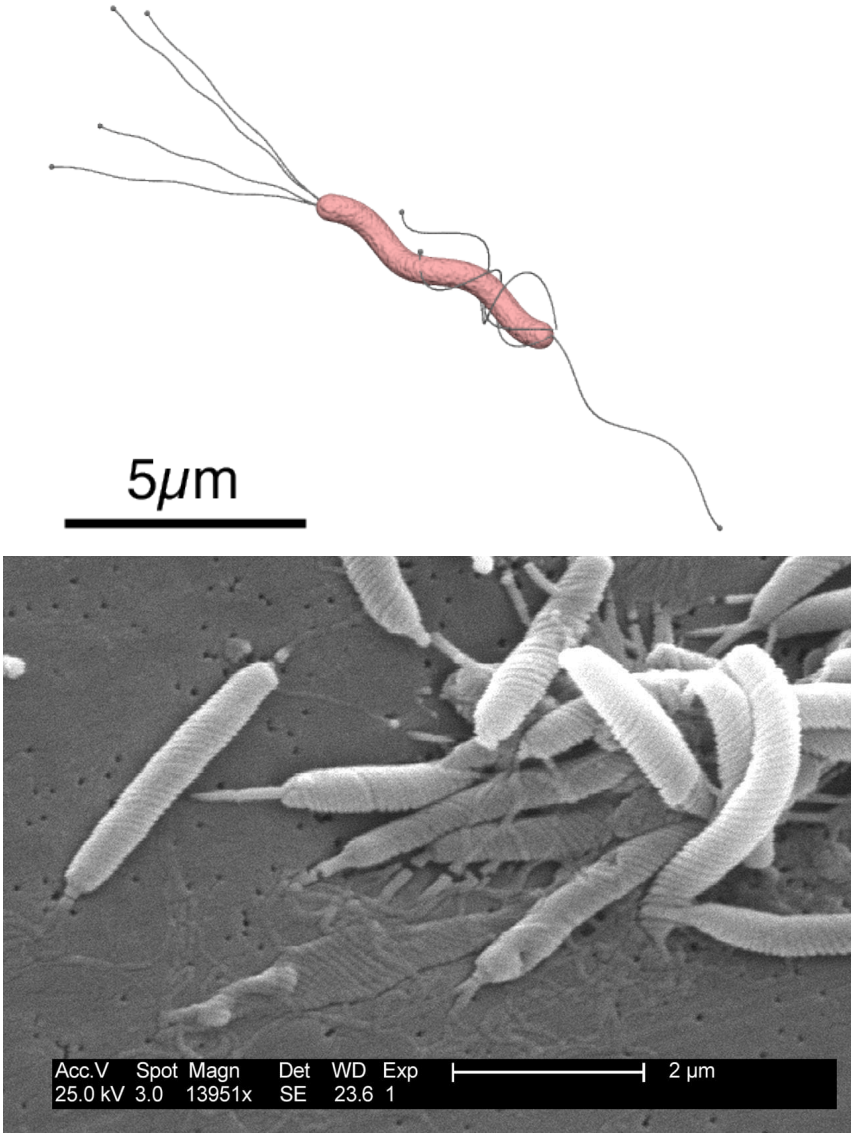
From *Haemophilus influenzae* Infections, by Mark R Schleiss, MD, Associate Professor, Department of Pediatrics, Division of Infectious Diseases, University of Cincinnati and Children's Hospital Research Foundation.

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Helicobacter pylori

Organism

- *Helicobacter* is a gram-negative spiral-shaped bacterium with polar flagella.
- Microaerophilic *(def)*.



*(left) Structure of Helicobacter pylori. (right) Scanning electron micrograph of **Helicobacter** bacteria (originally classified as Flexispira rappini, now deprecated). Obtained from the CDC Public Health Image Library. Image credit: CDC/Dr. Patricia Fields, Dr. Collette Fitzgerald (PHIL #5715), 2004.*

Habitat

- The human gastrointestinal tract is the primary source.

Source

- Person-to-person spread by the fecal-oral route.

Epidemiology

- In developing countries, 70%-90% of individuals are colonized by the age of 10; in developed countries, colonization is low during children but increases to around 45% in older adults.
- Between 70% and 90% of people with gastritis, peptic ulcers, or doedonal ulcers are infected with *H. pylori*.

Clinical Disease

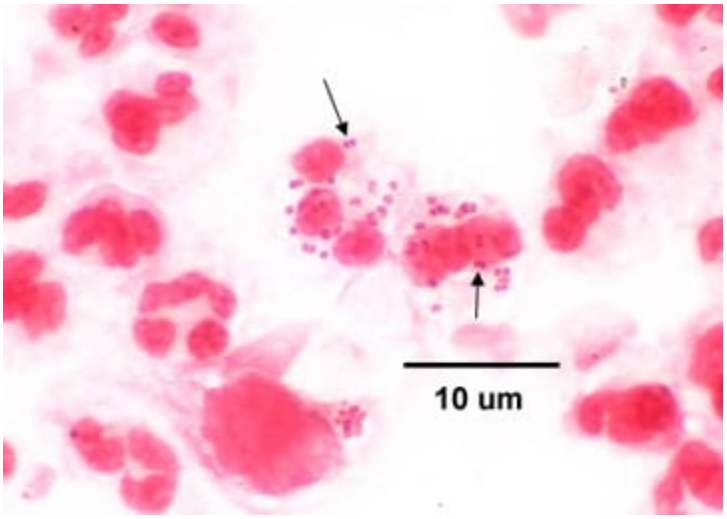
- Appears as gastritis *(def)*, peptic ulcers *(def)*, gastric adenocarcinoma *(def)*, and certain B-cell lymphomas *(def)*.
- Chronic gastritis is a risk factor for gastric carcinoma.

From *Helicobacter pylori* Infection, by Luigi Santacroce, MD, Assistant Professor, Department of Dentistry and Surgery, Section of General Surgery, Medical and Dentistry School, State University at Bari, Italy and Giuseppe Miragliotta, MD, Chairman, Professor, Section of Microbiology, University Hospital of Bari, Italy; Manoop S Bhutani, MD, Associate Professor of Medicine, Division of Gastroenterology, University of Texas Medical Branch at Galveston

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Neisseria gonorrhoeae

Positive GC smear for gonorrhea.



Note the *Neisseria gonorrhoeae* (gram-negative diplococci) inside the white blood cells.

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Neisseria meningitidis

Organism

- *Neisseria meningitidis* is a Gram-negative diplococcus, typically flattened where the cocci meet.
- Aerobic *(def)*.
- There are 13 serogroups of meningococci. Serogroups B and C commonly cause meningitis *(def)* and meningococcemia *(def)* in developed countries; serogroups Y and W135 typically cause pneumonia.

Habitat

- Humans are the only natural host.

Source

- Transmitted person-to-person by aerosolized respiratory tract secretions.

Clinical Disease

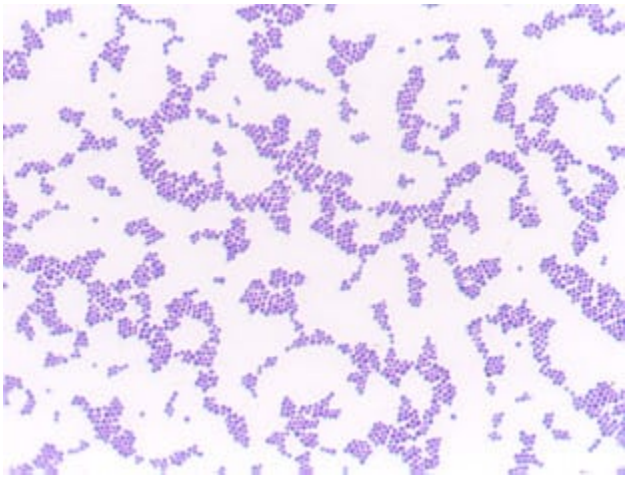
- There are between 2000 and 3000 cases of meningococcal meningitis per year in the U.S. A total of 2725 cases were reported to CDC in 1998.
- *N. meningitidis* infects the nasopharynx of humans causing a usually mild or subclinical upper respiratory infection. However in about 15% of these individuals, the organism invades the blood and disseminates, causing septicemia and from the there may cross the blood-brain barrier causing meningitis *(def)*. A petechial skin rash, caused by endotoxin in the blood, appears in about 75 percent of the septic cases and fatality rates for meningococcal septicemia are as high as 30 percent as a result of the shock cascade. A fulminating form of the disease, called Waterhouse-Frederichsen syndrome, can be fatal within several hours due to massive intravascular coagulation and resulting shock, probably a result of massive endotoxin release. *N. meningitidis* is especially dangerous in young children.
- Typical symptoms are headache, meningeal signs, and fever.
- Mortality is close to 100% if untreated; less than 10% with prompt and appropriate antibiotic therapy.

From Meningococcal Infections, by Thomas A Hoffman, MD, Professor, Department of Internal Medicine, Division of Infectious Diseases, Jackson Memorial Hospital, University of Miami.

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Staphylococcus aureus

Gram Stain of *Staphylococcus aureus*



Note gram-positive (purple) cocci in clusters.

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Streptococcus pneumoniae

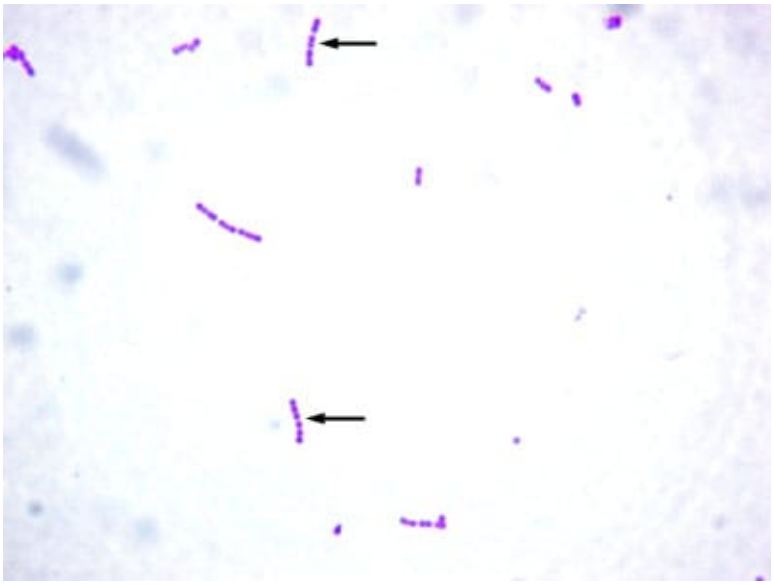
Streptococcus pneumoniae, or the pneumococcus, is a gram-positive lanceolate coccus usually appearing as a diplococcus, but occasionally appearing singularly or in short chains. Pneumococci are frequently found as normal flora of the nasopharynx of healthy carriers. From 10% to 40% of adults carry the bacterium in the nasopharynx. In the U.S., they are the most common cause of community-acquired pneumonia requiring hospitalization, causing around 500,000 cases per year and usually occurring as a secondary infection in the debilitated or immunocompromised host. The pneumococci also cause over 7,000,000 cases of otitis media per year, are the leading cause of sinusitis in people of all ages, are responsible for 500,000 cases of bacteremia, and 3000 cases of meningitis, being the most common cause of meningitis in adults and children over 4 years of age. Note gram-positive encapsulated diplococci. The large cells with the dark red nuclei are while blood cells.



Encapsulated Streptococcus pneumoniae. Encapsulated Streptococcus pneumoniae. © Gloria Delisle and Lewis Tomalty, authors. Licensed for use, ASM MicrobeLibrary.

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Streptococcus pyogenes



Note gram-positive (purple) cocci in chains (arrows).

Organism

- *Streptococcus pyogenes*, a group A beta streptococcus, is a Gram-positive coccus typically arranged in chains.
- Facultative anaerobe *(def)*.

Habitat

- Asymptomatic colonization of the upper respiratory tract in humans.

Source

- Pharyngitis is pread person to person primarily by respiratory droplets; skin infections are spread by direct contact with an infected person or through fomites *(def)*.

Epidemiology

- The group A beta hemolytic streptococci are responsible for most acute human streptococcal infections. Between 5% and 20% of children are asymptomatic carriers. The most common infection is pharyngitis *(def)* with the organism usually being limited to the mucous membranes and lymphatic tissue of the upper respiratory tract. Children are at greatest risk for infection.

Clinical Disease

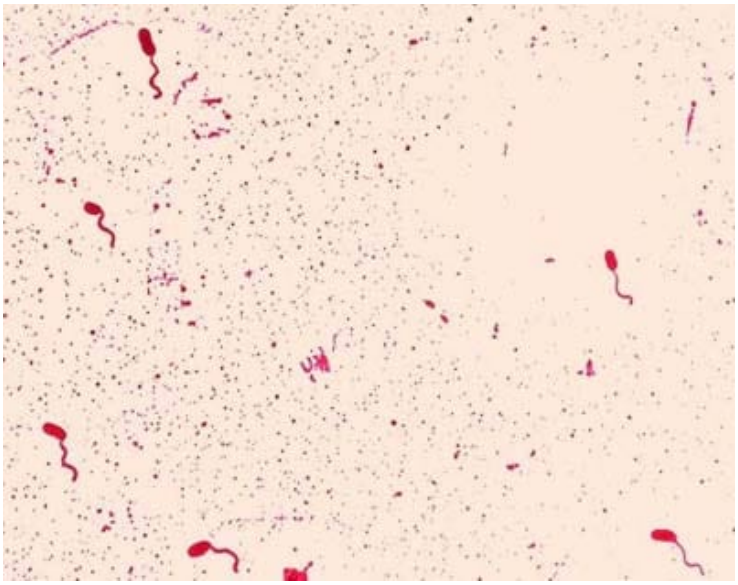
- The most common infection is pharyngitis (streptococcal sore throat) with the organism usually being limited to the mucous membranes and lymphatic tissue of the upper respiratory tract. From the pharynx, however, the streptococci sometimes spread to other areas of the respiratory tract resulting in laryngitis *(def)*, bronchitis *(def)*, pneumonia, and otitis media *(def)*.
- Occasionally, it may enter the lymphatic vessels or the blood and disseminate to other areas of the body, causing septicemia *(def)*, osteomyelitis *(def)*, endocarditis*(def)*, septic arthritis *(def)*, and meningitis *(def)*.
- If it enters injured skin, it may cause pyogenic *(def)* cutaneous infections such as impetigo , erysipelas *(def)*, orcellulitis *(def)*.
- Group A beta streptococcus infections can result in two autoimmune diseases *(def)*, rheumatic fever and acute glomerulonephritis, where antibodies made against streptococcal antigens cross react with joint membranes and heart valve tissue in the case of rheumatic fever, or glomerular cells and basement membranes of the kidneys in the case of acute glomerulonephritis.

- Certain strains of *S. pyogenes* cause invasive group A beta streptococcal infections. Each year in the U.S. there are between 750 and 1500 cases of necrotizing fasciitis where a streptococcal-coded protease called Exotoxin B destroys the muscle (myositis) or the muscle covering (necrotizing fasciitis). There are another 750 - 1500 cases of toxic shock-like syndrome *(def)* due to group A beta streptococci producing Streptococcal pyrogenic exotoxin (Spe).

From Streptococcus Group A Infections, by Sat Sharma, MD, FRCPC, FACP, FCCP, DABSM, Program Director, Associate Professor, Department of Internal Medicine, Divisions of Pulmonary and Critical Care Medicine, University of Manitoba; Site Coordinator of Respiratory Medicine, St Boniface General Hospital; and Godfrey Harding, MD, FRCPC, Program Director of Medical Microbiology, Professor, Department of Medicine, Section of Infectious Diseases and Microbiology, St Boniface Hospital, University of Manitoba, Canada.

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Vibrio cholerae



Monotrichous Flagellum of Vibrio cholerae. Courtesy of the Centers for Disease Control and Prevention.

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