

Chapter 43

The Immune System

Lecture Outline

Overview: Recognition and Response

- An animal must defend itself against **pathogens**, agents that cause disease.
 - Viruses, bacteria, fungi, and other pathogens infect a wide range of animals, including humans.
 - An animal body offers a ready source of nutrients, a protected setting for growth and reproduction, and a means of transport to new environments.
- Animals fight back in various ways.
 - Immune cells in the body fluids and tissues of most animals interact with and destroy pathogens.
 - Responses to infection include proteins that punch holes in bacterial membranes or block viruses from entering body cells.
- **Immune systems** help animals to avoid or limit many infections.
- **Innate immunity** is common to all animals. Such defenses are active immediately upon infection and are the same whether or not the pathogen has been encountered before.
 - External barriers, formed by the skin or shell, provide a barrier to pathogens.
 - Chemical secretions that trap or kill pathogens guard the body's entrances and exits.
 - The internal defenses include macrophages and other phagocytic cells that ingest and destroy pathogens.
- An animal's immune system must detect foreign particles and tissues that invade the body, distinguishing self from nonself.
 - This *molecular recognition* of nonself is accomplished by receptors that bind specifically to molecules from foreign cells or viruses.
- In innate immunity, a small preset group of receptor proteins bind to molecules or structures that are absent from animal bodies but common to a group of viruses, bacteria, or other pathogens.
 - Binding of an innate immune receptor to a foreign molecule activates internal defenses, enabling responses to a very broad range of pathogens.
- **Adaptive immunity** is found only in vertebrates.
 - Adaptive immune responses are activated after innate immune defenses and develop more slowly.
 - These adaptive defenses are enhanced by previous exposure to the infecting pathogen.
- Animals with adaptive immunity have a large number of receptors, each recognizing a feature typically found only on a particular molecule in a particular microbe.
 - As a result, adaptive immune systems detect pathogens with tremendous specificity.

Concept 43.1 In innate immunity, recognition and response rely on traits common to groups of pathogens.

Invertebrates have highly effective innate defenses.

- Insect exoskeletons are a first line of defense against infection.
- Composed largely of the polysaccharide chitin, the exoskeleton provides an effective barrier defense against most pathogens.
- A chitin-based barrier is also present in the insect intestine, where it blocks infection by many pathogens ingested with food.
 - **Lysozyme**, an enzyme that digests bacterial cell walls, also protects the digestive system.
- In insects, circulating cells called *hemocytes* travel through the hemolymph, the insect circulatory fluid.
 - Some hemocytes can **phagocytose** pathogens.
 - Other hemocytes trigger the production of chemicals that kill pathogens and entrap parasites.
- Hemocytes and other cells secrete *antimicrobial peptides* that bind to and destroy bacteria and fungi by disrupting their plasma membranes.
- Immune cells of insects bind to molecules found only in the outer layers of bacteria or fungi.
 - Fungal cell walls have unique polysaccharides, while bacterial cell walls contain combinations of sugars and amino acids not found in animal cells.
 - Insect immune cells secrete specialized recognition proteins, each of which binds to the macromolecule specific to a fungi or broad class of bacteria.
- Immune responses are distinct for different classes of pathogens.
- For example, when the fungus *Neurospora crassa* infects a fruit fly, pieces of the fungal cell wall bind a recognition protein.
 - Together, the complex activates the protein Toll, a receptor on the surface of hemocytes.
 - Signal transduction from the Toll receptor to the cell nucleus leads to synthesis of a particular set of antimicrobial peptides active against fungi.
- When the bacterium *Micrococcus luteus* infects a fly, a distinct recognition protein is activated, and the fly produces a different set of antimicrobial peptides.
- Because fruit flies secrete many distinct antimicrobial peptides in response to a single infection, it is difficult to study the activity of any one peptide.
 - Bruno Lemaitre and fellow researchers in France used modern genetic techniques to reprogram the fly immune system.
 - They found that the synthesis of a single type of antimicrobial peptide in the fly's body could provide an effective immune defense.
 - Furthermore, particular antimicrobial peptides act against pathogens from different subgroups.

The skin and mucous membrane provide first-line barriers to infection.

- In mammals, epithelial tissues block the entry of harmful viruses and bacteria.
- An invading microbe must penetrate the external barrier formed by the skin and mucous membranes, which line the digestive, respiratory, and genitourinary tracts.

- Mucous membranes produce *mucus*, a viscous fluid that traps pathogens and other particles.
- In the trachea, ciliated epithelial cells sweep out mucus with its trapped pathogens, preventing them from entering the lungs.
- Fungal and bacterial colonization is also inhibited by the washing action of saliva, tears, and mucous secretions that continually bathe the exposed epithelium.
- Beyond their role as a physical barrier, the skin and mucous membranes counter pathogens with chemical defenses.
 - Lysozymes in tears, saliva, mucous secretions, and tears kill bacteria that enter the upper respiratory tract or the openings around the eyes.
- Pathogens present in food or water, or those in swallowed mucus, must contend with the highly acidic environment of the stomach.
 - The acid destroys most pathogens before they can enter the intestinal tract.
- Secretions from sebaceous and sweat glands give the skin a pH ranging from 3 to 5, which is acidic enough to prevent colonization by many pathogens.

Phagocytic cells function early in infection.

- Pathogens that penetrate the first line of defense face are subject to phagocytosis.
- Phagocytic cells detect fungal or bacterial components through receptors that are very similar to the Toll receptor of insects.
 - Each mammalian **TLR**, or **Toll-like receptor**, binds to fragments of molecules characteristic of a set of pathogens.
 - TLR3 on the inner surface of endocytic vesicles is the sensor for double-stranded RNA, a form of nucleic acid characteristic of certain viruses.
 - TLR4 of immune cell plasma membranes recognizes lipopolysaccharide, a molecule found on the surface of many bacteria.
 - TLR5 recognizes flagellin, a protein that composes bacterial flagella.
- In each case, the recognized macromolecule is normally absent from the vertebrate body and is an essential component of a class of pathogens.
- After detecting invading pathogens, phagocytic cells engulf them and trap them in a vacuole.
 - The vacuole then fuses with a lysosome.
- Pathogens are destroyed within lysosomes in two ways.
 - Gases produced by the lysosome poison the engulfed pathogens.
 - Lysozyme and other enzymes degrade pathogen components.
- The two main types of phagocytic cells in the mammalian body are neutrophils and macrophages.
- Signals from infected tissues attract circulating **neutrophils**, which engulf and destroy pathogens.
- **Macrophages** are larger phagocytic cells. Some migrate throughout the body, whereas others reside permanently in organs and tissues where they are likely to encounter pathogens.
 - Some macrophages are located in the spleen, where pathogens become trapped.
- Two other types of phagocytic cells play a role in innate defense.
 - **Dendritic cells** populate tissues that are in contact with the environment, acting to stimulate the development of adaptive immunity.

- *Eosinophils* defend against large invaders, such as parasitic worms. These cells position themselves against the external wall of a parasite and discharge destructive enzymes.

Natural killer cells recognize and eliminate diseased cells in vertebrates.

- **Natural killer (NK) cells** circulate through the body and detect the abnormal array of surface proteins characteristic of some virus-infected and cancerous cells.
 - NK cells do not engulf stricken cells.
 - Instead, they release chemicals that lead to cell death, inhibiting further spread of the virus or cancer.
- Many cellular innate defenses of vertebrates involve the lymphatic system, a network that distributes lymph throughout the body.
 - Some macrophages reside in the lymph nodes, where they encounter and engulf pathogens that have flowed from the interstitial fluid into the lymph.
 - Dendritic cells reside outside the lymphatic system but migrate to lymph nodes after interaction with pathogens.
 - Within the lymph node, dendritic cells interact with other immune cells, stimulating adaptive immunity.

A variety of peptides and proteins attack pathogens.

- Pathogen recognition in mammals triggers the production and release of a variety of peptides and proteins that attack pathogens or impede their reproduction.
- Some of these molecules function like the antimicrobial peptides of insects, damaging broad groups of pathogens by disrupting membranes.
- Others, including the interferons and complement proteins, have activities unique to vertebrate immune systems.
- **Interferons** provide innate defenses by interfering with viral infection.
 - These proteins are secreted by virus-infected body cells and induce uninfected neighboring cells to produce substances that inhibit viral reproduction.
- The interferons limit the cell-to-cell spread of viruses, helping to control viral infection.
- Some white blood cells secrete a different type of interferon that helps activate macrophages, enhancing their phagocytic ability.
 - Interferons can be produced by recombinant DNA technology and have proven effective in the treatment of certain viral infections, such as hepatitis C.
- The **complement system** consists of roughly 30 proteins in blood plasma that circulate in an inactive state and are activated by substances on the surface of many pathogens.
 - Activation results in a cascade of biochemical reactions that lead to lysis of invading cells.
 - The complement system functions in inflammation as well as in adaptive defenses.

Damage to tissue triggers an inflammatory response.

- Damage to tissue by a physical injury or the entry of pathogens leads to the release of chemical signals that trigger a localized **inflammatory response**.
- One of the chemical signals of the inflammatory response is **histamine**, which is stored in the granules (vesicles) of **mast cells**, a type of connective tissues.
 - When injured, mast cells release histamine, which triggers both dilation and increased permeability of nearby capillaries.

- Activated macrophages and other cells discharge **cytokines**, signaling molecules that enhance the immune response.
 - Cytokines increase local blood supply and cause the characteristic redness and heat of inflammation.
 - Blood-engorged capillaries leak fluid into neighboring tissue, causing swelling.
- During inflammation, cycles of signaling and response transform the injured site.
 - Enhanced blood flow and vessel permeability aid in delivering clotting elements and antimicrobial proteins to the injured area.
 - Clotting marks the beginning of the repair process and helps block the spread of pathogens elsewhere.
 - Nearby endothelial cells secrete signals that attract neutrophils and macrophages.
- Increased blood flow and vessel permeability also increase the migration of phagocytic cells from the blood into the injured tissues.
 - The end result is an accumulation of *pus*, a fluid rich in white blood cells, dead pathogens, and cell debris.
- The body may also mount a systemic response to severe tissue damage or infection.
 - Injured cells secrete chemicals that stimulate the release of additional neutrophils from the bone marrow.
 - In a severe infection, the number of white blood cells may increase significantly within hours of the initial inflammation.
- Another systemic response to infection is fever, which may occur when substances released by activated macrophages set the body's thermostat at a higher temperature.
 - One hypothesis is that moderate fever enhances phagocytosis and hastens tissue repair.
- Certain bacterial infections can induce an overwhelming systemic inflammatory response leading to a condition known as *septic shock*.
 - Characterized by high fever and reduced blood flow through capillaries, septic shock is a life-threatening medical emergency that is fatal in more than one-third of cases.
- Some pathogens have adaptations that enable them to avoid destruction by phagocytic cells.
 - The outer capsule that surrounds certain bacteria interferes with molecular recognition and phagocytosis.
 - Some bacteria, after being engulfed by a host cell, resist breakdown within lysosomes.
 - An example is the bacterium that causes tuberculosis (TB). Rather than being destroyed within host cells, this bacterium grows and reproduces, hidden from the body's innate immune defenses.
 - TB kills more than a million people a year worldwide.

Concept 43.2 In adaptive immunity, lymphocyte receptors provide pathogen-specific recognition.

Vertebrates have adaptive immunity in addition to innate immunity.

- Lymphocytes provide the specificity and diversity of the vertebrate immune system.
- The vertebrate body is populated by two main types of lymphocytes: **B lymphocytes (B cells)** and **T lymphocytes (T cells)**.
 - Both types of lymphocytes are critical for adaptive immune defense.

- Lymphocytes that originate from stem cells in the bone marrow and migrate to the **thymus** mature into T cells.
- Lymphocytes that mature in the bone marrow develop as B cells.
- Lymphocytes of a third type remain in the blood and become the natural killer cells active in innate immunity.

Lymphocytes recognize specific antigens.

- Any foreign molecule that is specifically recognized by lymphocytes and elicits a response from them is called an **antigen**.
- B and T cells bind to an antigen via a protein called an **antigen receptor**.
 - A single antigen receptor is specific enough to bind to just one part of one molecule from a particular species of bacteria or from a particular virus.
- The cells of the immune system can produce millions of different antigen receptors, but the antigen receptors made by a single B or T cell are all identical.
- Infection by a virus, bacterium, or other pathogen triggers activation of B and T cells with antigen receptors specific for parts of that pathogen.
 - A single B or T cell actually has about 100,000 antigen receptors.
- Antigens are typically large molecules, either proteins or polysaccharides that protrude from the surface of foreign cells or viruses.
 - Other antigens, such as toxins secreted by bacteria, are released into extracellular fluid.
- A lymphocyte actually recognizes and binds to a small portion of an antigen called an **epitope** or *antigenic determinant*.
 - Because lymphocytes recognize and respond to particular pathogens and foreign molecules, they are said to display *specificity* for a particular epitope on an antigen.
- Each **B cell receptor** for an antigen is a Y-shaped molecule consisting of four polypeptide chains: two identical **heavy chains** and two identical **light chains** linked by disulfide bridges.
 - A transmembrane region near one end of each heavy chain anchors the receptor in the cell's plasma membrane.
 - A short region at the end of the tail extends into the cytoplasm.
- At the two tips of the Y-shaped molecules are the light- and heavy-chain *variable (V) regions* whose amino acid sequences vary from one B cell to another.
 - The remainder of the molecule is made up of *constant (C) regions*, which do not vary from cell to cell.
- Each B cell receptor has two identical antigen-binding sites formed from parts of a heavy-chain V region and parts of a light-chain V region.
- The binding of a B cell antigen receptor to an antigen is an early step in B cell activation, leading to formation of cells that secrete a soluble form of the receptor.
- This secreted protein is called an **antibody**, or **immunoglobulin (Ig)**.
 - Antibodies have the same Y-shaped organization as B cell antigen receptors, but they are secreted rather than membrane-bound.
 - It is the antibodies, rather than the B cells themselves, that actually help defend against pathogens.
- The antigen-binding site of a membrane-bound antibody has a unique shape that provides a lock-and-key fit for a particular epitope.

- Noncovalent bonds between an epitope and the binding surface provide a stable and specific interaction.
- Differences in the amino acid sequences of variable regions provide the variation in binding surfaces that enables this highly specific binding.
- B cell antigen receptors and antibodies bind to intact antigens on the surface of pathogens or free in body fluids.
- For a T cell, the antigen receptor consists of two different polypeptide chains, the α chain and the β chain, linked by a disulfide bridge.
 - Near the base of the T cell antigen receptor is a transmembrane region that anchors the molecule in the cell's plasma membrane.
 - At the outer tip of the molecule, the α chain and β chain variable (V) regions form a single antigen-binding site. The remainder of the molecule is made up of the constant (C) regions.
- T cell and B cell antigen receptors function in fundamentally different ways.
 - While the antigen receptors of B cells bind to epitopes of intact antigens circulating in body fluids, those of T cells bind only to fragments of antigens that are displayed, or *presented*, on the surface of host cells.
 - The host protein that displays the antigen fragment on the cell surface is called an **MHC (major histocompatibility) molecule**.
- Antigen recognition involving T cells begins when a pathogen or part of a pathogen either infects or is taken in by a host cell.
 - Inside the host cell, enzymes in the cell cleave the antigen into smaller peptides. Each peptide, called an *antigen fragment*, then binds to an MHC molecule inside the cell.
- Movement of the MHC molecule and bound antigen fragment to the cell surface results in **antigen presentation**, the display of the antigen fragment in an exposed groove of the MHC protein.
 - If the cell displaying an antigen fragment encounters a T cell with the right specificity, the antigen receptor on the T cell can bind to both the antigen fragment and the MHC molecule.
 - The interaction of an MHC molecule, an antigen fragment, and an antigen receptor allows a T cell to participate in an adaptive immune response.
- Consider four major characteristics of adaptive immunity:
 - First, there is an immense diversity of lymphocytes and receptors, enabling the immune system to detect pathogens never before encountered.
 - Second, adaptive immunity normally has self-tolerance, the lack of reactivity against an animal's own molecules and cells.
 - Third, B cells and T cells proliferate after being activated.
 - Fourth, there is a stronger and more rapid response to an antigen encountered previously, a feature known as *immunological memory*.
- Receptor diversity and self-tolerance arise as a lymphocyte matures.
 - Proliferation of cells and the formation of immunological memory occur later, after a mature lymphocyte encounters and binds to a specific antigen.

How do we generate such remarkable diversity in antigen receptors?

- Each person makes more than 1 million different B cell antigen receptors and more than 10 million different T cell antigen receptors.

- Yet there are only roughly 20,000 protein-coding genes in the human genome.
 - By combining variable elements, the immune system assembles many different receptors from a much smaller collection of parts.
- To understand the origin of receptor diversity, let's consider an immunoglobulin (Ig) gene that encodes the light chain of both secreted antibodies (immunoglobulins) and membrane-bound B cell antigen receptors.
- The capacity to generate diversity is built into the structure of Ig genes.
- A receptor light chain is encoded by three gene segments: a variable (*V*) segment, a joining (*J*) segment, and a constant (*C*) segment.
 - The *V* and *J* segments together encode the variable region of the receptor chain, while the *C* segment encodes the constant region.
 - The light-chain gene contains a single *C* segment, 40 different *V* segments, and 5 different *J* segments.
 - These alternative copies of the *V* and *J* segments are arranged within the gene in a series.
 - Because a functional gene is built from one copy of each type of segment, the pieces can be combined in 200 ($40 V \times 5 J \times 1 C$) different ways.
 - The number of different heavy-chain genes is even greater, resulting in more diversity.
- Assembling a functional Ig gene requires rearranging the DNA.
- Early in B cell development, an enzyme complex called *recombinase* links one light-chain *V* gene segment to one *J* gene segment.
 - This recombination event eliminates the long stretch of DNA between the segments, forming a single exon that is part *V* and part *J*.
 - Because there is only an intron between the *J* and *C* DNA segments, no further DNA rearrangement is required.
 - Instead, the *J* and *C* segments of the RNA transcript will be joined when splicing removes the intervening RNA.
- Recombinase acts randomly, linking any one of the 40 *V* gene segments to any one of the 5 *J* gene segments.
 - Heavy-chain genes undergo a similar rearrangement.
 - In any given cell, however, only one light-chain gene and one heavy-chain gene are rearranged.
 - The rearrangements are permanent and are passed on to the daughter cells when the lymphocyte divides.
- After both the light- and heavy-chain genes have rearranged, antigen receptors can be synthesized.
 - The rearranged genes are transcribed, and the transcripts are processed for translation.
 - Following translation, the light chain and heavy chain assemble together, forming an antigen receptor.
 - Each pair of randomly rearranged heavy and light chains results in a different antigen-binding surface.
 - For the total population of B cells in a human body, the number of such combinations has been calculated as 3.5×10^6 .
 - Furthermore, mutations introduced during *VJ* recombination add additional variation, making the number of possible antigen-binding specificities even greater.

How does adaptive immunity distinguish self from nonself?

- Because antigen receptor genes are randomly rearranged, some immature lymphocytes produce receptors specific for epitopes on the organism's own molecules.
 - If these self-reactive lymphocytes were not eliminated or inactivated, the immune system could not distinguish self from nonself and would attack body proteins, cells, and tissues.
- Instead, as lymphocytes mature in the bone marrow or thymus, their antigen receptors are tested for self-reactivity.
- Some B and T cells with receptors specific for the body's own molecules are destroyed by *apoptosis* or programmed cell death.
 - The remaining self-reactive lymphocytes are typically rendered nonfunctional, leaving only those that react to foreign molecules.
- Since the body normally lacks mature lymphocytes that can react against its own components, the immune system is said to exhibit *self-tolerance*.
- Only a tiny fraction of antigen receptors are specific for epitopes on a given antigen. Why is adaptive immunity so effective?
 - First, in the lymph nodes, an antigen is presented to a steady stream of lymphocytes until a match is made.
- The second part of the answer lies in changes in cell number and behavior triggered by the binding of antigen to lymphocyte.
 - The binding of an antigen receptor to an epitope on a specific antigen initiates events that activate the lymphocyte.
 - Once activated, a B cell or T cell undergoes multiple cell divisions.
 - The result of this proliferation is a clone, a population of cells that are identical to the original cell.
- Some cells from the clone become **effector cells**, which act against the antigen and any pathogens producing that antigen.
 - The effector forms of B cells are plasma cells, which secrete antibodies.
 - The effector forms of T cells are helper T cells and cytotoxic T cells.
- The remaining cells in the clone become **memory cells**, long-lived cells that produce effector cells if the same antigen is encountered later in the animal's life.
 - The proliferation of an activated lymphocyte into a clone of cells in response to binding to an antigen is called **clonal selection**.
 - An encounter with an antigen *selects* which lymphocyte will divide to produce a *clonal* population of thousands of cells, all specific for a particular epitope on that antigen.
- Immunological memory provides long-term protection from a prior infection or vaccination.
- Prior exposure to an antigen alters the speed, strength, and duration of the immune response.
- The production of effector cells from a clone of lymphocytes during the first exposure to an antigen is the basis for the **primary immune response**, which peaks 10 to 17 days after the initial exposure.
 - During this time, selected B cells and T cells give rise to their effector forms.
- If an individual is exposed again to the same antigen, the response is faster (peaking 2 to 7 days after exposure), of greater magnitude, and more prolonged.
 - This is the **secondary immune response**.

- Because selected B cells give rise to antibody-secreting effector cells, measuring the concentrations of specific antibodies in blood over time distinguishes the primary and secondary immune response.
 - The secondary immune response relies on the reservoir of T and B memory cells generated following initial exposure to an antigen.
 - Because these cells are long-lived, they provide the basis for immunological memory, which can span many decades.
 - Effector cells have much shorter life spans, which is why the immune response diminishes after an infection is overcome.
 - If an antigen is encountered again, memory cells specific for that antigen enable the rapid formation of clones of thousands of effector cells specific for this antigen, thus generating a greatly enhanced immune defense.

Concept 43.3 Adaptive immunity defends against infection of both body fluids and cells.

- The immune system can mount two types of immune responses to antigens: humoral and cell-mediated.
 - The **humoral immune response** occurs in the blood and lymph. In this response, antibodies help neutralize or eliminate toxins and pathogens in the blood and lymph.
 - In the **cell-mediated immune response**, specialized T cells destroy infected host cells.
 - Both responses include a primary immune response and a secondary immune response enabled by memory cells.

Helper T lymphocytes function in both humoral and cell-mediated immunity.

- A type of T cell called a **helper T cell** triggers both the humoral and cell-mediated immune responses, although helper T cells themselves do not carry out those responses.
 - Signals from helper T cells initiate production of antibodies that neutralize pathogens and activate T cells that kill infected cells.
- Two requirements must be met for a helper T cell to activate adaptive immune responses.
 - First, a foreign molecule must be present that can bind specifically to the antigen receptor of the T cell.
 - Second, this antigen must be displayed on the surface of an **antigen-presenting cell**. The antigen-presenting cell can be a dendritic cell, macrophage, or B cell.
- What distinguishes an antigen-presenting cell?
 - Most body cells have only class I MHC molecules, but antigen-presenting cells have both class I and class II MHC molecules.
 - The class II molecules provide a molecule signature by which an antigen-presenting cell is recognized.
- The antigen receptors on the surface of the helper T cell bind to the antigen fragment and to the class II MHC molecule displaying that fragment on the antigen-presenting cell.
 - At the same time, an accessory protein on the helper T cell surface binds to the class II MHC molecule, helping keep the cells joined.
 - As the two cells interact, signals in the form of cytokines are exchanged in both directions.
 - For example, cytokines secreted from a dendritic cell act in combination with the antigen to stimulate the helper T cell, causing it to produce its own set of cytokines.

- Extensive contact between the cell surfaces enables further information exchange.
- The different types of antigen-presenting cells interact with helper T cells in distinct contexts.
 - Antigen presentation by a dendritic cell or macrophage activates a helper T cell. The helper T cell then proliferates, forming a clone of activated helper T cells.
 - B cells present antigens to *already* activated helper T cells, which in turn activate the B cells themselves.
 - Activated helper T cells also help stimulate cytotoxic T cells, as we'll discuss next.

In the cell-mediated immune response, cytotoxic T cells are the effector cells.

- To become active, **cytotoxic T cells** require signaling molecules from helper T cells as well as interaction with a cell that presents an antigen.
 - The term *cytotoxic* refers to their use of toxic gene products to kill infected cells.
 - Once activated, cytotoxic T cells can eliminate cells that are infected by viruses or other intracellular pathogens.
- Fragments of foreign proteins produced in infected host cells associate with class I MHC molecules and are displayed on the cell surface, where they can be recognized by cytotoxic T cells.
 - As with helper T cells, cytotoxic T cells have an accessory protein that binds to the MHC molecule, helping keep the two cells in contact while the T cell is activated.
- The destruction of an infected host cell by a cytotoxic T cell involves the secretion of proteins that disrupt membrane integrity and trigger apoptosis.
 - The death of the infected cell deprives the pathogen of a place to reproduce and exposes cell contents to circulating antibodies, which mark them for disposal.
- After destroying an infected cell, the cytotoxic T cell may move on and kill other cells infected with the same pathogen.

The secretion of antibodies by clonally selected B cells is the hallmark of the humoral immune response.

- Activation of the humoral immune response typically involves B cells and helper T cells, as well as proteins on the surface of pathogens.
 - B cell activation by an antigen is aided by cytokines secreted from helper T cells that have encountered the same antigen.
 - Stimulated by both an antigen and cytokines, the B cell proliferates and differentiates into memory B cells and antibody-secreting effector cells called **plasma cells**.
- The pathway for antigen processing and display in B cells differs from that in other antigen-presenting cells.
- A macrophage or dendritic cell can present fragments from a wide variety of protein antigens, whereas a B cell presents only the antigen to which it specifically binds.
- When an antigen first binds to receptors on the surface of a B cell, the cell takes in a few foreign molecules by receptor-mediated endocytosis.
 - The class II MHC protein of the B cell then presents an antigen fragment to a helper T cell.
 - This direct cell-to-cell contact is usually critical to B cell activation.
- B cell activation leads to a robust humoral immune response: An activated B cell gives rise to thousands of identical plasma cells.

- These plasma cells stop expressing a membrane-bound antigen receptor and begin producing secreted antibodies.
- Each plasma cell secretes approximately 2,000 antibodies every second of the cell's 4- to 5-day life span.
- Most antigens recognized by B cells contain multiple epitopes.
- An exposure to a single antigen normally activates a variety of B cells, with different plasma cells producing antibodies directed against different epitopes on the common antigen.
- Antibodies do not kill pathogens, but by binding to antigens they mark pathogens in various ways for inactivation or destruction.
- In *neutralization*, antibodies bind to viral surface proteins and prevent infection of a host cell, thus neutralizing the virus.
 - Similarly, antibodies sometimes bind to toxins released in body fluids, preventing the toxins from entering body cells.
- In *opsonization*, antibodies bound to antigens on bacteria present a readily recognized structure for macrophages or neutrophils and therefore increase phagocytosis.
 - Each antibody has two antigen-binding sites, and antibodies may facilitate phagocytosis by linking bacterial cells, virus particles, or other foreign substances into aggregates.
- Antibodies may work together with the proteins of the complement system to dispose of pathogens.
 - The name *complement* reflects the fact that these proteins increase the effectiveness of antibody-directed attacks on bacteria.
- Binding of a complement protein to an antigen-antibody complex on a foreign cell (or an enveloped virus) triggers a cascade in which each protein of the complement system activates the next protein.
- Ultimately, activated complement proteins generate a *membrane attack complex* that forms a pore in the membrane of the foreign cell.
 - Ions and water rush into the cell, causing it to swell and lyse.
- Phagocytosis enables macrophages and dendritic cells to present antigens to and stimulate helper T cells, which in turn stimulate B cells whose antibodies contribute to phagocytosis.
 - This positive feedback between innate and adaptive immunity contributes to a coordinated, effective response to infection.
- Antibodies can also bring about the death of infected body cells.
 - When a virus uses a cell's biosynthetic machinery to produce viral proteins, these viral products can appear on the cell surface.
 - If antibodies specific for epitopes on these viral proteins bind to the exposed proteins, the presence of bound antibody at the cell surface can recruit a natural killer cell.
 - The natural killer cell then releases proteins that cause the infected cell to undergo apoptosis.
- B cells can express five different forms of immunoglobulin (Ig).
- For a given B cell, each form or *class* has an identical antigen-binding specificity, but a distinct heavy chain C region.
 - The B cell antigen receptor, known as IgD, is membrane bound.
- The other four classes consist of soluble antibodies.
 - IgM is the first class of soluble antibody produced.

- IgG, which follows next, is the most abundant antibody in blood.
- The remaining antibody classes are IgA and IgE).
- When a particular pathogen infects the body, clones of memory cells form, providing **active immunity**.
- In contrast, a distinct type of immunity results when the IgG antibodies in the blood of a pregnant female cross the placenta to her fetus.
 - The transferred antibodies immediately react with any pathogens for which they are specific.
 - This protection is called **passive immunity** because the antibodies provided by the mother guard against pathogens that have never infected the newborn.
 - Passive immunity does not involve the recipient's B and T cells, and persists only as long as the transferred antibodies last (a few weeks to a few months).
- After birth, a nursing mother continues to transfer protection against disease to her infant.
 - IgA antibodies present in breast milk provide additional passive immunity to the infant's digestive tract while the infant's immune system develops.
- Later in life, IgA functions in active immunity: IgA antibodies secreted in tears, saliva, and mucus protect the mucous membranes of both males and females.
- Both active immunity and passive immunity can be induced artificially.
- Active immunity can develop from the introduction of antigens into the body through **immunization**.
 - The first documented immunization or **vaccination** was the use of cowpox virus to induce adaptive immunity against the closely related smallpox virus.
- Today, many sources of antigen are used to make vaccines, including inactivated bacterial toxins, killed pathogens, parts of pathogens, weakened pathogens that generally do not cause illness, and even genes encoding microbial proteins.
 - Because all of these agents induce a primary immune response and immunological memory, an encounter with the pathogen from which the vaccine was derived triggers a rapid and strong secondary immune response.
- A worldwide vaccination campaign led to eradication of smallpox in the late 1970s.
- Routine active immunization of infants and children has dramatically reduced the incidence of diseases such as polio, measles, and whooping cough.
 - Unfortunately, not all pathogens are easily managed by vaccination and some vaccines are not readily available in impoverished areas of the globe.
- Misinformation about vaccine safety and disease risk has led some parents to refuse to immunize their children with available, effective vaccines.
 - The consequence has been a substantial and growing public health problem.
- In artificial passive immunization, antibodies from an immune animal are injected into a nonimmune animal.
 - For example, humans bitten by venomous snakes are sometimes treated with antivenin, a serum from sheep or horses that have been immunized against the venom of one or more species of poisonous snakes.
 - When injected immediately after snakebite, the antibodies in antivenin can neutralize toxins in the venom before the toxins do massive damage.

Antibodies are useful tools.

- The power of antibody specificity and antigen-antibody binding has been harnessed in research, diagnosis, and therapy.
- Some antibody tools are *polyclonal*: They are the products of many different clones of plasma cells, each specific for a different epitope.
- In contrast, other antibody tools are *monoclonal*: They are prepared from a single clone of B cells grown in culture.
 - The **monoclonal antibodies** produced by such a culture are identical and specific for the same epitope on an antigen.
- Monoclonal antibodies have provided the basis for many recent advances in biomedicine in both diagnosis and treatment.
- Home pregnancy kits use monoclonal antibodies to detect human chorionic gonadotropin (HCG).
 - HCG is produced as soon as an embryo implants in the uterus, and the presence of this hormone in a woman's urine is a reliable indicator for a very early stage of pregnancy.
- Monoclonal antibodies are being used to treat many human diseases.
 - For this therapy, researchers use mouse B cell clones to identify antibodies specific for an epitope on diseased cells.
 - The mouse antibody genes are altered to code for antibodies that appear less "foreign" to the human adaptive immune defenses.
 - Scientists then use the "humanized" genes to produce large amounts of antibody for injecting into patients.

Transplanted cells may be recognized as foreign and attacked by immune defenses.

- Like pathogens, cells from another person can be recognized as foreign and therefore be attacked by immune defenses.
 - Skin transplanted from one person to a genetically nonidentical person will look healthy for a week or so but will then be rejected by the recipient's immune response.
- It remains a largely unanswered question why a pregnant woman does not reject her fetus as nonself tissue.
- To avoid a blood transfusion being recognized as foreign by the recipient's immune system, ABO blood groups of the donor and recipient must be taken into account.
- Red blood cells are designated as type A if they have the type A carbohydrate on their surface.
 - The type B carbohydrate is found on type B red blood cells; both A and B carbohydrates are found on type AB red blood cells; and neither carbohydrate is found on type O red blood cells.
- Consider the immune response of someone with type A blood.
 - Certain bacteria normally present in the body have epitopes very similar to the A and B carbohydrates.
 - By responding to the bacterial epitope similar to the B carbohydrate, a person with type A blood makes antibodies that will react with the type B carbohydrate.
 - No antibodies are made against the bacterial epitope similar to the type A carbohydrate because lymphocytes reactive with the body's own molecules are inactivated or eliminated during development.
- If the person with type A blood receives a transfusion of type B blood, that person's anti-B antibodies cause an immediate and devastating transfusion reaction.

- The transfused red blood cells undergo lysis, which can lead to chills, fever, shock, and kidney malfunction.
- Anti-A antibodies in the donated type B blood will act against the recipient's type A red blood cells.
- In the case of tissue and organ transplants, or grafts, MHC molecules stimulate the immune response that leads to rejection.
- Each vertebrate species has many different alleles for each MHC gene, enabling presentation of antigen fragments that vary in shape and charge.
 - This diversity of MHC molecules guarantees that no two people, except identical twins, will have exactly the same set.
 - In the vast majority of graft and transplant recipients, some MHC molecules on the donated tissue are foreign to the recipient.
 - To minimize rejection, physicians try to use donor tissue bearing MHC molecules that match those of the recipient as closely as possible.
- The recipient takes medicines that suppress immune responses; this leaves the recipient more susceptible to infections during the course of treatment.
- Bone marrow transplants are used to treat leukemia and other cancers as well as various hematological (blood cell) diseases.
 - The recipient is typically treated with radiation to eliminate his or her own bone marrow cells, destroying the source of abnormal cells.
 - This treatment obliterates the recipient's immune system, eliminating graft rejection.
- However, lymphocytes in the donated marrow may react against the recipient.
 - This *graft versus host reaction* is limited if the MHC molecules of the donor and recipient are well matched.
- Bone marrow donor programs continually seek volunteers because the great variability of MHC molecules makes a diverse pool of donors essential.

Concept 43.4 Disruptions in immune system function can elicit or exacerbate disease.

- Malfunctions of the immune system can produce effects ranging from the minor inconvenience of mild allergies to the serious and often fatal consequences of certain autoimmune and immunodeficiency diseases.

Exaggerated immune responses can cause disease.

- Allergies are hypersensitive (exaggerated) responses to certain environmental antigens, called *allergens*.
- The most common allergies involve antibodies of the IgE class.
 - Hay fever, for example, occurs when plasma cells secrete IgE specific for pollen allergens.
- Some IgE antibodies attach by their base to mast cells present in connective tissue.
 - Later, pollen grains that enter the body attach to the antigen-binding sites of mast-cell-associated IgE, cross-linking adjacent antibody molecules.
 - This event triggers the mast cell to release histamines and other inflammatory chemicals from vesicles called granules.

- These inflammatory events lead to typical allergy symptoms: sneezing, runny nose, teary eyes, and smooth muscle contractions that can result in breathing difficulty.
 - Antihistamines diminish allergy symptoms by blocking receptors for histamine.
- Sometimes, an acute allergic response can result in *anaphylactic shock*, a whole-body, life-threatening reaction to injected or ingested allergens.
- Anaphylactic shock results when widespread release of mast cell contents triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure and constriction of branchioles.
 - Death may occur within minutes due to lack of blood flow and inability to breathe.
 - Triggers of anaphylactic shock in susceptible individuals include bee venom, penicillin, or foods such as peanuts or fish.
 - Some hypersensitive individuals carry syringes with epinephrine, which counteracts this allergic response.

Self-directed immune responses can cause disease.

- Sometimes the immune system is active against certain molecules of the body, causing an **autoimmune disease**.
- In *systemic lupus erythematosus (lupus)*, the immune system generates antibodies against various histones and DNA released by the normal breakdown of body cells.
 - Lupus is characterized by skin rashes, fever, arthritis, and kidney dysfunction.
- *Rheumatoid arthritis* leads to damage and painful inflammation of the cartilage and bone of joints.
- In *Type I diabetes mellitus*, the insulin-producing beta cells of the pancreas are the targets of autoimmune cytotoxic T cells.
- *Multiple sclerosis (MS)* is the most common chronic neurological disease in developed countries.
 - In MS, T cells reactive against myelin infiltrate the central nervous system and destroy the myelin sheath that surrounds many neurons.
 - People with MS may suffer from muscle paralysis through disruption of neuron function.
- Gender, genetics, and environment influence susceptibility to autoimmune disease.
 - Members of certain families show an increased susceptibility to particular autoimmune disorders.
 - Women are two to three times as likely as men to suffer from multiple sclerosis and rheumatoid arthritis and nine times more likely to contract lupus.
- Much remains to be learned about autoimmune disorders.

Exertion and stress influence immune system function.

- Moderate exercise improves immune system function and reduces the risk of infection.
 - Exercise to the point of exhaustion leads to more frequent infections with more severe symptoms.
- Physiological stress disrupts immune system regulation by altering the interplay of the hormonal, nervous, and immune systems.
- Rest is important for immunity: adults who averaged fewer than seven hours a night of sleep got sick three times as often when exposed to a cold virus as individuals who averaged at least eight hours of sleep.

Diminished immune responses can cause disease.

- In **immunodeficiency** diseases, the immune system response to pathogens is defective or absent.
 - An immunodeficiency disease caused by a genetic or developmental defect in the immune system is called an *inborn immunodeficiency*.
 - An immunodeficiency defect in the immune system that develops later in life, following exposure to a chemical or biological agent, is called an *acquired immunodeficiency*.
- Inborn immunodeficiencies result from defects in the development of various immune system cells or the production of specific proteins, such as antibodies or the proteins of the complement system.
- In severe combined immunodeficiency (SCID), functional lymphocytes are rare or absent.
 - Individuals with this disease require a bone marrow or stem cell transplant in order to supply functional lymphocytes.
- Immune deficiencies may also develop later in life.
 - Drugs used to fight autoimmune diseases or prevent transplant rejection suppress the immune system, leading to an immunodeficient state.
 - Certain cancers suppress the immune system. An example is Hodgkin's disease, which damages the lymphatic system.
- **Acquired immunodeficiency syndrome**, or **AIDS**, is caused by the human immunodeficiency virus (HIV).

Pathogens may evade the immune system.

- Pathogens have evolved mechanisms to thwart immune responses, using antigenic variation, latency, and direct attack on the immune system.
- A pathogen may escape attack by the immune system by altering its appearance.
 - Immunological memory is a record of the foreign epitopes an animal has encountered.
 - If the pathogen that expressed those epitopes no longer does so, it can reinfect or remain in a host without triggering the rapid and robust response that memory cells provide.
 - Such *antigenic variation* is a regular feature of some viruses and parasites.
- The parasite that causes sleeping sickness (trypanosomiasis) provides one example.
 - By periodically switching at random among 1,000 different versions of the protein found over its entire surface, this pathogen can persist in the body without facing an effective adaptive immune response.
- Antigenic variation is the major reason the influenza, or "flu," virus remains a major public health problem.
- Of much greater danger, however, is the fact that the human virus occasionally exchanges genes with influenza viruses that infect domesticated animals, such as pigs or chickens.
 - When this exchange occurs, influenza can take on such a radically different appearance that the memory cells in the human population are unable to recognize the new strain.
- In 2009, an influenza virus called H1N1 appeared that contains a novel combination of genes from flu viruses that normally circulate in pigs, birds, and humans.
 - The rapid spread of this flu across the human population was declared a *pandemic*, defined as an epidemic of worldwide proportions.

- Fortunately, a rapidly developed H1N1 vaccine soon provided public health officials with an excellent means of slowing the spread of this virus and reducing the impact of the outbreak.
- After infecting a host, some viruses become dormant and cease making viral proteins.
 - In this largely inactive state called *latency*, there are typically no free viral particles.
 - The viral genome persists in the nuclei of infected cells, either as a separate small DNA or as a copy integrated into the host genome.
 - Latency typically persists until conditions arise that appear favorable for viral transmission or unfavorable for host survival.
 - Such circumstances trigger the synthesis and release of particles that can infect new hosts.
- Herpes simplex viruses, which establish themselves in human sensory neurons, provide illustrative examples of latency.
 - The type 1 virus causes most oral herpes infections, whereas the type 2 virus is responsible for most cases of genital herpes.
 - Because sensory neurons express relatively few MHC I molecules, the infected cells are inefficient at presenting viral antigens to circulating lymphocytes.
 - Stimuli such as fever, emotional stress, or menstruation induce reactivation of the virus and infection of surrounding epithelial tissues.

HIV attacks the immune system.

- The human immunodeficiency virus (HIV), the pathogen that causes AIDS, escapes and attacks the adaptive immune response.
- HIV gains entry into cells by making use of proteins that participate in normal immune responses.
 - The main receptor for HIV on helper T cells is the cell's CD4 molecule.
 - HIV also infects some cell types that have low levels of CD4, including macrophages and brain cells.
- Once inside the cell, the HIV RNA is reverse-transcribed, and the product DNA is integrated into the host cell's genome.
 - In this form, the viral genome can direct the production of new viral particles.
- Although the body responds to HIV with an immune response sufficient to clear most viral infections, some HIV invariably escapes.
- One reason HIV persists is antigenic variation.
 - It mutates at a very fast rate during viral replication, and altered proteins on the surface of some mutated viruses reduce interaction with antibodies and cytotoxic T cells.
 - Some viruses survive, proliferate, and mutate further, evolving within the body.
- The continued presence of HIV is also helped by latency.
 - When the virus integrates into the chromosome of an infected cell but does not produce new virus proteins or particles, it is shielded from the immune system.
 - The antiviral agents currently used against HIV attack only an actively replicating virus.
- Over time, an untreated HIV infection not only avoids the adaptive immune response but also abolishes it.
- Virus reproduction and cell death triggered by the virus lead to loss of helper T cells, impairing both humoral and cell-mediated immune responses.

- The result is a susceptibility to infections and cancers that can be successfully rebuffed by people with a healthy immune system.
 - Kaposi's sarcoma, a cancer caused by a herpes virus, and pneumonia, caused by the fungus *Pneumocystis carinii*, are seldom found in healthy people but occur in AIDS patients.
 - People with AIDS are susceptible to opportunistic diseases, neurological disease, and physiological wasting.
- HIV infection cannot yet be cured, although certain drugs slow HIV reproduction and the progression to AIDS.
 - The mutational changes that occur with each round of virus reproduction can generate drug-resistant strains of HIV.
- The impact of viral drug resistance is reduced by the use of a combination of drugs; viruses newly resistant to one drug can be defeated by another.
 - Strains resistant to multiple drugs reduce the effectiveness of multidrug "cocktails" in some patients.
 - Frequent mutational changes in HIV surface antigens also have hampered efforts to develop an effective vaccine.
- In 2007, 2 million people died of AIDS, which is the leading cause of death in Africa.
- Transmission of HIV requires the transfer of body fluids containing infected cells, such as semen, blood, or breast milk from person to person.
 - Most HIV transmission is due to unprotected sex or the use of HIV-contaminated needles.
 - People infected with HIV transmit the disease most readily in the first few weeks of infection, *before* they express HIV-specific antibodies that can be detected in a blood test.
 - 10 to 50% of all new HIV infections are caused by recently infected individuals.

The frequency of certain cancers increases when the immune response is impaired.

- When adaptive immunity is inactivated, the frequency of certain cancers increases dramatically.
 - The risk of developing Kaposi's sarcoma is 20,000 times greater for untreated AIDS patients than for healthy people.
 - This observation was unanticipated: If the immune system recognizes only non-self, it should fail to recognize the uncontrolled growth of self cells that is the hallmark of cancer.
 - It turns out, however, that viruses are involved in about 15 to 20% of all human cancers.
 - Because the immune system can recognize viral proteins as foreign, it can act as a defense against viruses that can cause cancer and against cancer cells that harbor viruses.
- Scientists have identified six viruses that can cause cancer in humans.
 - The Kaposi's sarcoma herpes virus is one such virus.
 - Hepatitis B virus, which can trigger liver cancer, is another.
- A vaccine directed against hepatitis B virus was the first vaccine to help prevent a specific human cancer.
- Rapid progress on virus-induced cancers continues.
 - In 2006, a vaccine against the human papillomavirus (HPV) that causes cervical cancer was released.