

## Chapter 43

# The Immune System

### *Lecture Outline*

#### Overview: Reconnaissance, Recognition, and Response

- An animal must defend itself against **pathogens**, infectious agents that cause disease.
  - Viruses, bacteria, protists, and fungi infect a wide range of animals, including humans.
- Animals fight back in various ways.
  - Immune cells patrol the body fluids of animals, seeking out and destroying foreign cells.
  - 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.
  - External barriers, formed by the skin or shell, provide an obstacle to microbes.
  - Chemical secretions that trap or kill microbes 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.
- To identify pathogens, animal immune systems use receptors that specifically bind molecules from foreign cells or viruses.
- Two general strategies for molecular recognition form the basis for innate and acquired immunity.
- **Innate immunity** is common to all animals.
- Innate immune responses are active immediately upon infection and are the same whether or not the pathogen has been encountered previously.
- Innate immunity includes the barrier defenses (for example, skin) as well as defenses that combat pathogens after they enter the body.
- The activation of many of these internal defenses relies on the recognition of pathogens.
  - Innate immune cells produce a small, preset group of receptor proteins that accomplish this recognition.
  - Each innate immune receptor binds a molecule or structure that is absent from animal bodies but is shared among a large class of microbes.
  - In this way, innate immune systems detect a very broad range of pathogens.
- **Acquired immunity**, also known as *adaptive immunity*, is found only in vertebrates.
- Acquired immune responses are activated after innate immune defenses and develop more slowly.
- These acquired defenses are enhanced by previous exposure to the infecting pathogen.

- Animals with acquired 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, acquired immune systems detect pathogens with tremendous specificity.

**Concept 43.1 In innate immunity, recognition and response rely on shared pathogen traits.**

*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 microbes ingested with food.
  - **Lysozyme**, an enzyme that digests microbial cell walls, and low pH also protect the digestive system.
- In insects, circulating cells called *hemocytes* flow throughout the *hemolymph*, the insect equivalent blood.
- Some hemocytes can **phagocytose** microbes.
- Other hemocytes trigger the production of chemicals that kill microbes and entrap parasites.
- Hemocytes and other cells secrete *antimicrobial peptides* that bind to and destroy bacteria and fungi by disrupting their plasma membranes.
  - Hemocytes recognize unique structures in the outer layers of bacteria and 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 particular type of microbe.
- 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 that activates the protein Toll, a receptor on the surface of immune response cells.
  - Signal transduction from the Toll receptor to the cell nucleus leads to synthesis of a particular set of antimicrobial peptides.
  - When the bacterium *Micrococcus luteus* infects a fly, a distinct recognition protein is activated, and the fly produces a different set of antimicrobial peptides.

*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 microbes and other particles.
  - In the trachea, ciliated epithelial cells sweep out mucus with its trapped microbes, preventing them from entering the lungs.
  - Microbial 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 saliva, mucous secretions, and tears kill bacteria that enter the upper respiratory tract or the openings around the eyes.
- Microbes present in food or water, or those in swallowed mucus, must contend with the highly acidic environment of the stomach.
  - The acid destroys many microbes 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 microbes.

*Phagocytic cells function early in infection.*

- Pathogens that penetrate the first line of defense face phagocytic white blood cells (leukocytes).
- Leukocytes recognize microbes through receptors that are very similar to the Toll receptor of insects.
- Each mammalian **TLR**, or *Toll-like receptor*, functions to recognize molecules common to a set of pathogens.
  - TLR4 of immune cell plasma membranes recognizes lipopolysaccharide, a molecule found on the surface of many bacteria.
  - TLR3 on the inner surface of endocytic vesicles is the sensor for double-stranded RNA, a form of nucleic acid characteristic of certain viruses.
- In each case, the recognized macromolecule is normally absent from the vertebrate body and is an essential component of a class of microbes.
- Phagocytosis is often the first step in internal defenses.
- White blood cells recognize and engulf microorganisms, forming a vacuole that fuses with a lysosome.
- Microbes are destroyed within lysosomes in two ways.
  - Lysosomes contain nitric oxide and other gases that poison the engulfed microbes.
  - Lysozymes and other enzymes degrade microbial components.
- The most abundant phagocytic cells in the mammalian body are **neutrophils**.
- Signals from infected tissues attract neutrophils, which engulf and destroy microbes.
- **Macrophages** are even more effective phagocytic cells.
- Some macrophages migrate throughout the body, whereas others reside permanently in certain tissues, especially in lymph nodes and the spleen.
- Microbes that enter the blood become trapped in the spleen, whereas microbes in interstitial fluid flow into lymph and are trapped in lymph nodes.
  - In either location, microbes soon encounter resident macrophages.
- **Eosinophils** contribute to defense against large invaders, such as parasitic worms.
- Eosinophils position themselves against the external wall of a parasite and discharge destructive enzymes.
- **Dendritic cells** populate tissues that are in contact with the environment, acting to stimulate the development of acquired immunity.

*A variety of peptides and proteins attack microbes.*

- Pathogen recognition in mammals triggers the production and release of a variety of peptides and proteins that attack microbes directly 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.
- The **interferons** provide innate defenses against 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.
- One type of interferon activates 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 microbes.
- Activation results in a cascade of biochemical reactions that lead to lysis (bursting) of invading cells.
  - The complement system functions in inflammation as well as in acquired defenses.

*Damage to tissue triggers an inflammatory response.*

- Damage to tissue by a physical injury or the entry of microbes 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 **mast cells** in connective tissues.
- When injured, mast cells release their histamine.
- Histamine triggers both dilation and increased permeability of nearby capillaries.
- Activated macrophages and other cells discharge additional signals that promote more blood flow to the injured site.
- Increased local blood supply leads to the characteristic swelling, redness, and heat of inflammation.
- Blood-engorged capillaries leak fluid into neighboring tissue, causing swelling.
- Enhanced blood flow and vessel permeability aid in delivering clotting elements and antimicrobial proteins to the injured area.
  - Activated complement proteins promote the release of more histamine and help attract phagocytes.
  - Clotting marks the beginning of the repair process and helps block the spread of microbes 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 microbes, 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 called *pyrogens* released by activated macrophages set the body's thermostat at a higher temperature.
  - Moderate fever may facilitate phagocytosis and hasten 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 low blood pressure, septic shock is a life-threatening medical emergency that is fatal in more than one-third of those affected.

***Natural killer cells help recognize and eliminate diseased cells in vertebrates.***

- **Natural killer (NK) cells** do not attack microorganisms directly but destroy virus-infected body cells.
  - NK cells also attack abnormal body cells that could become cancerous.
  - With the exception of red blood cells, all body cells have class I MHC molecules on their surface. The role of class I MHC molecules in immune function will be discussed later.
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- Due to viral infection or conversion to a cancerous state, cells may not express this protein.
- NK cells attach to such cells and release chemicals that bring about cell death, inhibiting the spread of the virus or cancer.
- Some pathogens can avoid destruction by phagocytic cells.
  - For example, the outer capsule that surrounds certain bacteria hides polysaccharides on their surface, preventing recognition.
- Some bacteria do not avoid recognition but are resistant to breakdown within lysosomes following phagocytosis.
  - One example is the bacterium that causes the disease tuberculosis.
  - Rather than being destroyed within the host's cells, such microbes grow and reproduce, effectively hidden from the acquired defenses of the body.
  - Tuberculosis, also known as TB, kills more than a million people a year worldwide.

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

***Lymphocytes provide the specificity and diversity of the 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 acquired 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.
- B and T cells recognize and inactivate foreign cells and molecules.
- Both types of cells also contribute to *immunological memory*, an enhanced response to a foreign molecule encountered previously.

- Although B cells and T cells function only in the acquired immune system, innate and acquired immunity are not independent.
- At the start of an infection, signals from phagocytic cells activate lymphocytes, stimulating an acquired response.
  - For example, phagocytic cells secrete **chemokines** that help recruit and activate lymphocytes.
- Macrophages and dendritic cells also have a direct role in pathogen recognition by B cells and T cells.

*The basic facts of acquired immunity can be briefly summarized.*

- Each B cell and T cell has on its surface many receptor proteins that can bind a foreign molecule.
- The receptor proteins on a single lymphocyte are all the same, but there are millions of lymphocytes in the body that differ in the foreign molecules that their receptors recognize.
- When a host animal is infected, B and T cells with receptors that can recognize the microbe are activated.
  - Activation involves the B and T cells interacting with fragments of microbes displayed on the surface of cells.
- Some T cells assist in activating other lymphocytes, while other T cells detect and kill infected host cells.
- Foreign molecules and cells that circulate in body fluids are subject to attack by soluble receptor proteins secreted by specialized B cells.
- Activated lymphocytes also undergo cell division, with some of the daughter B and T cells being set aside to fight any future infections of the host by the same microbe.

*Lymphocytes recognize specific antigens.*

- Any foreign molecule that is specifically recognized by lymphocytes and elicits a response from them is called an **antigen**.
- Most antigens are large molecules such as proteins or polysaccharides.
- Most antigens are cell-associated molecules that protrude from the surface of pathogens or transplanted cells.
- Others, such as toxins secreted by bacteria, are released into extracellular fluid.
- Each B cell and T cell has many antigen-specific receptors embedded in its plasma membranes.
  - A single B or T lymphocyte bears about 100,000 identical **antigen receptors**.
- B cells sometimes give rise to **plasma cells** that secrete a soluble form of the antigen receptor.
- This secreted protein is called an **antibody**, or **immunoglobulin**.
- A lymphocyte actually recognizes and binds to a small portion of an antigen called an **epitope** or *antigenic determinant*.
  - A single antigen usually has several different epitopes, each capable of inducing a response from a lymphocyte.
- Because lymphocytes recognize and respond to particular microbes 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.
- Antibodies are similar to B cell receptors, except that they lack the transmembrane region and cytoplasmic tail.
- As a result, antibodies are secreted rather than membrane-bound.
- Each **T cell receptor** for an antigen consists of two different polypeptide chains: an  $\alpha$  chain and a  $\beta$  chain, linked by a disulfide bridge.
  - Near the base of the molecule is a transmembrane region that anchors the molecule in the cell's plasma membrane.
  - At the outer tip of the molecule, the  $\alpha$  and  $\beta$  chain variable (*V*) regions form a single antigen-binding site.
  - The remainder of the molecule is made up of the constant (*C*) regions.
- B cell and T cell receptors have closely related but distinct functions.
- Both types of receptors bind to antigens via noncovalent bonds between the epitope and the binding surface.
- T cell receptors recognize and bind with antigens with the same specificity as B cell receptors.
- While the receptors on B cells recognize intact antigens, however, the receptors on T cells recognize small fragments of antigens that are displayed on the surface of host cells.
- The host cell protein responsible for presenting an antigen fragment to T cell receptors in this way is encoded by a group of genes called the **major histocompatibility complex (MHC)**.
- The process for antigen recognition by T cells begins with a pathogen either infecting or being engulfed by a host cell.
- Once the pathogen is inside a host cell, enzymes in the cell cleave the pathogen proteins into smaller pieces, called peptide antigens or antigen fragments.
- These peptide antigens then bind to an MHC molecule.
- The MHC molecule and bound peptide are transported to the cell surface, resulting in **antigen presentation**, display of the antigen fragment on the cell surface.
- If an antigen-presenting cell encounters a T cell, the receptors on the T cell can bind the peptide antigen.
- Antigen presentation by MHC proteins activates immune responses against an antigen and targets infected cells displaying the antigen for destruction.
- The type of cell that presents the antigen determines which response occurs.
- When a phagocyte or lymphocyte that has engulfed a pathogen displays an antigen, it signals the immune system that an infection is under way.
  - The immune system responds by increasing its response to that antigen and the pathogen that produces it.
- When a body cell displays an antigen, it signals the immune system that the cell is infected.
  - The immune system responds by eliminating such cells, disrupting further spread of the infection.

- To recognize the type of cell displaying an antigen, the immune system relies on two classes of MHC molecules: I and II.
- **Class I MHC molecules**, found on almost all nucleated cells of the body, bind peptides derived from foreign antigens that have been synthesized within the cell.
  - Any body cell that becomes infected or cancerous can display such peptide antigens by virtue of its class I MHC molecules.
  - Class I MHC molecules that display bound peptide antigens are recognized by a subgroup of T cells called **cytotoxic T cells**.
    - The term *cytotoxic* refers to their use of toxic gene products to kill infected cells.
- **Class II MHC molecules** are made by dendritic cells, macrophages, and B cells.
  - In these cells, class II MHC molecules bind peptides derived from foreign materials that have been internalized and fragmented by phagocytosis or endocytosis.
  - Dendritic cells, macrophages, and B cells, known as **antigen-presenting cells**, display antigens for recognition by cytotoxic T cells and **helper T cells**, a group of T cells that assists both B cells and cytotoxic T cells.
- The acquired immune system has three major properties.
  1. Tremendous receptor diversity, which allows pathogens never previously encountered to be recognized as foreign.
  2. Lack of reactivity against the molecules that make up the animal's own cells and tissues.
  3. Immunological memory. The response to an antigen that has been encountered previously is stronger and more rapid than the initial response.

*There is tremendous receptor diversity in the acquired immune system.*

- Differences in the amino acid sequence of the variable (*V*) region account for the specificity of antigen receptors on lymphocytes.
  - A single B or T cell displays about 100,000 identical antigen receptors.
  - It is highly unlikely that any two B cells or T cells have the same antigen receptor.
- The variable regions at the tip of a particular antigen receptor differ in amino acid sequence from one cell to the other.
- Because the variable regions form the antigen-binding site, a particular amino acid sequence generates specificity for a certain epitope.
- Each person has more than 1 million different B cells and 10 million different T cells, each with a particular antigen-binding specificity.
- How do 25,000 protein-coding genes in the human genome generate such remarkable diversity in antigen receptors?
- The answer is the variety of combinations: By combining variable elements, the immune system assembles many different receptors from a smaller collection of parts.
- Consider the *immunoglobulin (Ig)* gene, which encodes one chain of the B cell receptor.
  - This gene is used to make secreted antibodies (immunoglobulins) and membrane-bound receptors.
  - All B cell antigen receptor and T cell antigen receptor genes undergo very similar transformations.
- A receptor light chain is assembled from three pieces: a variable (*V*) segment, a joining (*J*) segment, and a constant (*C*) segment.
  - The *V* and *J* segments together produce the variable region of the receptor chain, while the *C* segment encodes the entire constant region.



- The light-chain gene contains a single *C* segment, 40 different *V* gene segments, and 5 different *J* gene segments.
- Since a functional light-chain 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 larger.
- Assembly of a functional light-chain gene requires rearranging the DNA.
  - Early in B cell development, a set of enzymes collectively called recombinase links one *V* gene segment to one *J* gene segment, forming a single exon that is part *V* and part *J*.
  - The *J* and *C* segments are joined after transcription by splicing out 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, only one light-chain gene and one heavy-chain gene are rearranged.
  - These permanent rearrangements are passed on to the daughter cells when the lymphocyte divides.
- After both the light-chain 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  $1.65 \times 10^6$ .
  - Mutations introduced during *VJ* recombination add additional variation.

***Acquired immunity does not react against the molecules that make up the animal's own cells and tissues.***

- Because antigen receptor genes are randomly rearranged, some immature lymphocytes produce receptors specific for epitopes on the body's own molecules.
- If 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.
- As lymphocytes mature in the bone marrow or thymus, their antigen receptors are tested for self-reactivity.
- Lymphocytes with receptors specific for the body's own molecules are typically either destroyed by apoptosis or rendered nonfunctional, leaving only those that react to foreign molecules.
- Because the body normally lacks mature lymphocytes that can react against its own components, the immune system is said to exhibit self-tolerance.
  - Failure of self-tolerance can lead to autoimmune diseases, such as multiple sclerosis.

***Clonal selection amplifies lymphocytes, producing immunological memory.***

- Because the body contains an enormous variety of antigen receptors, few are specific for the epitopes on a given antigen.
- As a result, it is very rare for an antigen to encounter a lymphocyte with a receptor specific for that antigen.
- The binding of an antigen receptor to its specific antigen initiates events that activate the lymphocyte.

- Activated B cells or T cells amplify the response by dividing many times, forming two types of clones: effector cells and memory cells.
  - **Effector cells**, which are short-lived, attack the antigen and any pathogens that produce that antigen.
  - **Memory cells**, which are long-lived but fewer in number, bear receptors specific for the antigen.
- The proliferation of a lymphocyte into a clone of cells in response to binding an antigen is called **clonal selection**.
  - The presentation of an antigen to specific receptors on a lymphocyte leads to repeated rounds of cell division.
  - The result is a clonal population of thousands of cells, all specific for that antigen.
- The production of effector cells from a clone of lymphocytes during the first exposure to an antigen represents the **primary immune response**.
  - The primary immune response peaks about 10 to 17 days after the initial exposure.
  - During this time, selected B cells generate antibody-secreting effector B cells, called **plasma cells**, and selected T cells are activated to their effector forms, consisting of helper cells and cytotoxic cells.
- If an individual is exposed again to the same antigen, the response is faster (typically only 2 to 7 days), of greater magnitude, and more prolonged.
- This is the **secondary immune response**.
- Measures of antibody concentrations in the blood serum over time clearly show the difference between primary and secondary immune responses.
- The secondary immune response relies on the reservoir of T and B memory cells generated following initial exposure to an antigen.
- Because these memory cells are long-lived, they provide the basis for immunological memory that can span many decades.
- If and when an antigen is encountered again, memory cells specific for that antigen enable the rapid formation of large clones of effector cells and thus a greatly enhanced immune defense.

### **Concept 43.3 Acquired immunity defends against infection of body cells and fluids.**

- The immune system can mount two types of immune responses to antigens: humoral and cell-mediated.
  - The **humoral immune response** involves the activation and clonal selection of effector B cells, which secrete antibodies that circulate in the blood plasma and lymph.
  - The **cell-mediated immune response** involves the activation and clonal selection of cytotoxic T lymphocytes, which identify and destroy target cells.
  - A third population of lymphocytes, the helper T cells, aids both responses.

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

- Activated by encounters with antigen-presenting cells, helper T cells play a central role in enhancing humoral and cell-mediated responses.
- The helper T cell proliferates after interacting with peptide antigens displayed by antigen-presenting cells.
- The resulting clone of cells differentiates into activated helper T cells and memory helper T cells.

- The activated helper T cells then secrete cytokines that stimulate the activation of nearby B cells and cytotoxic T cells.
- The T cell receptors on the surface of the helper T cell bind the peptide antigen that is held by a class II MHC molecule on the antigen-presenting cell.
- At the same time, a protein called **CD4**, found on the surface of most helper T cells, binds the class II MHC molecule.
- CD4 helps keep the helper T cell and the antigen-presenting cell joined.
- As the two cells interact, signals in the form of cytokines are exchanged in both directions.
  - For example, cytokines stimulate the helper T cell, which produces its own set of cytokines.
- The net result is activation of the helper T cell.
- The three principal types of antigen-presenting cells—dendritic cells, macrophages, and B cells—interact with helper T cells in different contexts.
- Dendritic cells serve as sentinels in the epidermis and other tissues frequently exposed to foreign antigens, acting to trigger a primary immune response.
  - After dendritic cells capture antigens, they migrate from the infection site to lymphoid tissues, where they present antigens, via class II MHC molecules, to helper T cells.
- Macrophages play the key role in initiating a secondary immune response by presenting antigens to memory helper T cells.
- B cells mainly present antigens to helper T cells in the humoral response.

*In the cell-mediated response, cytotoxic T cells counter intracellular pathogens.*

- Cytotoxic T cells are the effector cells in cell-mediated immune response.
- To become active, they require signals from helper T cells as well as interaction with an antigen-presenting cell.
- Once activated, they eliminate body cells infected by viruses or other intracellular pathogens.
- Fragments of nonself proteins synthesized in target cells associate with class I MHC molecules and are displayed on the cell surface, where they can be recognized by cytotoxic T cells.
- A surface protein called **CD8**, found on most cytotoxic T cells, enhances the interaction between a target cell and a cytotoxic T cell.
- Binding of CD8 to the side of a class I MHC molecule helps keep the two cells in contact while the cytotoxic T cell is activated.
- Thus, the roles of class I MHC molecules and CD8 are similar to those of class II MHC molecules and CD4, except that different cell types are involved.
- The targeted destruction of an infected cell by a cytotoxic T cell involves the secretion of proteins that cause cell rupture and cell death, depriving the pathogen of a place to reproduce and exposing it to circulating antibodies, which mark it for disposal.
- After destroying an infected cell, the cytotoxic T cell moves on to kill other cells infected with the same pathogen.

*In the humoral response, B cells make antibodies against extracellular pathogens.*

- The secretion of antibodies by clonally selected B cells is the hallmark of the humoral response.
  - Activation of this response typically involves B cells and helper T cells, as well as antigenic proteins or polysaccharides on the surface of bacteria.
- B cell activation by an antigen is aided by cytokines secreted from helper T cells that have encountered the same antigen.

- The B cell then proliferates and differentiates into a clone of antibody-secreting plasma cells and a clone of memory B cells.
- The pathway for antigen processing and display in B cells differs from the pathway in other antigen-presenting cells.
- A macrophage or dendritic cell can present peptide fragments from a wide variety of 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 B cell then presents an MHC-antigen complex bound to a helper T cell, achieving the direct cell-to-cell contact that is usually critical to B cell activation.
- A single antigen can provoke a robust humoral response.
  - An activated B cell gives rise to a clone of thousands of plasma cells, each of which secretes approximately 2,000 antibody molecules every second of the cell's four- to five-day life span.
- Because most antigens recognized by B cells contain multiple epitopes, exposure to a single antigen normally activates a variety of B cells, with different clones of plasma cells directed against different epitopes on the common antigen.
- A B cell response can occur without involvement of cytokines or helper T cells.
- Although such responses generate no memory B cells, they play an important role in defending against many bacteria.

***There are five major classes of antibodies.***

- The antibodies produced by a given B cell differ from the B cell receptor only in the constant (*C*) region of the heavy chain, which contains sequences that determine where the *d* is distributed and how it mediates antigen disposal.
- The five major types of heavy-chain constant regions determine the five major classes of antibodies.
  - Two classes exist primarily as polymers of the basic antibody molecule: IgM as a pentamer and IgA as a dimer.
  - The other three classes—IgG, IgE, and IgD—exist exclusively as monomers.
- The power of antibody specificity and antigen-antibody binding has been applied in laboratory research and clinical diagnosis.
- Some antibody tools are *polyclonal*—the products of many different clones of B cells, each specific for a different epitope.
- Others are *monoclonal*, prepared from a single clone of B cells grown in culture.
- These cells produce **monoclonal antibodies**, identical and specific for the same epitope on an antigen.
- Monoclonal antibodies are useful for tagging specific molecules.
  - For example, home pregnancy tests use monoclonal antibodies to detect human chorionic gonadotropin (HCG), produced as soon as an embryo implants in the uterus.

***The binding of antibodies to antigens can interfere with pathogen function.***

- The binding of antibodies to antigens is the basis of several antigen disposal mechanisms.
  - In viral *neutralization*, antibodies bind to surface proteins on a virus, blocking the virus's ability to infect a host cell.
  - Antibodies sometimes bind to and neutralize toxins released in body fluids.

- In *opsonization*, bound antibodies enhance macrophage attachment to and phagocytosis of microbes.
- Antibodies may work with the proteins of the complement system to dispose of pathogens.
  - The term *complement* reflects the fact that these proteins increase the effectiveness of antibody-directed attacks on bacteria.
- Binding of antigen-antibody complexes on a microbe or foreign cell to one of the complement proteins triggers a cascade as each protein of the complement system activates the next.
- Ultimately, activated complement proteins generate a *membrane attack complex (MAC)*, which forms a pore in the bacterial membrane, resulting in cell lysis.
- Whether activated as part of innate or acquired defenses, the complement cascade results in the lysis of microbes and produces activated complement proteins that promote inflammation or stimulate phagocytosis.
- When antibodies facilitate phagocytosis, they also help fine-tune the humoral immune response.
  - This positive feedback between the innate and acquired immune systems contributes to a coordinated, effective response to infection.
- Antibodies can 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 the exposed proteins, the presence of bound antibody at the cell surface can recruit an NK cell to release proteins that cause the infected cell to undergo apoptosis.

***Immunity can be achieved naturally or artificially.***

- In response to infection, clones of memory cells form, providing **active immunity**.
- A different type of immunity results when the IgG antibodies of a pregnant woman cross the placenta to her fetus.
  - The transferred antibodies can destroy the pathogens for which they are specific.
  - Antibodies transferred from one individual to another provide **passive immunity**.
  - Because passive immunity does not involve the recipient's B and T cells, it persists only as long as the transferred antibodies last (a few weeks to a few months).
- IgA antibodies are passed from a mother to her infant in breast milk.
  - These antibodies provide additional protection against infection to the infant while its immune system develops.
- Both active and passive immunity can be induced artificially.
- Active immunity can develop from the introduction of antigens into the body through **immunization**, also known as **vaccination**.
  - Vaccines include inactivated bacterial toxins, killed microbes, parts of microbes, viable but weakened microbes, and even genes encoding microbial proteins.
  - These agents can act as antigens, stimulating an immune response and, more important, producing immunological memory.
  - A vaccinated person who encounters the actual pathogen will have the same quick secondary response based on memory cells as a person who has had the disease.
- Routine immunization of infants and children has dramatically reduced the incidence of infectious diseases such as polio, measles, and whooping cough, and has led to the eradication of smallpox, a viral disease.

- Unfortunately, not all infectious agents are easily managed by vaccination.
- Also, some vaccines are not readily available in poor parts of the world.
- Even in developed countries, the failure to immunize children with available vaccines has led to outbreaks of serious but preventable diseases.
- Passive immunity can be transferred artificially by injecting antibodies from an animal that is already immune to a disease into another animal.
- This confers short-term, but immediate, protection against that disease.
  - For example, a person bitten by a venomous snake may be treated with antivenin, a serum from sheep or horses that have been immunized against the venom of a poisonous snake.
  - The antibodies in antivenin neutralize toxins in venom before they can do massive damage.

*Harmful immune reactions may jeopardize transplants and transfusions.*

- One source of potential problems with blood transfusions is an immune reaction caused by incompatible blood types.
  - In the ABO blood groups, an individual with type A blood has A antigens on the surface of red blood cells.
  - B antigens are found on type B red blood cells.
  - Both A and B antigens are found on type AB red blood cells.
  - Neither antigen is found on type O red blood cells.
- A person with type A blood already has antibodies to the B antigen, even if the person has never been exposed to type B blood.
  - These antibodies arise in response to bacteria normally present in the body that have epitopes very similar to blood group antigens.
- An individual with type A blood does not make antibodies to A-like bacterial epitopes—these are considered self—but that person does make antibodies to B-like bacterial epitopes.
- If a person with type A blood receives a transfusion of type B blood, the preexisting anti-B antibodies induce 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 also act against the recipient's type A red blood cells.
- Major histocompatibility complex (MHC) molecules may stimulate rejection of tissue grafts and organ transplants.
- Because MHC creates a unique protein fingerprint for each individual, foreign MHC molecules are antigenic, inducing immune responses against the donated tissue or organ.
  - To minimize rejection, attempts are made to match MHC of tissue donor and recipient as closely as possible.
  - In the absence of identical twins, siblings usually provide the closest tissue-type match.
- In addition to MHC matching, various medicines are used to suppress the immune response to the transplant.
  - However, this strategy leaves the recipient more susceptible to infection during the course of treatment.
- In bone marrow transplants, it is the graft itself, rather than the recipient, that is the source of potential immune rejection.
  - Bone marrow transplants are used to treat leukemia and other cancers as well as various hematological diseases.

- Prior to the transplant, the recipient is typically treated with irradiation to eliminate the recipient's immune system, eliminating all abnormal cells and leaving little chance of graft rejection.
- However, the donated marrow, containing lymphocytes, may react against the recipient, producing *graft versus host reaction*, unless well matched.

### **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 some 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 *degranulate*—that is, to release histamines and other inflammatory agents from vesicles called granules.
- High levels of histamines cause dilation and increased permeability of small blood vessels.
  - These inflammatory events lead to typical allergy symptoms: sneezing, runny nose, tearing 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 mast cell degranulation triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure.
  - Death may occur within minutes.
  - 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 loses tolerance for self and turns against certain molecules of the body, causing one of many **autoimmune diseases**.
- In *systemic lupus erythematosus (lupus)*, the immune system generates antibodies against various self molecules, including 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 *insulin-dependent 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 some neurons.
  - People with MS experience a number of serious neurological abnormalities.
- 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.
- Although much remains to be learned about autoimmunity, there has been substantial progress, including the identification of regulatory T cells that ordinarily help prevent attack by any self-reactive lymphocytes that remain functional in adults.

*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.

*Diminished immune responses can cause disease.*

- In **immunodeficiency** diseases, the ability of the immune system to protect against pathogens is compromised, leading to frequent and recurrent infections and increased susceptibility to certain cancers.
- 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.
  - Several gene therapy approaches are in clinical trials to attempt to reverse SCID.
- 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 an acquired immune deficiency.

*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 a remarkable 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 acquired 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 birds.
- 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.
- Some viruses remain in a host without activating immune defenses, ceasing the production of viral products targeted by lymphocytes.
- 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 acquired 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 aggressive 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, preventing recognition and elimination by the immune system.
  - 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 surveillance by 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 acquired immune response but also abolishes it.
- Virus reproduction and cell death triggered by the virus lead to loss of 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 2006, more than 2.5 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 or blood, 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.

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

- The increase in cancer rates with an impaired immune response may occur because the immune system normally attacks body cells that become cancerous.
- There is an alternative explanation: Impairment of the immune response leaves the body open to infection, which causes inflammatory responses, now known to be a contributing event to the development of many cancers.
- Determining the link between cancer and immunity and finding out whether passive or active immunization can be used to fight cancer are active areas of investigation.