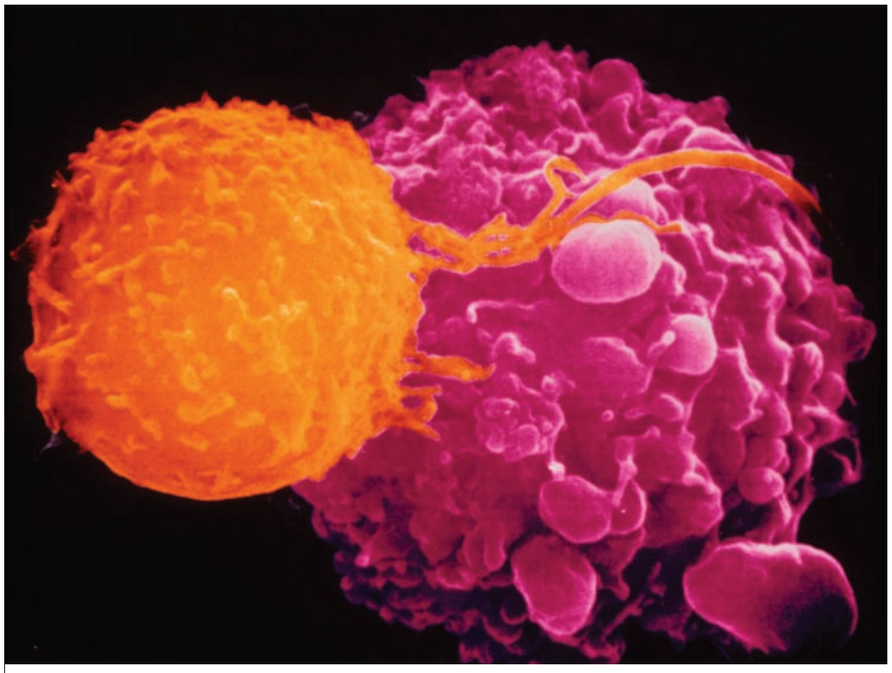


Death of a cancer cell. A cytotoxic T cell (orange) induces a cancer cell (mauve) to undergo apoptosis (programmed cell death). Cytotoxic T cells are part of the body's immune response system programmed to seek out, attach themselves, and kill cancer cells and pathogen-infected host cells.

Study Plan

43 Defenses against Disease

Why It Matters

Acquired immune deficiency syndrome (AIDS), which was first identified in the early 1980s, now infects about 40 million people worldwide, and continues to spread. Thousands of health-care workers, physicians, and researchers have joined the effort to control AIDS and develop effective treatments. Their primary aim is to develop an anti-AIDS *vaccine*—a substance that, when swallowed or injected, provides protection against infection by HIV (human immunodeficiency virus), which causes the disease.

The development of vaccines began with efforts to control smallpox, a dangerous and disfiguring viral disease that once infected millions of people worldwide. As early as the twelfth century, healthy individuals in China sought out people who were recovering from mild smallpox infections, ground up scabs from their lesions, and inhaled the powder or pushed it into their skin. Variations on this treatment were effective in protecting many people against smallpox infection.

In 1796, an English country doctor, Edward Jenner, used a more scientific approach. He knew that milkmaids never got smallpox if they had contracted cowpox, a similar but mild disease of cows that can be transmitted to humans. Jenner decided to see if a deliberate

infection with cowpox would protect humans from smallpox. He scratched material from a cowpox sore into a boy's arm, and 6 weeks later, after the cowpox infection had subsided, he scratched fluid from human smallpox sores into the boy's skin. (Jenner's use of the boy as an experimental subject would now be considered unethical.) Remarkably, the boy remained free from smallpox. Jenner carried out additional, carefully documented case studies with other patients with the same results. His technique became the basis for worldwide **vaccination** (*vacca* = cow) against smallpox. With improved vaccines, smallpox has now been eradicated from the human population.

Vaccination takes advantage of the **immune system** (*immunis* = exempt), the natural protection that is our main defense against infectious disease. This chapter focuses on the immune system and other defenses against infection, such as the skin. Our description emphasizes human and other mammalian systems, in which most of the scientific discoveries revealing the structure and function of the immune system have been made. At the end of the chapter we compare mammalian systems with the protective systems of nonmammalian vertebrates and invertebrates.

43.1 Three Lines of Defense against Invasion

Every organism is constantly exposed to *pathogens,* disease-causing viruses or organisms such as infectious bacteria, protists, fungi, and parasitic worms. Humans and other mammals have three lines of defense against these threats. The first line of defense involves physical barriers that prevent infection; it is not part of the immune system. The second line of defense is the *innate immunity system,* the inherited mechanisms that protect the body from many kinds of pathogens in a nonspecific way. The third line of defense, the *adaptive immunity system,* involves inherited mechanisms leading to the synthesis of molecules that target pathogens in a specific way. Reaction to an infection takes minutes in the case of the innate immunity system versus days for the adaptive immunity system.

Epithelial Surfaces Are Anatomical Barriers That Help Prevent Infection

An organism's first line of defense is the body surface—the skin covering the body exterior and the epithelial surfaces covering internal body cavities and ducts, such as the lungs and intestinal tract. The body surface forms a barrier of tight junctions between epithelial cells that keeps most pathogens (as well as toxic substances) from entering the body.

Many epithelial surfaces are coated with a mucus layer secreted by the epithelial cells that protects against pathogens as well as toxins and other chemicals. In the respiratory tract, ciliated cells constantly sweep the mucus, with its trapped bacteria and other foreign matter, into the throat, where it is coughed out or swallowed.

Many of the body cavities lined by mucous membranes have environments that are hostile to pathogens. For example, the strongly acidic environment of the stomach kills most bacteria and destroys many viruses that are carried there, including those trapped in swallowed mucus from the respiratory tract. Most of the pathogens that survive the stomach acid are destroyed by the digestive enzymes and bile secreted into the small intestine. The vagina, too, is acidic, which prevents many pathogens from surviving there. The mucus coating in some locations contains the enzyme lysozyme, which was secreted by the epithelial cells. Lysozyme breaks down the walls of some bacteria, causing them to lyse.

Two Immunity Systems Protect the Body from Pathogens That Have Crossed External Barriers

The body's second line of defense is a series of generalized internal chemical, physical, and cellular reactions that attack pathogens that have breached the first line. These defenses include inflammation, which creates internal conditions that inhibit or kill many pathogens, and specialized cells that engulf or kill pathogens or infected body cells.

Innate immunity is the term for this initial response by the body to eliminate cellular pathogens, such as bacteria and viruses, and prevent infection. You are born with an innate immune system. Innate immunity provides an immediate, *nonspecific* response; that is, it targets any invading pathogen and has no memory of prior exposure to the pathogen. It provides some protection against invading pathogens while a more powerful, specific response system is mobilized.

The third and most effective line of defense, **adaptive** (also called **acquired**) **immunity,** is *specific:* it recognizes individual pathogens and mounts an attack that directly neutralizes or eliminates them. It is so named because it is stimulated and shaped by the presence of a specific pathogen or foreign molecule. This mechanism takes several days to become protective. Adaptive immunity is triggered by specific molecules on pathogens that are recognized as being foreign to the body. The body retains a memory of the first exposure to a foreign molecule, enabling it to respond more quickly if the pathogen is encountered again in the future.

Innate immunity and adaptive immunity together constitute the immune system, and the defensive reactions of the system are termed the **immune response.** Functionally, the two components of the immune sys-

tem interconnect and communicate at the chemical and cellular levels. The immune system is the product of a long evolutionary history of compensating adaptations by both pathogens and their targets. Over millions of years of vertebrate history, the mechanisms by which pathogens attack and invade have become more efficient, but the defenses of animals against the invaders have kept pace.

Study Break

1. What features of epithelial surfaces protect against pathogens?
2. What are the key differences between innate immunity and adaptive immunity?

43.2 Nonspecific Defenses: Innate Immunity

In most cases, the body needs 7 to 10 days to develop a fully effective immune response against a new pathogen, one that is invading the body for the first time. Innate immunity holds off invading pathogens in the meantime, killing or containing them until adaptive immunity comes fully into play. We have already discussed the body's anatomical barriers. Now let us look at the internal mechanisms of innate immunity: secreted molecules and cellular components. As you will see, cellular pathogens (such as bacteria) and viral pathogens elicit different responses.

Innate Immunity Provides an Immediate, General Defense against Invading Cellular Pathogens

Cellular pathogens—typically microorganisms—usually enter the body when injuries break the skin or epithelial surfaces. How does the host body recognize the pathogen as foreign? The answer is that the host has mechanisms to distinguish self from nonself. The innate immune system recognizes particular molecules that are common to many pathogens but absent in the host. An example is the lipopolysaccharide of gram-negative bacteria. The host then responds immediately to combat the pathogen.

Several types of specific cell-surface receptors in the host recognize the various types of molecules on microbial pathogens. The response depends on the receptor. For some receptors, the response is secretion of *antimicrobial peptides,* which kill the microbial pathogen. Other receptors include those that trigger the host cell to engulf, and destroy the pathogen, initiating inflammation, and the soluble receptors of the *complement system.*

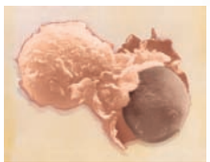
Antimicrobial Peptides. All of our epithelial surfaces, namely skin, the lining of the gastrointestinal tract, the lining of the nasal passages and lungs, and the lining of the genitourinary tracts, are protected by antimicrobial peptides called *defensins.* Epithelial cells of those surfaces secrete defensins upon attack by a microbial pathogen. The defensins attack the plasma membranes of the pathogens, eventually disrupting them, thereby killing the cells. In particular, defensins play a significant role in innate immunity of the mammalian intestinal tract.

Inflammation. A tissue's rapid response to injury, including infection by most pathogens, involves **inflammation** (*inflammare* = to set on fire), the heat, pain, redness, and swelling that occur at the site of an infection.

Several interconnecting mechanisms initiate inflammation **(Figure 43.1).** Let us consider bacteria entering a tissue as a result of a wound. **Monocytes** (a type of leukocyte) enter the damaged tissue from the bloodstream through the endothelial wall of the blood vessel. Once in the damaged tissue, the monocytes differentiate into **macrophages** ("big eaters"), which are phagocytes that are usually the first to recognize pathogens at the cellular level. (**Table 43.1** lists the major types of leukocytes such as macrophages; see also Figure 42.7.) Cell-surface receptors on the macrophages recognize and bind to surface molecules on the pathogen, activating the macrophage to phagocytize (engulf) the pathogen (see Figure 43.1, step 1). Activated macrophages also secrete **cytokines,** molecules that bind to receptors on other host cells and, through signal transduction pathways, trigger a response. Usually, not enough macrophages are present in the area of a bacterial infection to handle all of the bacteria.

The death of cells caused by the pathogen at the infection site activates cells dispersed through connective tissue called **mast cells,** which then release histamine (step 2). This histamine, along with the cytokines from activated macrophages, dilates local blood vessels around the infection site and increases their permeability, which increases blood flow and leakage of fluid from the vessels into body tissues (step 3). The response initiated by cytokines directly causes the heat, redness, and swelling of inflammation.

Cytokines also make the endothelial cells of the blood vessel wall stickier, causing circulating **neutrophils** (another type of phagocytic leukocyte) to attach to it in massive numbers. From there, the neutrophils are attracted to the infection site by **chemokines,** proteins also secreted by activated macrophages (step 4). To get to the infection site, the neutrophils pass between endothelial cells of the blood vessel wall. Neutrophils may also be attracted to the pathogen directly by molecules released from the pathogens themselves. Like macrophages, neutrophils have cell-surface recep-



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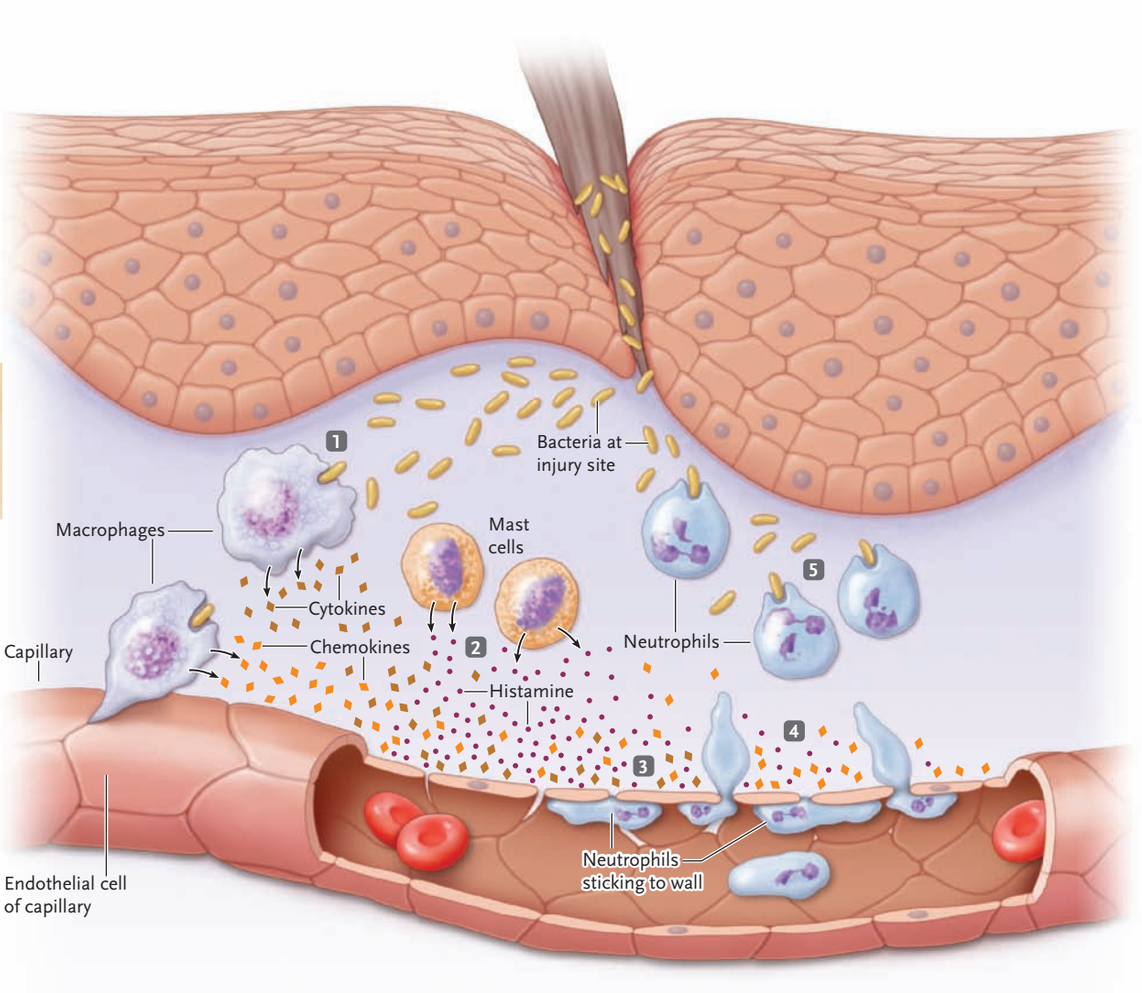


1 A break in the skin introduces bacteria, which reproduce at the wound site. Activated macrophages engulf the pathogens and secrete cytokines and chemokines.

2 Activated mast cells release histamine.

3 Histamine and cytokines dilate local blood vessels and increase their permeability. The cytokines also make the blood vessel wall sticky, causing neutrophils to attach.

4 Chemokines attract neutrophils, which pass between cells of the blood vessel wall and migrate to the infection site.

5 Neutrophils engulf the pathogens and destroy them.

Figure 43.1
The steps producing inflammation. The colorized micrograph on the left shows a macrophage engulfing a yeast cell.

tors that enable them to recognize and engulf pathogens (step 5).

Once a macrophage or neutrophil has engulfed the pathogen, it uses a variety of mechanisms to destroy it. These mechanisms include attacks by enzymes and defensins located in lysosomes and the production of toxic chemicals. The harshness of these attacks usually kills the neutrophils as well, while macrophages usually survive to continue their pathogen-scavenging activities. Dead and dying neutrophils, in fact, are a major component of the pus formed at infection sites. The pain of inflammation is caused by the migration of macrophages and neutrophils to the infection site and their activities there.

Some pathogens, such as parasitic worms, are too large to be engulfed by macrophages or neutrophils. In that case, macrophages, neutrophils, and **eosinophils** (another type of leukocyte) cluster around the pathogen and secrete lysosomal enzymes and defensins in amounts that are often sufficient to kill the pathogen.

The Complement System. Another nonspecific defense mechanism activated by invading pathogens is the **complement system**, a group of more than 30 interacting soluble plasma proteins circulating in the blood and interstitial fluid **(Figure 43.2).** The proteins are normally inactive; they are activated when they recognize molecules on the surfaces of pathogens. Activated complement proteins participate in a cascade of reactions on pathogen surfaces, producing large numbers of different complement proteins, some of which assemble into **membrane attack complexes.** These complexes insert into the plasma membrane of many

types of bacterial cells and create pores that allow ions and small molecules to pass readily through the membrane. As a result, the bacteria can no longer maintain osmotic balance, and they swell and lyse. For the other types of bacterial cells, the cascade of reactions coats the pathogen with fragments of the complement proteins. Cell-surface receptors on phagocytes then recognize these fragments, and engulf and destroy the pathogen.

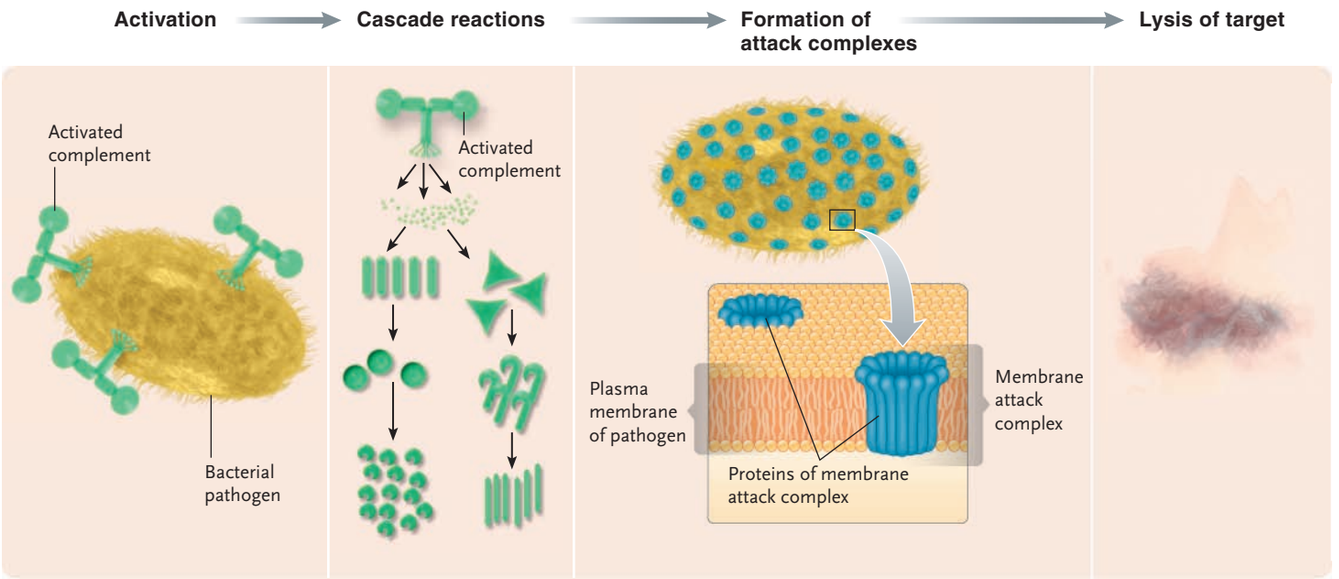
Several activated proteins in the complement cascade also act individually to enhance the inflammatory response. For example, some of the proteins stimulate mast cells to enhance histamine release, while others cause increased blood vessel permeability.

Combating Viral Pathogens Requires a Different Innate Immune Response

You have learned that specific molecules on cellular pathogens such as bacteria are key to initiating innate immune responses. By contrast, the innate immunity system is unable to distinguish effectively the surface molecules of viral pathogens from those of the host. The host must, therefore, use other strategies to provide some immediate protection against viral infec-

Table 43.1 **Major Types of Leukocytes and Their Functions**

Type of Leukocyte	Function
Monocyte	Differentiates into a macrophage when released from blood into damaged tissue
Macrophage	Phagocyte that engulfs infected cells, pathogens, and cellular debris in damaged tissues; helps activate lymphocytes carrying out immune response
Neutrophil	Phagocyte that engulfs pathogens and tissue debris in damaged tissues
Eosinophil	Secretes substances that kill eukaryotic parasites such as worms
Lymphocyte	Main subtypes involved in innate and adaptive immunity are natural killer (NK) cells, B cells, plasma cells, helper T cells, and cytotoxic T cells. NK cells function as part of innate immunity to kill virus-infected cells and some cancerous cells of the host. The other cell types function as part of adaptive immunity: they produce antibodies, destroy infected and cancerous body cells, and stimulate macrophages and other leukocyte types to engulf infected cells, pathogens, and cellular debris
Basophil	Located in blood, responds to IgE antibodies in an allergic response by secreting histamine, which stimulates inflammation



1 Complement proteins are activated by binding directly to a bacterial surface.

2 Cascading reactions produce huge numbers of different complement proteins. These assemble into many molecules, which form many membrane attack complexes.

3 The membrane attack complexes insert into the plasma membrane of the pathogen. Each forms a large pore across the membrane.

4 The pores promote lysis of the pathogen, which dies because of the severe disruption of its structure.

Figure 43.2
The role of complement proteins in combating microbial pathogens.

tions until the adaptive immunity system, which can discriminate between viral and host proteins, is effective. Three main strategies involve RNA interference, interferon, and natural killer cells.

RNA Interference. *RNA interference (RNAi)* is a cellular mechanism that is triggered by a virus's double-stranded (ds) RNA molecules (see Section 16.3). Such molecules are a natural part of the life cycles of a number of viruses. The RNAi system destroys dsRNA molecules, thereby inhibiting the virus's life cycle.

Interferon. Viral dsRNA also causes the infected host cell to produce two cytokines, called interferon-α and interferon-β. **Interferons** can be produced by most cells of the body. These proteins act both on the infected cell that produces them, an autocrine effect, and on neighboring uninfected cells, a paracrine effect (see Section 40.1). They work by binding to cell-surface receptors, triggering a signal transduction pathway that changes the gene expression pattern of the cells. The key changes include activation of a ribonuclease enzyme that degrades most cellular RNA and inactivation of a key protein required for protein synthesis, thereby inhibiting most protein synthesis in the cell. These effects on RNA and protein synthesis inhibit replication of the viral genome, while putting the cell in a weakened state from which it often can recover.

Natural Killer Cells. Cells that have been infected with virus must be destroyed. That is the role of **natural killer (NK) cells.** NK cells are a type of **lymphocyte,** a leukocyte that carries out most of its activities in tissues and organs of the lymphatic system (see Figure 42.20). NK cells circulate in the blood and kill target host cells—not only cells that are infected with virus, but also some cells that have become cancerous.

NK cells can be activated by cell-surface receptors or by interferons secreted by virus-infected cells. NK cells are not phagocytes; instead, they secrete granules containing *perforin,* a protein that creates pores in the target cell's membrane. Unregulated diffusion of ions and molecules through the pores causes osmotic imbalance, swelling, and rupture of the infected cell. NK cells also kill target cells indirectly through the secretion of *proteases* (protein-degrading enzymes) that pass through the pores. The proteases trigger **apoptosis,** or programmed cell death (see *Insights from the Molecular Revolution* in Chapter 7). That is, the proteases activate other enzymes that cause the degradation of DNA which, in turn, induces pathways leading to the cell's death.

How does an NK cell distinguish a target cell from a normal cell? The surfaces of most vertebrate cells contain particular *major histocompatibility complex (MHC) proteins*. You will learn about the role of these proteins in adaptive immunity in the next section; for now, just consider them to be tags on the cell surface. NK cells monitor the level of MHC proteins and respond differently depending on their level. An appropriately high level, as on normal cells, inhibits the killing activity of NK cells. Viruses often inhibit the synthesis of MHC proteins in the cells they infect, lowering the levels of those proteins and identifying them to NK cells. Cancer cells also have low or, in some cases, no MHC proteins on their surfaces, which makes them a target for destruction by NK cells as well.

Study Break

1. What are the usual characteristics of the inflammatory response?
2. What processes specifically cause each characteristic of the inflammatory response?
3. What is the complement system?
4. Why does combating viral pathogens require a different response by the innate immunity system than combating bacterial pathogens? What are the three main strategies a host uses to protect against viral infections?

43.3 Specific Defenses: Adaptive Immunity

Adaptive immunity is a defense mechanism that recognizes specific molecules as being foreign and clears those molecules from the body. The foreign molecules recognized may be free, as in the case of toxins, or they may be on the surface of a virus or cell, the latter including pathogenic bacteria, cancer cells, pollen, and cells of transplanted tissues and organs. Adaptive immunity develops only when the body is exposed to the foreign molecules and, hence, takes several days to become effective. This would be a significant problem in the case of invading pathogens were it not for the innate immune system, which combats the invading pathogens in a nonspecific way within minutes after they enter the body. There are two key distinctions between innate and adaptive immunity: innate immunity is nonspecific whereas adaptive immunity is specific, and innate immunity retains no memory of exposure to the pathogen whereas adaptive immunity retains a memory of the foreign molecule that triggered the response, thereby enabling a rapid, more powerful response if that pathogen is encountered again at a later time.

In Adaptive Immunity, Antigens Are Cleared from the Body by B Cells or T Cells

A foreign molecule that triggers an adaptive immunity response is called an **antigen** (meaning "*anti*body *gen*erator"). Antigens are macromolecules; most are large

proteins (including glycoproteins and lipoproteins) or polysaccharides (including lipopolysaccharides). Some types of nucleic acids can also act as antigens, as can various large, artificially synthesized molecules.

Antigens may be *exogenous,* meaning they enter the body from the environment, or *endogenous,* meaning they are generated within the body. Exogenous antigens include antigens on pathogens introduced beneath the skin, antigens in vaccinations, and inhaled and ingested macromolecules, such as toxins. Endogenous antigens include proteins encoded by viruses that have infected cells, and altered proteins produced by mutated genes, such as those in cancer cells.

Antigens are recognized in the body by two types of lymphocytes, B cells and T cells. **B cells** differentiate from stem cells in the bone marrow (see Section 42.2). It is easy to remember this as "B for bone." However, the "B" actually refers to the *bursa of Fabricus,* a lymphatic organ found only in birds; B cells were first discovered there. After their differentiation, B cells are released into the blood and carried to capillary beds serving the tissues and organs of the lymphatic system. Like B cells, **T cells** are produced by the division of stem cells in the bone marrow. Then, they are released into the blood and carried to the **thymus**, an organ of the lymphatic system (the "T" in "T cell" refers to the thymus).

The role of lymphocytes in adaptive immunity was demonstrated by experiments in which all of the leukocytes in mice were killed by irradiation with X rays. These mice were then unable to develop adaptive immunity. Injecting lymphocytes from normal mice into the irradiated mice restored the response; other body cells extracted from normal mice could not restore the response. (For more on the use of mice as an experimental organism in biology, see *Focus on Research Organisms.*)

There are two types of adaptive immune responses: **antibody-mediated immunity** (also called *humoral immunity*) and **cell-mediated immunity.** In antibody-mediated immunity, B-cell derivatives called **plasma cells** secrete **antibodies,** highly specific soluble protein molecules that circulate in the blood and lymph recognizing and binding to antigens and clearing them from the body. In cell-mediated immunity, a subclass of T cells becomes activated and, with other cells of the immune system, attacks foreign cells directly and kills them.

The steps involved in the adaptive immune response are similar for antibody-mediated immunity and cell-mediated immunity:

1. Antigen encounter and recognition: Lymphocytes encounter and recognize an antigen.
2. Lymphocyte activation: The lymphocytes are activated by binding to the antigen and proliferate by cell division to produce large clones of identical cells.
3. Antigen clearance: The large clones of activated lymphocytes are responsible for clearing the antigen from the body.
4. Development of immunological memory: Some of the activated lymphocytes differentiate into **memory cells** that circulate in the blood and lymph, ready to initiate a rapid immune response upon subsequent exposure to the same antigen.

These steps will be expanded upon in the following discussions of antibody-mediated immunity and cell-mediated immunity.

Antibody-Mediated Immunity Involves Activation of B Cells, Their Differentiation into Plasma Cells, and the Secretion of Antibodies

An adaptive immune response begins as soon as an antigen is encountered and recognized in the body.

Antigen Encounter and Recognition by Lymphocytes. Exogenous antigens are encountered by lymphocytes in the lymphatic system. As already mentioned, the two key lymphocytes that recognize antigens are B cells and T cells. Each B cell and each T cell is specific for a particular antigen, meaning that the cell can bind to only one particular molecular structure. The binding is so specific because the plasma membrane of each B cell and T cell is studded with thousands of identical receptors for the antigen; in B cells they are called **B-cell receptors (BCRs)** and in T cells they are called **T-cell receptors (TCRs) (Figure 43.3).** Considering the entire populations of B cells and T cells in the body, there are multiple cells that can recognize each antigen but, most importantly, the populations (in normal persons) contain cells capable of recognizing any antigen. For example, each of us has about 10 trillion B cells that collectively have about 100 million different kinds of BCRs. And, these cells are present *before* the body has encountered the antigens.

The binding between antigen and receptor is an interaction between two molecules that fit together like an enzyme and its substrate. A given BCR or TCR typically does not bind to the whole antigen molecule, but to small regions of it called **epitopes** or *antigenic determinants.* Therefore, several different B cells and T cells may bind to the population of a particular antigen encountered in the lymphatic system.

BCRs and TCRs are encoded by different genes and thus have different structures. The BCR on a B cell (see Figure 43.3a) corresponds to the antibody secreted by that particular B cell when it is activated and differentiates into a plasma cell. As you will learn in more detail shortly, an antibody molecule is a protein consisting of four polypeptide chains. At one end, it has two identical *antigen-binding sites,* regions that bind to a specific antigen. In the case of the BCR, at the opposite end of the

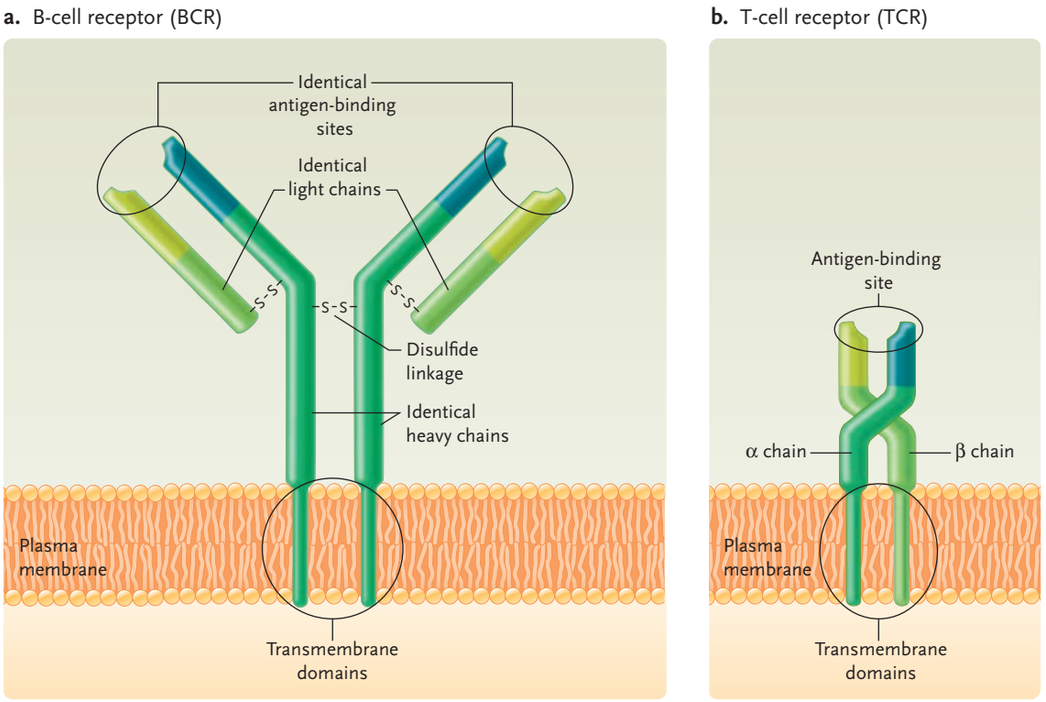
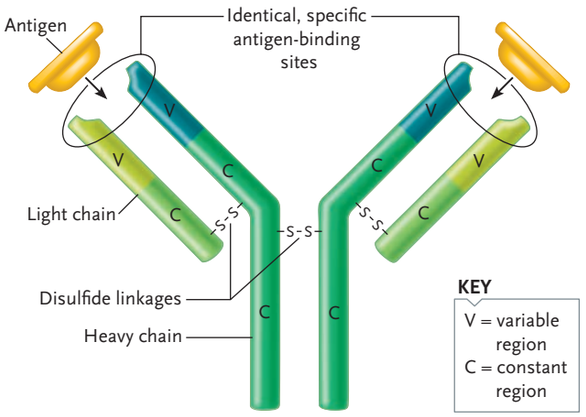


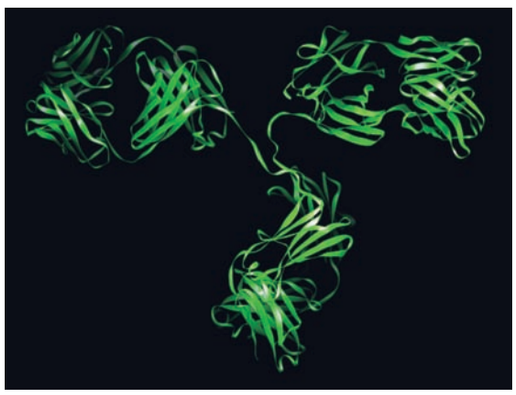
Figure 43.3
Antigen-binding receptors on B cells and T cells.

molecule from the antigen-binding sites are *transmembrane domains,* which embed in the plasma membrane. TCRs are simpler than BCRs, consisting of a protein made up of two different polypeptides (see Figure 43.3b). Like BCRs, TCRs have an antigen-binding site at one end and transmembrane domains at the other end.

Antibodies. Antibodies are the core molecules of antibody-mediated immunity. Antibodies are large, complex proteins that belong to a class of proteins known as **immunoglobulins** (Ig). Each antibody molecule consists of four polypeptide chains: two identical **light chains** and two identical **heavy chains** about twice or more the size of the light chain **(Figure 43.4).** The chains are held together in the complete protein by disulfide (—S—S—) linkages and fold into a Y-shaped structure. The bonds between the two arms of the Y form a hinge that allows the arms to flex independently of one another.

Each polypeptide chain of an antibody molecule has a *constant region* and a *variable region*. The constant region of each antibody type has the same amino acid sequence for that part of the heavy chain, and likewise for that part of the light chain. The variable region of





From Harris, L. J., Larson, S. B., Hasel, K. W., McPherson, A., *Biochemistry* 36, p. 1581 (1997). Structure rendered with RIBBONS.

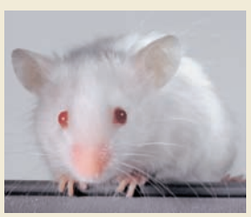
Figure 43.4
The arrangement of light and heavy polypeptide chains in an antibody molecule. As shown, two sites, one at the tip of each arm of the Y, bind the same antigen.

Focus on Research

Research Organisms: The Mighty Mouse

The "wee, sleekit, tim'rous, cowrin' beastie," as the poet Robert Burns called the mouse *(Mus musculus),* has a much larger stature among scientists. The mouse and its cells have been used to great advantage as models for research on mammalian developmental genetics, immunology, and cancer. The availability of the mouse as a research tool enables scientists to carry out experiments with a mammal that would not be practical or ethical with humans.

Mice are grown by the millions in laboratories all over the world. Its small size makes the mouse relatively inexpensive and easy to maintain in the laboratory, and its short generation time, compared with most other mammals, allows genetic crosses to be carried out within a reasonable time span. Mice can be mated when they are 10 weeks old; within 18 to 22 days the female gives birth to a litter of about 5 to 10 offspring. A female may be rebred within little more than a day after giving birth.



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Mice have a long and highly productive history as experimental animals. Gregor Mendel, the founder of genetics, is known to have kept mice as part of his studies. Toward the end of the nineteenth century, August Weissmann helped disprove an early evolutionary hypothesis, the inheritance of acquired characters, by cutting off the tails of mice for 22 successive generations and finding that it had no effect on tail length. The first example of a lethal allele was also found in mice, and pioneering experiments on the transplantation of tissues between individuals were conducted with mice. During the 1920s, Fred Griffith laid the groundwork for the research showing that DNA is the hereditary molecule in his work with pneumonia-causing bacteria in mice (see Section 14.1). More recently, genetic experiments with mice have revealed more than 500 mutants that cause hereditary diseases, immunological defects, and cancer in mammals including humans.

The mouse has also been the mammal of choice for experiments that introduce and modify genes through genetic engineering. One of the most spectacular results of this research was the production of giant mice by introducing a human growth hormone gene into a line of dwarfed mice that were deficient for this hormone.

Genetic engineering has also produced "knockout" mice, in which a gene of interest is completely nonfunctional (see Section 18.2). The effects of the lack of function of a gene in the knockout mice often allow investigators to determine the role of the normal form of the gene. Some knockout mice have been developed to be defective in genes homologous to human genes that cause serious diseases, such as cystic fibrosis. This allows researchers to study the disease in mice with the goal of developing cures or therapies.

The revelations in developmental genetics from studies with the mouse have been of great interest and importance in their own right. But more and more, as we find that much of what applies to the mouse also applies to humans, the findings in mice have shed new light on human development and opened pathways to the possible cure of human genetic diseases.

In 2002 the sequence of the mouse genome was reported. The sequence is enabling researchers to refine and expand their use of the mouse as a model organism for studies of mammalian biology and mammalian diseases.

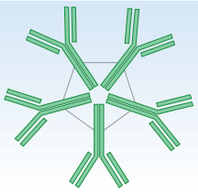
both the heavy and light chains, by contrast, has a different amino acid sequence for each antibody molecule in a population. Structurally, the variable regions are the top halves of the polypeptides in the arms of the Y-shaped molecule. The three-dimensional folding of the heavy chain and light chain variable regions of each arm creates the antigen-binding site. The antigen-binding site is identical for the two arms of the same antibody molecule because of the identity of the two heavy chains and the two light chains in a molecule, as mentioned earlier. However, the antigen-binding sites are different from antibody molecule to antibody molecule because of the amino acid differences in the variable regions of the two chain types.

The constant regions of the heavy chains in the tail part of the Y-shaped structure determine the *class* of the antibody. Humans have five different classes of antibodies—*IgM, IgG, IgA, IgE,* and *IgD* **(Table 43.2).** Due to differences in their heavy chain constant regions, they have specific structural and functional differences.

IgM remains bound to the cells that make it due to a region at the end opposite from the antigen-binding end that inserts into the plasma membrane of the cell. BCRs on B cells for antigen recognition are IgM molecules; as we shall see, IgM is also the first type of antibody secreted from plasma cells in the early stages of an antibody-mediated response. (When secreted, they exist as a pentamer.) IgM antibodies activate the complement system when they bind an antigen, and stimulate the phagocytic activity of macrophages.

IgG is the most abundant antibody circulating in the blood and lymphatic system, where it stimulates phagocytosis and activates the complement system when it binds an antigen. IgG is produced in large

Table 43.2 **Five Classes of Antibodies**

Class	Structure (Secreted Form)	Location	Functions
IgM		Surfaces of unstimulated B cells (as monomer); free in circulation (as pentamer)	First antibodies to be secreted by B cells in primary response. When bound to antigen, promotes agglutination reaction, activates complement system, and stimulates phagocytic activity of macrophages.
IgG		Blood and lymphatic circulation	Most abundant antibody in primary and secondary responses. Crosses placenta, conferring passive immunity to fetus; stimulates phagocytosis and activates complement system.
IgA		Body secretions such as tears, breast milk, saliva, and mucus	Blocks attachment of pathogens to mucous membranes; confers passive immunity for breastfed infants.
IgE		Skin and tissues lining gastrointestinal and respiratory tracts (secreted by plasma cells)	Stimulates mast cells and basophils to release histamine; triggers allergic responses.
IgD		Surface of unstimulated B cells	Membrane receptor for mature B cells; probably important in B-cell activation (clonal selection).

amounts when the body is exposed a second time to the same antigen.

IgA is found mainly in body secretions such as saliva, tears, breast milk, and the mucus coating of body cavities such as the lungs, digestive tract, and vagina. In these locations, the antibodies bind to surface groups on pathogens and block their attachment to body surfaces. Breast milk transfers IgA antibodies and thus immunity to a nursing infant.

IgE is secreted by plasma cells of the skin and tissues lining the gastrointestinal tract and respiratory tract. IgE binds to basophils and mast cells where it mediates many allergic responses, such as hay fever, asthma, and hives. Binding of a specific antigen to IgE stimulates the cell to which it is bound to release histamine, which triggers an inflammatory response. IgE also contributes to mechanisms that combat infection by parasitic worms.

IgD occurs with IgM as a receptor on the surfaces of B cells; its function is uncertain.

The Generation of Antibody Diversity. The human genome has approximately 20,000–25,000 genes, far fewer than necessary to encode 100 million different antibodies if two genes encoded one antibody, one gene for the heavy chain and one for the light chain. Antibody diversity is generated in a different way from one gene per chain, however, instead involving three rearrangements during B-cell differentiation of DNA segments that encode parts of the light and heavy chains. Let us consider how this process produces light-chain genes for the B-cell receptor **(Figure 43.5);** the production of heavy-chain genes is similar. The genes for the two different subunits of the TCR undergo similar rearrangements to produce the great diversity in antigen-binding capability of those receptors.

An undifferentiated B cell has three types of light-chain DNA segments: V, J, and C. One of each type is needed to make a complete, functional light-chain gene (see Figure 43.5, top). In humans, there are about 40 different V segments encoding most of the variable region of the chain, 5 different J (joining) segments encoding the rest of the variable region, and only one copy of the segment for the constant (C) part of the chain.

During B-cell differentiation, a DNA rearrangement occurs in which one random V and one random J segment join with the C segment to form a functional light-chain gene (see Figure 43.5, step 1). The rearrangement involves deletion of the DNA between the V and J segments. The positions at which the DNA breaks and rejoins in the V and J joining reaction occur randomly over a distance of several nucleotides, which adds greatly to the variability of the final gene assembly. The DNA between the J segment and the C segment is an intron in the final assembled gene.

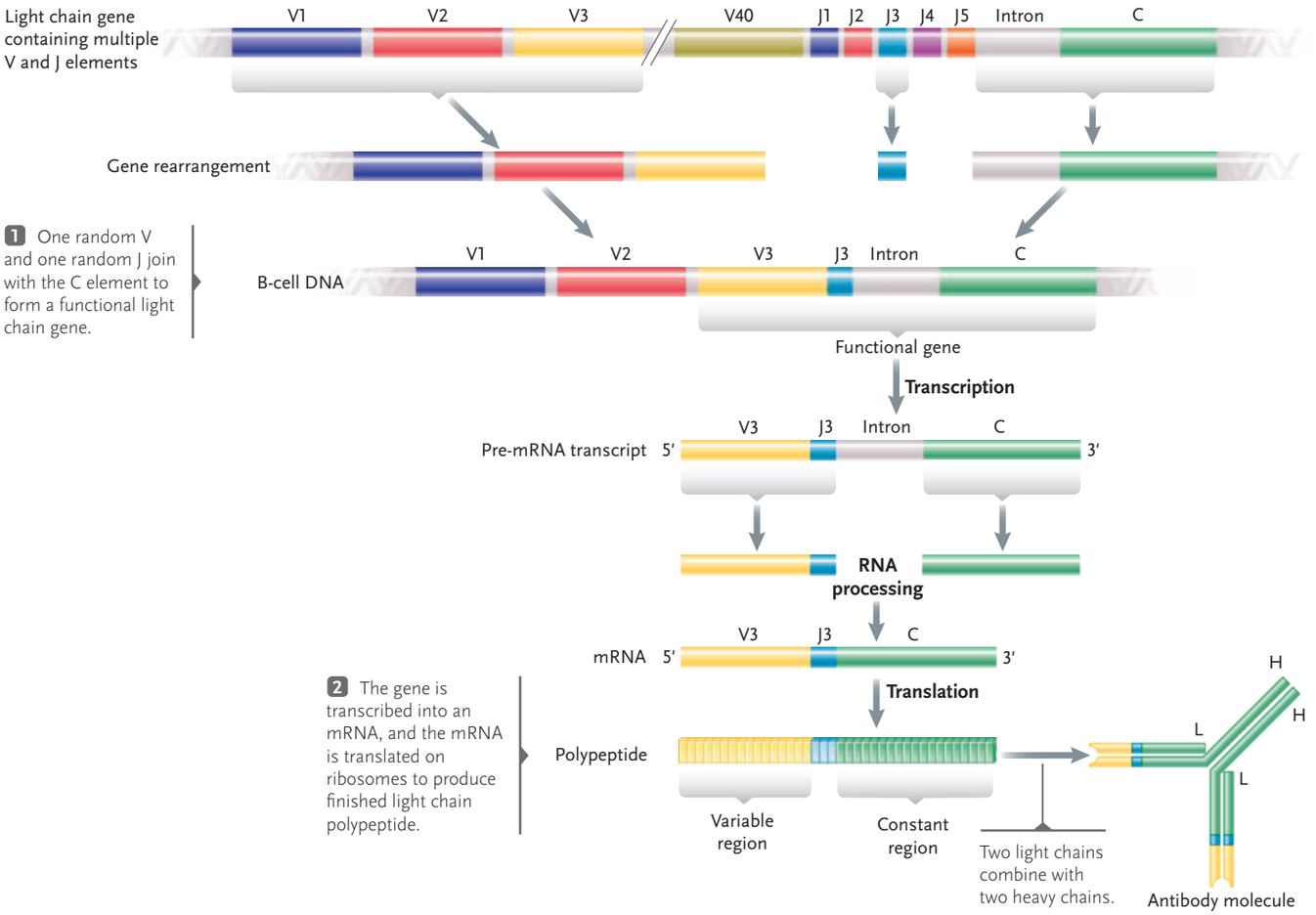


Figure 43.5
The DNA rearrangements producing a functional light-chain gene, in simplified form.

Transcription of this newly assembled gene produces a typical pre-mRNA molecule (see Section 15.3). The intron between the J and C segments is removed during the production of the mRNA by RNA processing. Translation of the mRNA produces the light chain with variable and constant regions (step 2).

As noted earlier, the assembly of functional heavy-chain genes occurs similarly. However, whereas light-chain genes have one C segment, heavy-chain genes have five types of C segments, each of which encodes one of the constant regions of IgM, IgD, IgG, IgE, and IgA. The inclusion of one of the five C segment types in the functional heavy-chain gene therefore specifies the class of antibody that will be made by the cell. Thus, the various DNA rearrangements producing the various light chain and heavy chain genes, along with the various combinations of light and heavy chains, generates the 100 million different antibodies.

T-Cell Activation. Let us now follow the development of an antibody-mediated immune response by linking the recognition of an antigen by lymphocytes, the activation of lymphocytes by antigen binding, and the production of antibodies. Typically, the pathway begins when a type of T cell becomes activated, following the steps outlined in **Figure 43.6.** Let us learn about this pathway by considering the fate of pathogenic bacteria that have been introduced under the skin. Circulating viruses in the blood follow the same pathway.

First, a type of phagocyte called a **dendritic cell** engulfs a bacterium in the infected tissue by phagocytosis (**Figure 43.7,** step 1). Dendritic cells are so named because they have many surface projections resembling dendrites of neurons. They have the same origin as leukocytes, and recognize a bacterium as foreign by the same recognition mechanism used by macrophages in the innate immunity system. In essence, the dendritic cell is part of the innate immunity system, but its primary role is to stimulate the development of an adaptive immune response.

Engulfment of a bacterium activates the dendritic cell; the cell now migrates to a nearby lymph node. Then, within the dendritic cell, the endocytic vesicle containing the engulfed bacterium fuses with a lysosome. In the lysosome, the bacterium's proteins are

Antibody-mediated immune response: T-cell activation

Dendritic cell (a phagocyte) is activated by engulfing a pathogen such as a bacterium.

↓

Pathogen macromolecules are degraded in dendritic cell, producing antigens.

↓

Dendritic cell becomes an antigen-presenting cell (APC) by displaying antigens on surface bound to class II MHC proteins.

↓

APC presents antigen to $CD4^+$ T cell and activates the T cell.

↓

$CD4^+$ T cell proliferates to produce a clone of cells.

↓

Clonal cells differentiate into helper T cells, which aid in effecting the specific immune response to the antigen.

Figure 43.6
An outline of T-cell activation in antibody-mediated immunity.

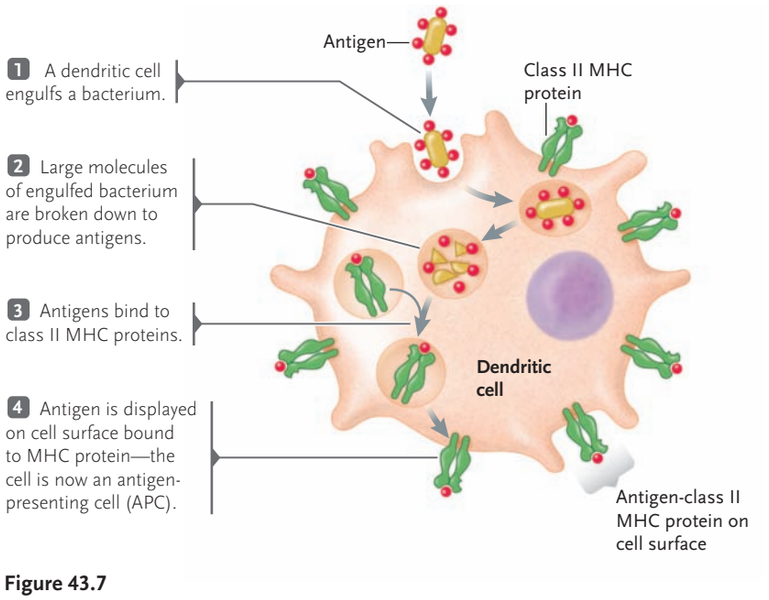
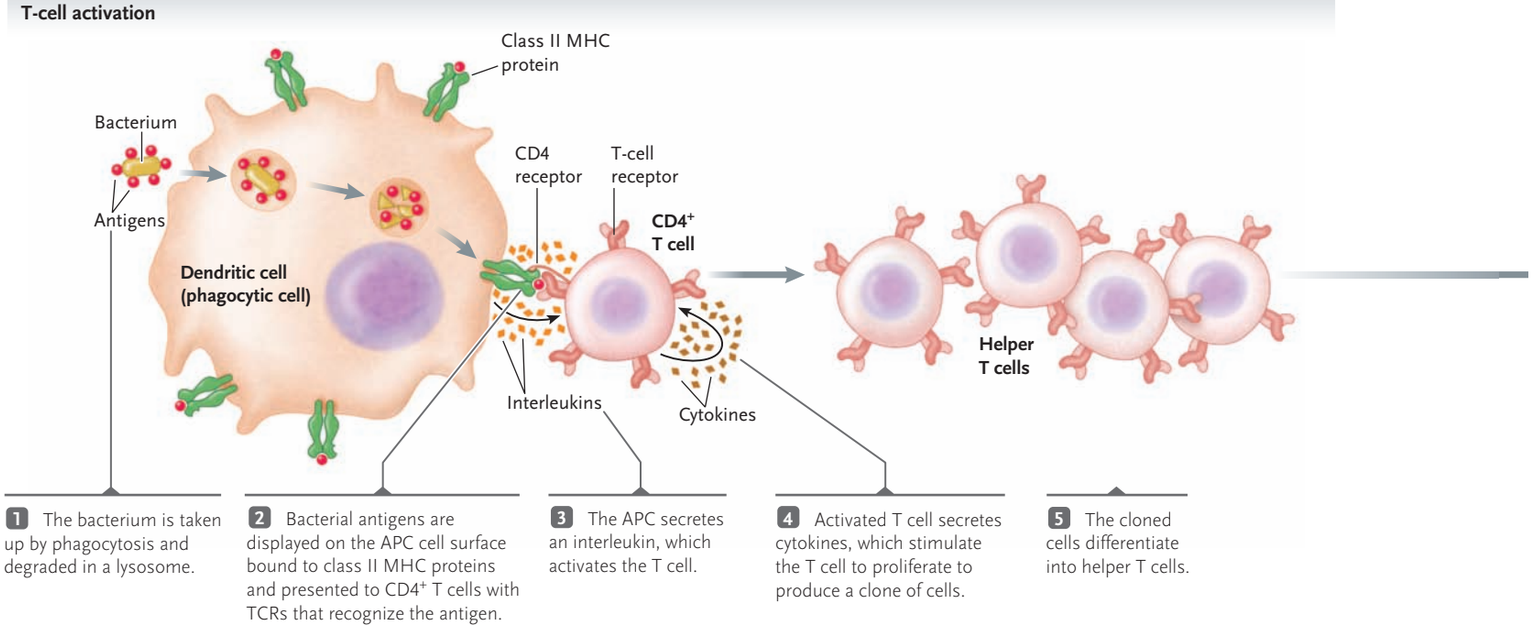


Figure 43.7
Generation of an antigen-presenting cell when a dendritic cell engulfs a bacterium.

degraded into short peptides, which function as antigens (step 2). The antigens bind intracellularly to **class II major histocompatibility complex (MHC)** proteins (step 3); the interacting molecules then migrate to the cell surface where the antigen is displayed (step 4). These steps, which occur in the dendritic cell after it has migrated to the lymph node, convert the cell into an **antigen-presenting cell (APC)**, ready to present the antigen to T cells in the next step of antibody-mediated immunity. The process is recapped in **Figure 43.8.**

Antibody-mediated immune response

T-cell activation



MHC proteins are named for a large cluster of genes encoding them, called the **major histocompatibility complex.** The complex spans 4 million base pairs and contains 128 genes. Many of these genes play important roles in the immune system. Each individual of each vertebrate species has a unique combination of MHC proteins on almost all body cells, meaning that no two individuals of a species except identical siblings are likely to have exactly the same MHC proteins on their cells. There are two classes of MHC proteins, class I and class II, which have different functions in adaptive immunity, as we will see.

The key function of an APC is to present the antigen to a lymphocyte. In the antibody-mediated immune response, the APC presents the antigen, bound to a class II MHC protein, to a type of T cell in the lymphatic system called a **$CD4^+$ T cell** because it has receptors named CD4 on its surface. A specific $CD4^+$ T cell having a TCR with an antigen-binding site that recognizes the antigen (epitope, actually) binds to the antigen on the APC (see Figure 43.8, step 2). The CD4 receptor on the T cell helps link the two cells together.

When the APC binds to the $CD4^+$ T cell, the APC secretes an *interleukin* (meaning "between leukocytes"), a type of cytokine, which activates the associated T cell (step 3). The activated T cell then secretes cytokines (step 4), which act in an autocrine manner (see Section 40.1) to stimulate **clonal expansion**, the proliferation of the activated $CD4^+$ T cell by cell division to produce a clone of cells. These clonal cells differentiate into **helper T cells**, so named because they assist with the activation of B cells (step 5). A helper T cell is an example of an **effector T cell**, meaning that it is involved in effecting—bringing about—the specific immune response to the antigen.

B-Cell Activation. Antibodies are produced in and secreted by activated B cells. The activation of a B cell requires the B cell to present the antigen on its surface, and then to link with a helper T cell that has differentiated as a result of encountering and recognizing the same antigen. The process is outlined in **Figure 43.9,** and diagrammed in the second phase of Figure 43.8).

The process of antigen presentation on a B-cell surface begins when BCRs on the B cell interact directly with soluble bacterial (in our example) antigens in the blood or lymph. Once the antigen binds to a BCR, the complex is taken into the cell and the antigen is processed in the same way as in dendritic cells, culminating with a presentation of antigen pieces on the B-cell surface in a complex with class II MHC proteins (see Figure 43.8, step 6).

When a helper T cell encounters a B cell displaying the same antigen, usually in a lymph node or in the spleen, the T and B cells become tightly linked together (step 7). The linkage depends on the TCRs, which recognize and bind the antigen fragment displayed by class II MHC molecules on the surface of the B cell, and on CD4, which stabilizes the binding as it did for T-cell binding to the dendritic cell. The linkage between the cells first stimulates the helper T cell to secrete interleukins that activate the B cell and then stimulates the B cell to proliferate, producing a clone of those B cells with identical B-cell receptors (step 8). Some of the cloned cells differentiate into relatively short-lived **plasma cells,** which now secrete the same antibody that

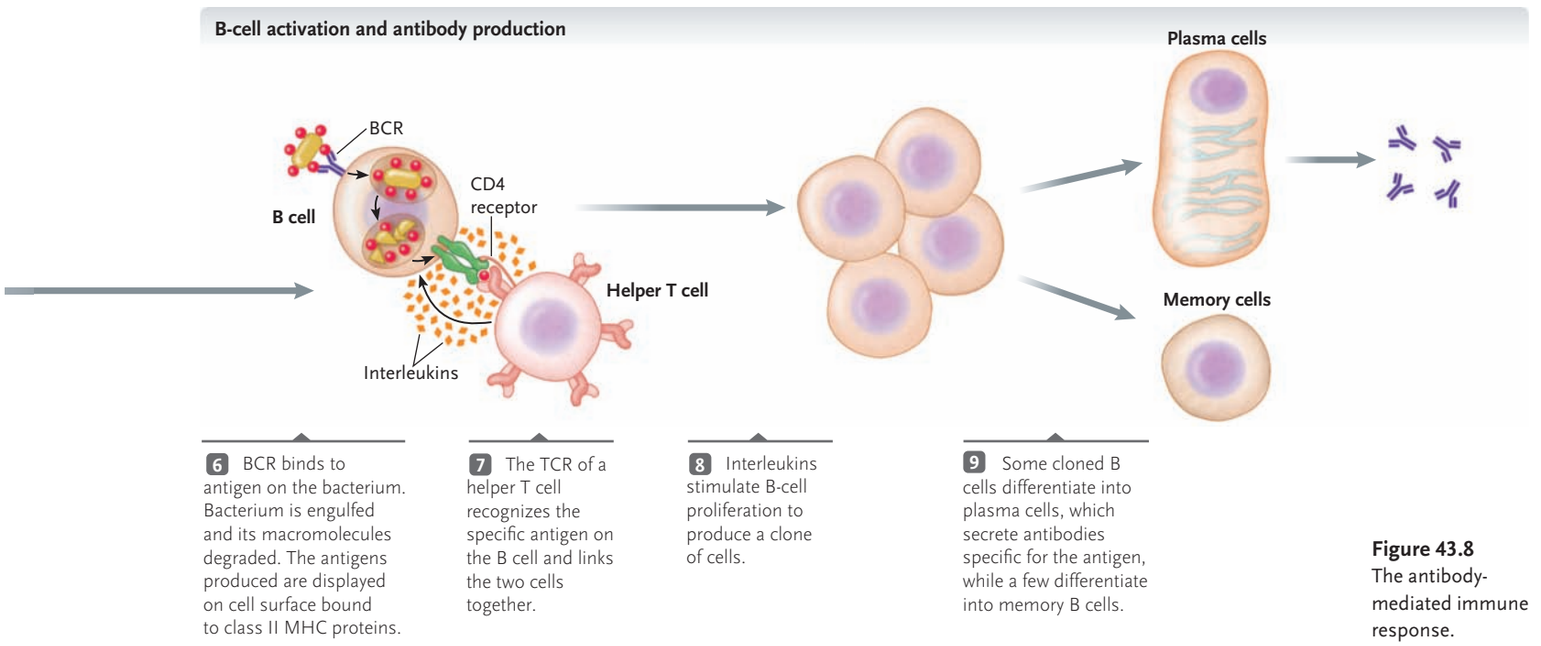


Figure 43.8
The antibody-mediated immune response.

Antibody-mediated immune response: B-cell activation

A BCR on a B cell recognizes antigens on the same bacterial type and engulfs the bacterium.

↓

Pathogen macromolecules are degraded in the B cell, producing antigens.

↓

B cell displays antigens on its surface bound to class II MHC proteins.

↓

Helper T cell with TCR that recognizes the same antigen links to the B cell.

↓

Helper T cell secretes interleukins that activate the B cell.

↓

B cell proliferates to produce a clone of cells.

↓

Some B-cell clones differentiate into plasma cells, which secrete antibodies specific to the antigen, and others differentiate into memory B cells.

Figure 43.9
An outline of B-cell activation in antibody-mediated immunity.

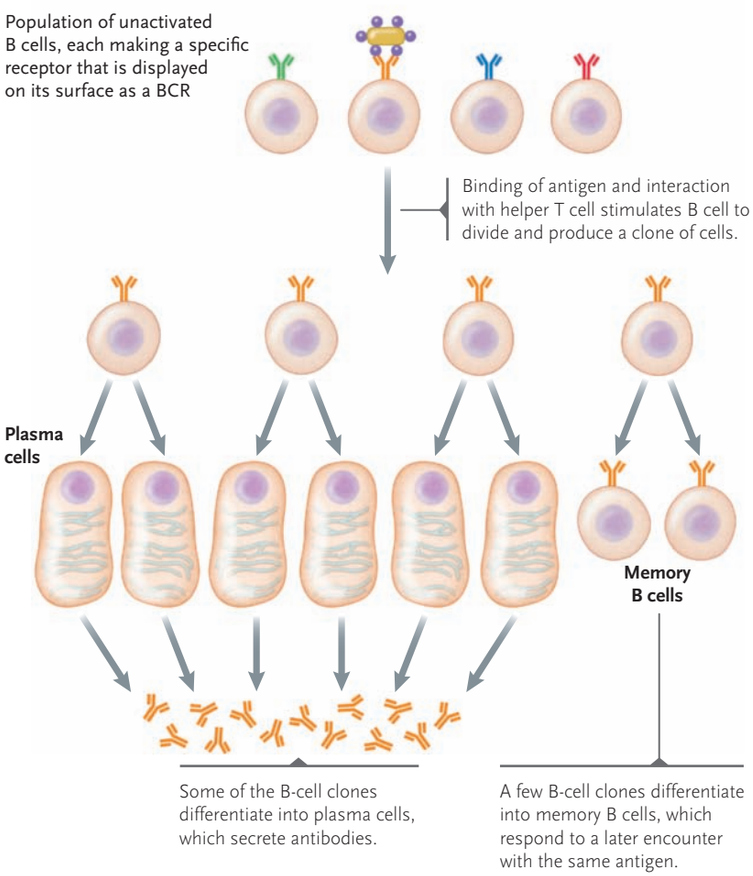


Figure 43.10
Clonal selection. The binding of an antigen to a B cell already displaying a specific antibody to that antigen stimulates the B cell to divide and differentiate into plasma cells, which secrete the antibody, and memory cells, which remain in the circulation ready to mount a response against the antigen at a later time.

was displayed on the parental B cell's surface to circulate in lymph and blood. Others differentiate into **memory B cells**, which are long-lived cells that set the stage for a much more rapid response should the same antigen be encountered later (step 9).

Clonal selection is the process by which a particular lymphocyte is specifically selected for cloning when it recognizes a particular foreign antigen **(Figure 43.10).** Remember that there is an enormous diversity of randomly generated lymphocytes, each with a particular receptor that may potentially recognize a particular antigen. The process of clonal selection was proposed in the 1950s by several scientists, most notably F. Macfarlane Burnet, Niels Jerne, and David Talmage. Their proposals, made long before the mechanism was understood, described clonal selection as a form of natural selection operating in miniature: antigens select the cells recognizing them, which reproduce and become dominant in the B-cell population. Burnet received the Nobel Prize in 1960 for his research in immunology.

Clearing the Body of Foreign Antigens. How do the antibodies produced in an antibody-mediated immune response clear foreign antigens from the body? Let us consider some examples concerning bacteria and viruses.

Toxins produced by invading bacteria, such as tetanus toxin, can be *neutralized* by antibodies **(Figure 43.11a).** The antibodies bind to the toxin molecules, preventing them from carrying out their damaging action. For intact bacteria at an infection site or in the circulatory system, antibodies will bind to antigens on their surfaces. Because the two arms of an antibody molecule bind to different copies of the antigen molecule, an antibody molecule may bind to two bacteria with the same antigen. A population of antibodies against the bacterium, then, link many bacteria to-

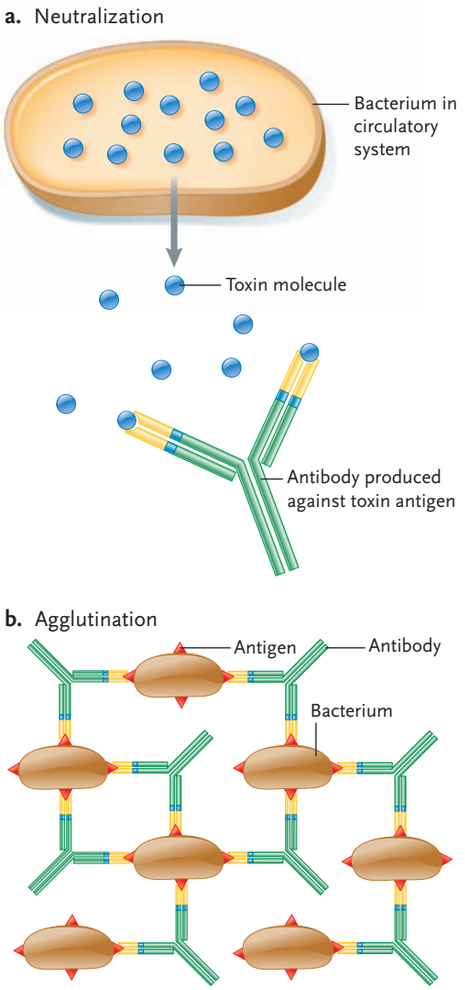


Figure 43.11
Examples of clearing antigens from the body.

gether into a lattice causing *agglutination,* that is, clumping of the bacteria **(Figure 43.11b).** Agglutination immobilizes the bacteria, preventing them from infecting cells. Antibodies can also agglutinate viruses, thereby preventing them from infecting cells.

More importantly, antibodies aid the innate immune response set off by the pathogens. That is, antibodies bound to antigens stimulate the complement system. Membrane attack complexes are formed and insert themselves into the plasma membranes of the bacteria, leading to their lysis and death. In the case of viral infections, membrane attack complexes can insert themselves into the membranes surrounding enveloped viruses, which disrupts the membrane and prevents the viruses from infecting cells.

Antibodies also enhance phagocytosis of bacteria and viruses. Phagocytic cells have receptors on their surfaces that recognize the heavy-chain end of antibodies (the end of the molecule opposite the antigen-binding sites). Antibodies bound to bacteria or viruses therefore bind to phagocytic cells, which then engulf the pathogens and destroy them.

For simplicity, the adaptive immune response has been described here in terms of a single antigen. Pathogens have many different types of antigens on their surfaces, which means that many different B cells are stimulated to proliferate and many different antibodies are produced. Pathogens therefore are attacked by many different types of antibodies, each targeted to one antigen type on the pathogen's surface.

Immunological Memory. Once an immune reaction has run its course and the invading pathogen or toxic molecule has been eliminated from the body, division of the plasma cells and T-cell clones stops. Most or all of the clones die and are eliminated from the bloodstream and other body fluids. However, long-lived memory B cells and **memory helper T cells** (which differentiated from helper T cells), derived from encountering the same antigen, remain in an inactive state in the lymphatic system. Their persistence provides an **immunological memory** of the foreign antigen.

Immunological memory is illustrated in **Figure 43.12.** When exposed to a foreign antigen for the first time, a **primary immune response** results, following the steps already described. The first antibodies appear in the blood in 3 to 14 days and, by week 4, the primary response has essentially gone away. IgM is the main antibody type produced in a primary immune response. The primary immune response curve is followed whenever a new foreign antigen enters the body.

When a foreign antigen enters the body for a second or subsequent time, a **secondary immune response** results, while any new antigen introduced at the same time produces a primary response (see Figure 43.12). The secondary response is more rapid than a primary response because it involves the memory B cells and memory T cells that have been stored in the meantime, rather than having to initiate the clonal selection of a new B cell and T cell. Moreover, less antigen is needed

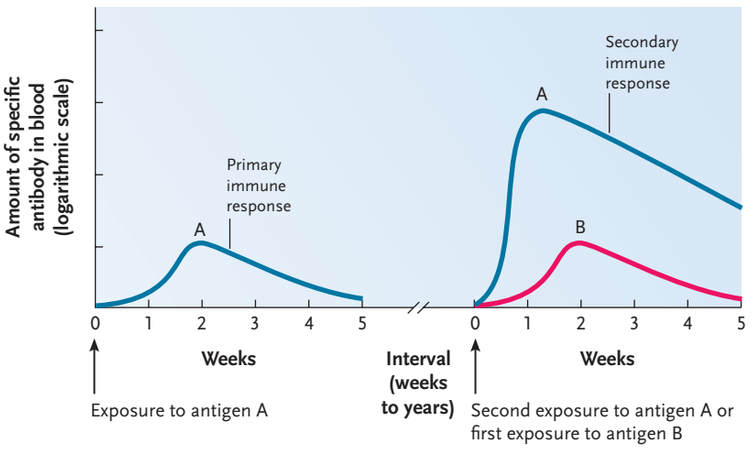


Figure 43.12
Immunological memory: primary and secondary responses to the same antigen.

to elicit a secondary response than a primary response, and many more antibodies are produced. The predominant antibody produced in a secondary immune response is IgG; the switch occurs at the gene level in the memory B cells.

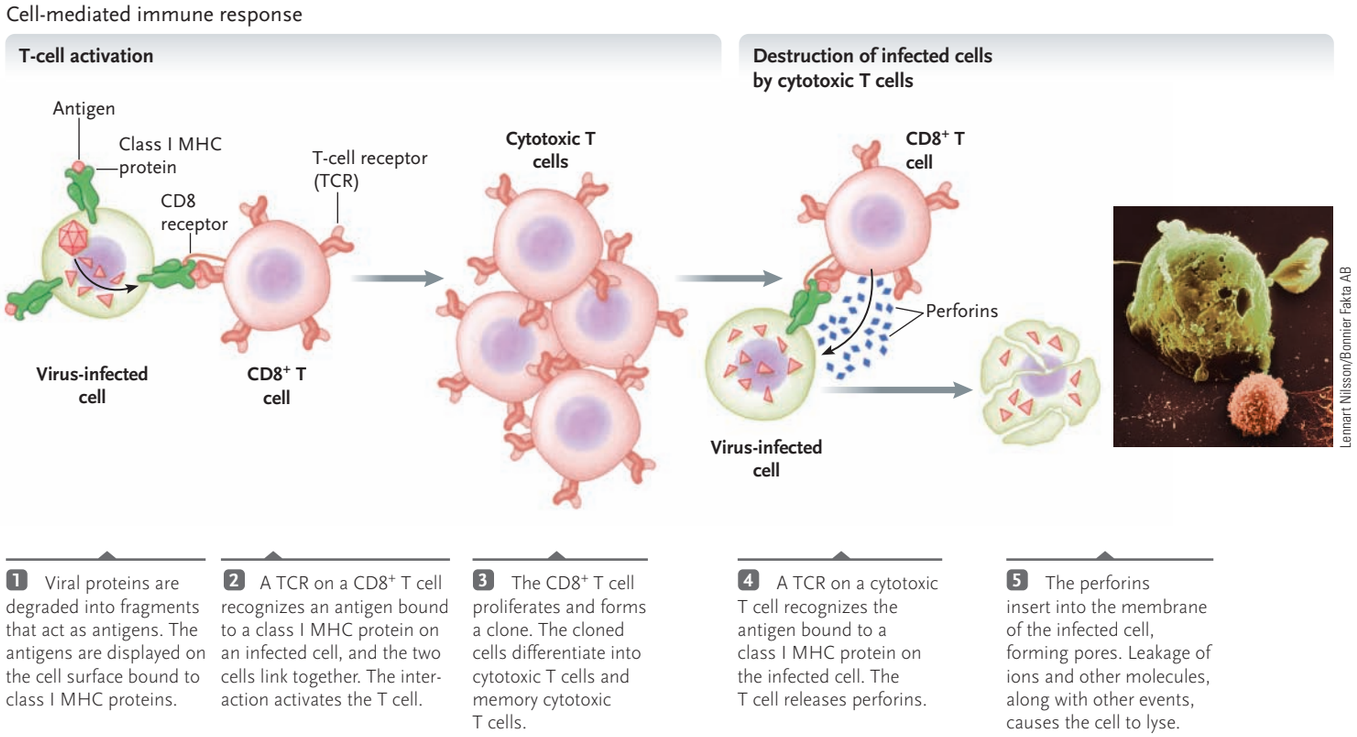
Immunological memory forms the basis of vaccinations, in which antigens in the form of living or dead pathogens or antigenic molecules themselves are introduced into the body. After the immune response, memory B cells and memory T cells remaining in the body can mount an immediate and intense immune reaction against similar antigens in the dangerous pathogen. In Edward Jenner's technique, for example, introducing the cowpox virus, a related, less virulent form of the smallpox virus, into healthy individuals initiated a primary immune response. After the response ran its course, a bank of memory B cells and memory T cells remained in the body, able to recognize quickly the similar antigens of the smallpox virus and initiate a secondary immune response. Similarly, a polio vaccine developed by Jonas Salk uses polio viruses that have been inactivated by exposing them to formaldehyde. Although the viruses are inactive, their surface groups can still act as antigens. The antigens trigger an immune response, leaving memory B and T cells able to mount an intense immune response against active polio viruses.

Active and Passive Immunity. **Active immunity** is the production of antibodies in the body in response to exposure to a foreign antigen—the process that has been described up until now. **Passive immunity** is the acquisition of antibodies as a result of direct transfer from another person. This form of immunity provides immediate protection against antigens that the antibodies recognize without the person receiving the antibodies having developed an immune response. Examples of passive immunity include the transfer of IgG antibodies from the mother to the fetus through the placenta and the transfer of IgA antibodies in the first breast milk fed from the mother to the baby. Compared with active immunity, passive immunity is a short-lived phenomenon with no memory, in that the antibodies typically break down within a month. However, in that time, the protection plays an important role. For example, a breast-fed baby is protected until it is able to mount an immune response itself, an ability that is not present until about a month after birth.

Drug Effects on Antibody-Mediated Immunity. Several drugs used to reduce the rejection of transplanted organs target helper T cells. Cyclosporin A, used routinely after organ transplants, blocks the activation of helper T cells and, in turn, the activation of B cells. Unfortunately, cyclosporin and other immunosuppressive drugs also leave the treated individual more susceptible to infection by pathogens.

In Cell-Mediated Immunity, Cytotoxic T Cells Expose "Hidden" Pathogens to Antibodies by Destroying Infected Body Cells

In **cell-mediated immunity**, cytotoxic T cells directly destroy host cells infected by pathogens, particularly those infected by a virus **(Figure 43.13).** The killing pro-



Lennart Nilsson/Bonnier Fakta AB

Figure 43.13 The cell-mediated immune response.

Insights from the Molecular Revolution

Some Cancer Cells Kill Cytotoxic T Cells to Defeat the Immune System

Among the arsenal of weapons employed by cytotoxic T cells to eliminate infected and cancerous body cells is the *Fas–FasL* system. Fas is a receptor that occurs on the surfaces of many body cells; FasL is a signal molecule that is displayed on the surfaces of some cell types, including cytotoxic T cells. If a cell carrying the Fas receptor contacts a cytotoxic T cell with the FasL signal displayed on its surface, the effect for the Fas-bearing cell is something like stepping on a mine. When FasL is bound by the Fas receptor, a cascade of internal reactions initiates apoptosis and kills the cell with the Fas receptor.

Surprisingly, cytotoxic T cells also carry the Fas receptor, so they can kill each other by displaying the FasL signal. This mutual killing plays an important role in reducing the level of an immune reaction after a pathogen has been eliminated. In addition, cells in some regions of the body, such as the eye, the nervous system, and the testis, can be severely damaged by inflammation; these cells can make and display FasL, which kills cytotoxic T cells and reduces the severity of inflammation.

Molecular research by a group of Swiss investigators at the Universities of Lausanne and Geneva now shows that some cancer cells survive elimination by the immune system by making and displaying the FasL signal, and thus killing any cytotoxic T cells attacking the tumor. The researchers were led to their discovery by the observation that many patients with malignant melanoma, a dangerous skin cancer, had a breakdown product associated with FasL in their bloodstream.

The investigators extracted proteins from melanoma cells and tested them with antibodies against FasL. The test was positive, showing that FasL was in the tumor cells. The investigators were also able to detect an mRNA encoding FasL in the tumor cells, showing that the gene encoding FasL was active. As a final confirmation, they tagged antibodies against the FasL protein with a dye molecule to make them visible in the light microscope and added them to sections of melanoma tissue from patients. Intense staining of the cells with the dye showed that FasL was indeed present. Tests for the presence of the Fas receptor were negative, showing that Fas synthesis was turned off in the melanoma cells.

Thus the FasL in melanoma cells kills cytotoxic T cells that invade the tumor. At the same time, the absence of Fas receptors ensures that the tumor cells do not kill each other. The presence of FasL and absence of the Fas receptor may explain why melanomas are rarely destroyed by an immune reaction, and also why many other types of cancer also escape immune destruction.

Melanoma cells originate from pigment cells in the skin called *melanocytes.* Normal melanocytes do not contain FasL, indicating that synthesis of the protein is turned on as a part of the changes transforming normal melanocytes into cancer cells.

The findings of the Swiss group could lead to an effective treatment for cancer using the Fas–FasL system. If melanoma cells could be induced to make Fas as well as FasL, for example, they might eliminate a tumor by killing each other!

cess begins when some of the pathogens break down inside the infected host cells, releasing antigens that are fragmented by enzymes in the cytoplasm. The antigen fragments bind to class I MHC proteins, which are delivered to the cell surface by essentially the same mechanisms as in B cells (step 1). At the surface, the antigen fragments are displayed by the class I MHC protein and the cell then functions as an APC.

In a cell-mediated immune response, the APC presents the antigen fragment to a type of T cell in the lymphatic system called a **$CD8^+$ T cell** because it has receptors named **CD8** on its surface in addition to TCRs. The presence of a CD8 receptor distinguishes this type of T cell from that involved in antibody-mediated immunity. A specific $CD8^+$ T cell having a TCR with an antigen-binding site that recognizes the antigen fragment binds to that fragment on the APC (step 2). The CD8 receptor on the T cell helps the two cells link together.

The interaction between the APC and the $CD8^+$ T cell activates the T cell, which then proliferates to form a clone. Some of the cells differentiate to become **cytotoxic T cells** (step 3), while a few differentiate into *memory cytotoxic T cells.* Cytotoxic T cells are another type of effector T cell. TCRs on the cytotoxic T cells again recognize the antigen fragment bound to class I MHC proteins on the infected cells (the APCs) (step 4). The cytotoxic T cell then destroys the infected cell in mechanisms similar to those used by NK cells. That is, an activated cytotoxic T cell releases perforin, which creates pores in the membrane of the target cell. The leakage of ions and other molecules through the pores causes the infected cell to rupture. The cytotoxic T cell also secretes proteases that enter infected cells through the newly created pores and cause it to self-destruct by apoptosis (step 5, and photo inset). Rupture of dead, infected cells releases the pathogens to the interstitial fluid, where they are open to attack by antibodies and phagocytes.

Cytotoxic T cells can also kill cancer cells if their class I MHC molecules display fragments of altered cellular proteins that do not normally occur in the body. Another mechanism used by cytotoxic T cells to kill cells, and a process used by some cancer cells to defeat the mechanism, is described in *Insights from the Molecular Revolution.*

Figure 43.14 Research Method

Production of Monoclonal Antibodies

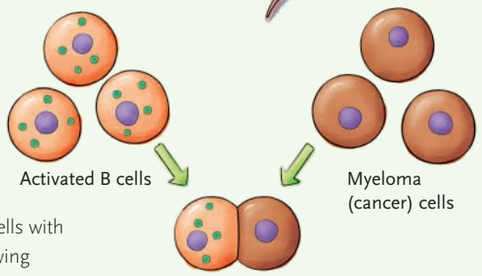
PURPOSE: Injecting an antigen into an animal produces a collection of different antibodies that react against different parts of the antigen. Monoclonal antibodies are produced to provide antibodies that all react against the same epitope of a single antigen.

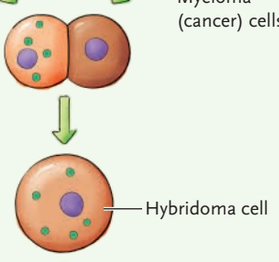
PROTOCOL:

1. Inject antigen into mouse.

2. Extract activated B cells from spleen.

3. Fuse antibody-producing B cells with cancer cells to form fast-growing hybridoma cells.





4. Grow clone from single hybridoma cells; test antibodies produced by clone for reaction against antigen.

5. Grow clone producing antibodies against antigen to large size.

6. Extract and purify antibodies.

Antibodies Have Many Uses in Research

The ability of the antibody-mediated immune system to generate antibodies against essentially any antigen provides an invaluable research tool to scientists, who can use antibodies to identify biological molecules and to determine their locations and functions in cells. To obtain the antibodies, a molecule of interest is injected into a test animal such as a mouse, rabbit, goat, or sheep. In response, the animal develops antibodies capable of binding to the molecule. The antibodies are then extracted and purified from a blood sample.

To identify the cellular location of a molecule, antibodies made against the molecule are combined with a visible marker such as a dye molecule or heavy metal atom. When added to a tissue sample, the marked antibodies can be seen in the light or electron microscope localized to cellular structures such as membranes, ribosomes, or chromosomes, showing that the molecule forms part of the structure.

Antibodies can also be used to "grab" a molecule of interest from a preparation containing a mixture of all kinds of cellular molecules. For such studies, the antibodies are often attached to plastic beads that are packed into a glass column. When the mixture passes through the column, the molecule is trapped by attachment to the antibody and remains in the column. It is then released from the column in purified form by adding a reagent that breaks the antigen-antibody bonds.

Injecting a molecule of interest into a test animal typically produces a wide spectrum of antibodies that react with different parts of the antigen. Some of the antibodies also cross-react with other, similar antigens, producing false results that can complicate the research. These problems have been solved by producing **monoclonal antibodies**, each of which reacts only against the same segment (epitope) of a single antigen.

Georges Kohler and Cesar Milstein pioneered the production of monoclonal antibodies in 1975. In their technique, a test animal (usually a mouse) is injected with a molecule of interest **(Figure 43.14).** After the animal has developed an immune response, fully activated B cells are extracted from the spleen and placed in a cell culture medium. Because B cells normally stop dividing and die within a week when cultured, they are induced to fuse with cancerous lymphocytes called *myeloma cells,* forming single, composite cells called **hybridomas.** Hybridomas combine the desired characteristics of the two cell types—they produce antibodies like fully activated B cells, and they divide continuously and rapidly like the myeloma cells.

Single hybridoma cells are then separated from the culture and used to start clones. Because all the cells of a clone are descended from a single hybridoma cell, they all make the same, highly specific antibody, able to bind the same part of a single antigen. In addition to their use in scientific research, monoclonal antibodies are also widely used in medical applications such as pregnancy tests, screening for prostate cancer, and testing for AIDS and other sexually transmitted diseases.

Study Break

1. How, in general, do the antibody-mediated and cell-mediated immune responses help clear the body of antigens?
2. Describe the general structure of an antibody molecule.
3. What are the principles of the mechanism used for generating antibody diversity?
4. What is clonal selection?
5. How does immunological memory work?

43.4 Malfunctions and Failures of the Immune System

The immune system is highly effective, but it is not foolproof. Some malfunctions of the immune system cause the body to react against its own proteins or cells, producing *autoimmune disease*. In addition, some viruses and other pathogens have evolved means to avoid destruction by the immune system. A number of these pathogens, including the AIDS virus, even use parts of the immune response to promote infection. Another malfunction causes the *allergic reactions* that most of us experience from time to time.

An Individual's Own Molecules Are Normally Protected against Attack by the Immune System

B cells and T cells are involved in the development of **immunological tolerance**, which protects the body's own molecules from attack by the immune system. Although the process is not understood, molecules present in an individual from birth are not recognized as foreign by circulating B and T cells, and do not elicit an immune response. Evidently, during their initial differentiation in the bone marrow and thymus, any B and T cells that are able to react with self molecules carried by MHC molecules are induced to kill themselves by apoptosis, or enter a state in which they remain in the body but are unable to react if they encounter a self molecule. The process of excluding self-reactive B and T cells goes on throughout the life of an individual.

Evidence that immunological tolerance is established early in life comes from experiments with mice. For example, if a foreign protein is injected into a mouse at birth, during the period in which tolerance is established, the mouse will not develop antibodies against the protein if it is injected later in life. Similarly, if mutant mice are produced that lack a given complement protein, so that the protein is absent during embryonic development, they will produce antibodies against that protein if it is injected during adult life. Normal mice do not produce antibodies if the protein is injected.

Autoimmune Disease Occurs When Immunological Tolerance Fails

The mechanisms setting up immunological tolerance sometimes fail, leading to an **autoimmune reaction**—the production of antibodies against molecules of the body. In most cases, the effects of such anti-self antibodies are not serious enough to produce recognizable disease. However, in some individuals, about 5% to 10% of the human population, anti-self antibodies cause serious problems.

For example, type 1 diabetes (see Section 40.4) is an autoimmune reaction against the pancreatic beta cells producing insulin. The anti-self antibodies gradually eliminate the beta cells until the individual is incapable of producing insulin. *Systemic lupus erythematosus (lupus)* is caused by production of a wide variety of anti-self antibodies against blood cells, blood platelets, and internal cell structures and molecules such as mitochondria and proteins associated with DNA in the cell nucleus. People with lupus often become anemic and have problems with blood circulation and kidney function because antibodies, combined with body molecules, accumulate and clog capillaries and the microscopic filtering tubules of the kidneys. Lupus patients may also develop anti-self antibodies against the heart and kidneys. *Rheumatoid arthritis* is caused by a self-attack on connective tissues, particularly in the joints, causing pain and inflammation. *Multiple sclerosis* results from an autoimmune attack against a protein of the myelin sheaths insulating the surfaces of neurons. Multiple sclerosis can seriously disrupt nervous function, producing such symptoms as muscle weakness and paralysis, impaired coordination, and pain.

The causes of most autoimmune diseases are unknown. In some cases, an autoimmune reaction can be traced to injuries that expose body cells or proteins that are normally inaccessible to the immune system, such as the lens protein of the eye, to B and T cells. In other cases, as in type 1 diabetes, an invading virus stimulates the production of antibodies that can also react with self proteins. Antibodies against two viruses, the Epstein-Barr and hepatitis B viruses, can react against myelin basic protein, the protein attacked in multiple sclerosis. Sometimes, environmental chemicals, drugs, or mutations alter body proteins so that they appear foreign to the immune system and come under attack.

Some Pathogens Have Evolved Mechanisms That Defeat the Immune Response

Several pathogens regularly change their surface groups to avoid destruction by the immune system. By the time the immune system has developed antibodies

Focus on Research

Applied Research: HIV and AIDS

Acquired immune deficiency syndrome (AIDS) is a constellation of disorders that follows infection by the **human immunodeficiency virus, HIV (Figure a).** First reported in various countries in the late 1970s, HIV now infects more than 40 million people worldwide, 64% of them in Africa. AIDS is a potentially lethal disease, although drug therapy has reduced the death rate for HIV-infected individuals in many countries, including the United States.

HIV is transmitted when an infected person's body fluids, especially blood or semen, enter the blood or tissue fluids of another person's body. The entry may occur during vaginal, anal, or oral intercourse, or via contaminated needles shared by intravenous drug users. HIV can also be transmitted from infected mothers to their infants during pregnancy, birth, and nursing. AIDS is rarely transmitted through casual contact, food, or body products such as saliva, tears, urine, or feces.

The primary cellular hosts for HIV are macrophages and helper T cells, which are ultimately destroyed in large numbers by the virus. The infection makes helper T cells unavailable for the stimulation and proliferation of B cells and cytotoxic T cells. The assault on lymphocytes and macrophages cripples the immune system and makes the body highly vulnerable to infections and to development of otherwise rare forms of cancer.

In 1996 researchers confirmed the process by which HIV initially infects its primary target, the helper T cells.

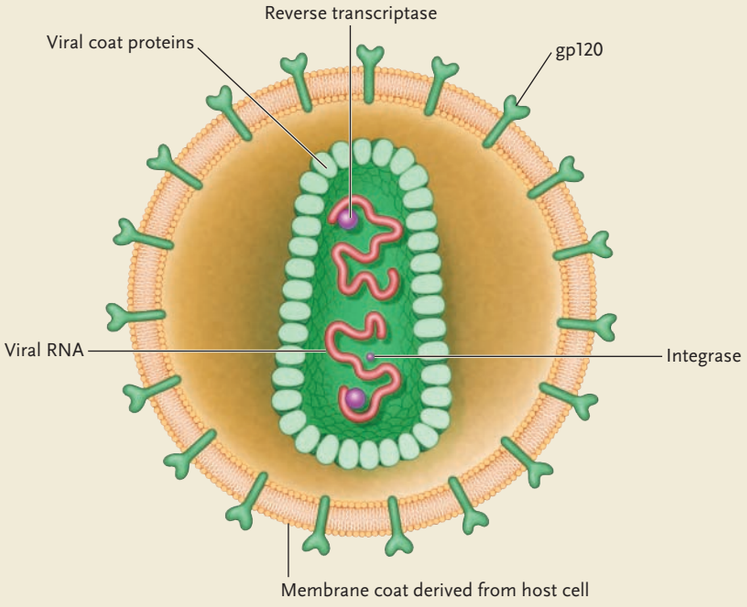


Figure a
Structure of a free HIV viral particle.

First, a glycoprotein of the viral coat, called *gp120,* attaches the virus to a helper T cell by binding to its CD4 receptor. Then, another viral protein triggers fusion of the viral surface membrane with the T-cell plasma membrane, releasing the virus into the cell **(Figure b).** Once inside, a viral enzyme, *reverse transcriptase,* uses the viral RNA as a template for making a DNA copy. (The genetic material of HIV is RNA rather than DNA when it is outside a host cell.) Another viral enzyme, *integrase,* then splices the viral DNA into the host cell's DNA. Once it is part of the host cell DNA, the viral DNA is replicated and passed on as the cell divides. As part of the host cell DNA, the virus is effectively hidden in the helper T cell and protected from attack by the immune system.

The viral DNA typically remains dormant until the helper T cell is stimulated by an antigen. At that point, the viral DNA is copied into new viral RNA molecules, and into mRNAs that direct host cell ribosomes to make viral proteins. The viral RNAs are added to the viral proteins to make infective HIV particles, which are released from the host cell by budding **(Figure c).** The viral particles may infect more body cells or another person. The viral infection also leads uninfected helper T cells to destroy themselves in large numbers by apoptosis, through mechanisms that are still unknown.

At the time of initial infection, many people suffer a mild fever and other symptoms that may be mistaken for the flu or the common cold. The symptoms disappear as antibodies against viral proteins appear in the body, and the number of viral particles

against one version of the surface proteins, the pathogens have switched to different surface proteins that the antibodies do not match. These new proteins take another week or so to stimulate the production of specific antibodies; by this time, the surface groups change again. The changes continue indefinitely, always keeping the pathogens one step ahead of the immune system. Pathogens that use these mechanisms to sidestep the immune system include the protozoan causing African sleeping sickness, the bacterium causing gonorrhea, and the viruses causing influenza, the common cold, and AIDS.

Some viruses use parts of the immune system to get a free ride to the cell interior. For example, the

drops in the bloodstream. However, the virus's genome is still present, integrated into the DNA of T cells, and the virus steadily spreads to infect other T cells. An infected person may remain apparently healthy for years, yet can infect others. Both the transmitter and recipient of the virus may be unaware that the disease is present, making it difficult to control the spread of HIV infections.

With time, more and more helper T cells and macrophages are destroyed, eventually wiping out the body's immune response. The infected person becomes susceptible to opportunistic, secondary infections, such as a pneumonia caused by a fungus *(Pneumocystis carinii);* drug-resistant tuberculosis; persistent yeast *(Candida albicans)* infections of the mouth, throat, rectum, or vagina; and infection by many common bacteria and viruses that rarely infect healthy humans. These secondary infections signal the appearance of full-blown AIDS. Steady debilitation and death typically follow within a period of years in untreated persons.

As yet, there is no cure for HIV infection and no vaccine that can protect against infection. HIV coat proteins mutate constantly, making a vaccine developed against one form of the virus useless when the next form appears. Most of these mutations occur during replication of the virus, when reverse transcriptase makes a DNA copy of the viral RNA.

The development of AIDS can be greatly slowed by drugs that interfere with reverse transcription of the viral genomic RNA into the DNA copy that integrates into the host's genome.

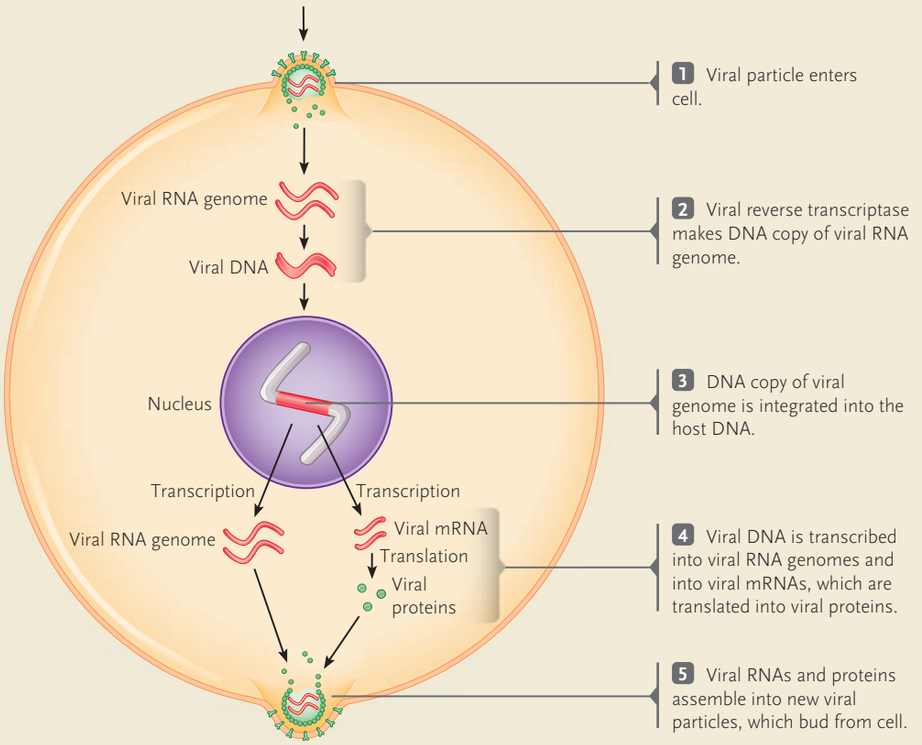


Figure b
The steps in HIV infection of a host cell.

Treatment with a "cocktail" of drugs called *reverse transcriptase inhibitors (RTIs)* inhibits viral reproduction and destruction of helper T cells and extends the lives of people with the AIDS virus. The inhibiting cocktails are not a cure for AIDS, however, because the virus is still present in dormant form in helper T cells. If the therapy is stopped, the virus again replicates and the T-cell population drops.

Presently, the only certain way to avoid HIV infection is to refrain from unprotected sex with people whose HIV status is unknown, and from the use of contaminated needles of the type used to administer drugs intravenously.

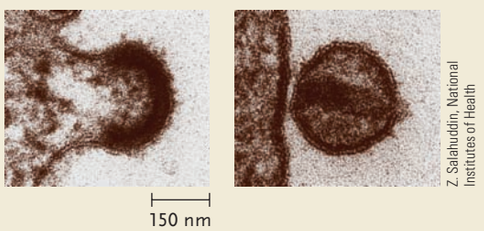


Figure c
An HIV particle budding from a host cell. As it passes from the host cell, it acquires a membrane coat derived from the host cell plasma membrane.

AIDS virus has a surface molecule that is recognized and bound by the CD4 receptor on the surface of helper T cells. Binding to CD4 locks the virus to the cell surface and stimulates the membrane covering the virus to fuse with the plasma membrane of the helper T cell. (The protein coat of the virus is wrapped in a membrane derived from the plasma membrane of the host cell in which it was produced.) The fusion introduces the virus into the cell, initiating the infection and leading to destruction and death of the T cell. (Further details of HIV infection and AIDS are presented in *Focus on Applied Research*.)

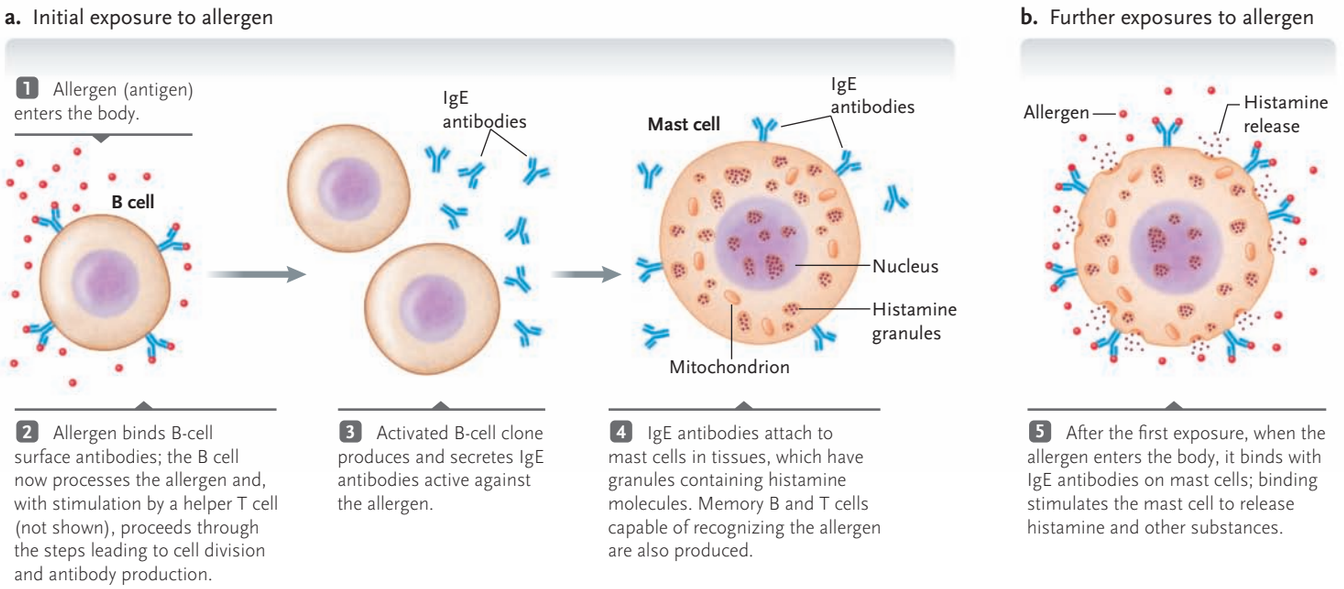


Figure 43.15
The response of the body to allergens. **(a)** The steps in sensitization after initial exposure to an allergen. **(b)** Production of an allergic response by further exposures to the allergen.

Allergies Are Produced by Overactivity of the Immune System

The substances responsible for allergic reactions form a distinct class of antigens called **allergens**, which induce B cells to secrete an overabundance of IgE antibodies **(Figure 43.15).** The IgE antibodies, in turn, bind to receptors on mast cells in connective tissue and on **basophils**, a type of leukocyte in blood (see Table 43.1), inducing them to secrete histamine, which produces a severe inflammation. Most of the inflammation occurs in tissues directly exposed to the allergen, such as the surfaces of the eyes, the lining of the nasal passages, and the air passages of the lungs. Signal molecules released by the activated mast cells also stimulate mucosal cells to secrete floods of mucus and cause smooth muscle in airways to constrict (histamine also causes airway constriction). The resulting allergic reaction can vary in severity from a mild irritation to serious and even life-threatening debilitation. *Asthma* is a severe response to allergens involving constriction of airways in the lungs. Antihistamines (substances that block histamine receptors) are usually effective in countering the effects of the histamine released by mast cells.

An individual is *sensitized* by a first exposure to an allergen, which may produce only mild allergic symptoms or no reaction at all (see Figure 43.15a). However, the sensitization produces memory B and T cells; at the next and subsequent exposures, the system is poised to produce a greatly intensified allergic response (see Figure 43.15b).

In some persons, inflammation stimulated by an allergen is so severe that the reaction brings on a life-threatening condition called **anaphylactic shock.** Extreme swelling of air passages in the lungs interferes with breathing, and massive leakage of fluid from capillaries causes the blood pressure to drop precipitously. Death may result in minutes if the condition is not treated promptly. In persons who have become sensitized to the venom of wasps and bees, for example, a single sting may bring on anaphylactic shock within minutes. Allergies developed against drugs such as penicillin and certain foods can have the same drastic effects. Anaphylactic shock can be controlled by immediate injection of epinephrine (adrenaline), which reverses the condition by constricting blood vessels and dilating air passages in the lungs.

Study Break

1. What is immunological tolerance?
2. Explain how a failure in the immune system can result in an allergy.

43.5 Defenses in Other Animals

Other Vertebrate Groups Have Defenses against Infections

This chapter has emphasized the mammalian immune system, the focus of most immunology research. We know relatively little about defenses against infections in most other vertebrate groups. Yet like all other physi-

ological systems, the mammalian defenses against pathogens are the result of evolution, and evidence of their functions can be seen in other vertebrate groups and also in invertebrates.

For example, molecular studies in sharks and rays have revealed DNA sequences that are clearly related to the sequences coding for antibodies in mammals. If injected with an antigen, sharks produce antibodies, formed from light- and heavy-chain polypeptides, capable of recognizing and binding the antigen. Although embryonic gene segments for the two polypeptides are arranged differently in sharks than they are in mammals, antibody diversity is produced by the same kinds of genetic rearrangements in both. Sharks also mount nonspecific defenses, including the production of a steroid that appears to kill bacteria and neutralize viruses nonspecifically and with high efficiency.

Invertebrates lack specific immune defenses equivalent to antibodies and the activities of B and T cells, so their reactions to invading pathogens most closely resemble the nonspecific defenses of humans and other vertebrates. However, all invertebrates have phagocytic cells, which patrol tissues and engulf pathogens and other invaders. Some of the signal molecules that stimulate phagocytic activity, such as interleukins, appear to be similar in invertebrates and vertebrates.

Antibodies do not occur in invertebrates, but proteins of the immunoglobulin family are widely distributed. In at least some invertebrates, these Ig proteins have a protective function. In moths, for example, an

Unanswered Questions

How does gene expression in a bacterial pathogen change during infection?

Characterizing the genetic events involved in the interactions between pathogens and hosts is important for understanding the development of an infectious disease in the host, and for producing effective therapeutic treatments. You learned in this chapter that pathogenic bacteria are first combated by the innate immunity system. Researchers in James Musser's lab at Baylor College of Medicine in collaboration with researchers at Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases in Montana, have now obtained information about changes in gene expression for a bacterial pathogen, group A *Streptococcus* (GAS), during infection of a mammal.

GAS is a Gram-positive bacterium that is the cause of pharyngitis ("strep throat"; 2 million cases annually in the United States) and various other infections, including rheumatic heart disease. The researchers studied how gene expression in GAS changed during an 86-day period following infection that caused pharyngitis in macaque monkeys. They are an excellent model for the study because the progression of pharyngitis caused by GAS in these monkeys is highly similar to that seen in human infections. There are three distinct phases, during which GAS can be detected by culturing throat swabs. In the first phase, colonization, GAS establishes infection of host cells, producing only mild pharyngitis. In the second phase, the acute phase, pharyngitis symptoms peak, as does the number of GAS bacteria. In the third phase, the asymptomatic phase, symptoms decrease and disappear along with a decrease in GAS bacteria.

Experimentally, the researchers analyzed gene expression from the entire genome of GAS in the three phases of pharyngitis using DNA microarrays (see Section 18.3). They found that the pattern of GAS gene expression changed over the course of the disease. Significantly, they saw characteristic gene expression patterns for each of the three phases of pathogen–host interaction. These results indicate that GAS regulates expression of its genes extensively as it establishes an infection, and as the host mounts an innate immune response against it. This work will help direct future research efforts to control infections caused by GAS. More broadly, genomic studies of this kind are likely to provide insights into genetic events contributing to pathogenesis in other pathogen–host interactions.

How does HIV evade the adaptive immunity system?

In cell-mediated immunity, a pathogen-infected antigen-presenting cell (APC) presents an antigen fragment bound to a class I MHC protein to a $CD8^+$ T cell, stimulating the T cell to differentiate into cytotoxic T cells. The cytotoxic T cells then bind to the infected APCs and destroy them. Cytotoxic T cells act particularly against host cells infected by viral pathogens. HIV infects host cells but, rather than being eliminated by the host, this virus establishes a chronic infection that leads to the development of AIDS. That is, HIV evades the adaptive immunity system.

Kathleen Collins and her group at the University of Michigan Medical School have investigated the mechanism of this evasion. They have learned that the virus down-regulates the display of class I MHC proteins on the surfaces of HIV-infected APCs, which thereby limits the presentation of viral antigens by those cells. The down-regulation occurs by the action of the HIV Nef (*ne*gative *f*actor) protein. Nef binds to class I MHC molecules and inhibits them from moving through the Golgi complex to the cell surface. Without class I MHC molecules on the cell surface to present antigens, the immune response is compromised. The action of Nef, therefore, enhances the ability of HIV to induce AIDS. Research now being pursued is directed toward characterizing more completely the role of Nef in disrupting class I MHC movement from the ER through the Golgi complex to the cell surface, identifying and characterizing other proteins that may interact with Nef in an HIV-infected cell, and developing pharmaceutical reagents aimed at blocking Nef action.

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Ig-family protein called *hemolin* binds to the surfaces of pathogens and marks them for removal by phagocytes.

Many invertebrates produce antimicrobial proteins such as lysozyme that are able to kill bacteria and other invading cells. Insects, for example, secrete lysozyme in response to bacterial infections.

Study Break

Compare invertebrate and mammalian immune defenses.

Review

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43.1 Three Lines of Defense against Invasion

- Humans and other vertebrates have three lines of defense against pathogens. The first, which is nonspecific, is the barrier set up by the skin and mucous membranes.
- The second line of defense, also nonspecific, is innate immunity, an innate system that defends the body against pathogens and toxins penetrating the first line.
- The third line of defense, adaptive immunity, is specific: it recognizes and eliminates particular pathogens and retains a memory of that exposure so as to respond rapidly if the pathogen is encountered again. The response is carried out by lymphocytes, a specialized group of leukocytes.

43.2 Nonspecific Defenses: Innate Immunity

- In the innate immunity system, molecules on the surfaces of pathogens are recognized as foreign by receptors on host cells. The pathogen is then combated by the inflammation and complement systems.
- Epithelial surfaces secrete defensins, a type of antimicrobial peptide, in response to attack by a microbial pathogen. Defensins disrupt the plasma membranes of pathogens, killing them.
- Inflammation is characterized by heat, pain, redness, and swelling at the infection site. Several interconnecting mechanisms initiate inflammation, including pathogen engulfment, histamine secretion, cytokine release, and local blood vessel dilation and permeability increase. (Figure 43.1).
- Large arrays of complement proteins are activated when they recognize molecules on the surfaces of pathogens. Some complement proteins form membrane attack complexes, which insert into the plasma membrane of many types of bacteria and cause their lysis. Fragments of other complement proteins coat pathogens, stimulating phagocytes to engulf them (Figure 43.2).
- Three nonspecific defenses are used to combat viral pathogens: RNA interference, interferons, and natural killer cells.

Animation: Innate defenses

Animation: Complement proteins

Animation: Inflammatory response

Animation: Immune responses

Animation: Human lymphatic system

43.3 Specific Defenses: Adaptive Immunity

- Adaptive immunity, which is carried out by B and T cells, targets particular pathogens or toxin molecules.
- Antibodies consist of two light and two heavy polypeptide chains, each with variable and constant regions. The variable regions of the chains combine to form the specific antigen-binding site (Figure 43.4).
- Antibodies occur in five different classes: IgM, IgD, IgG, IgA, and IgE. Each class is determined by its constant region (Table 43.2).
- Antibody diversity is produced by genetic rearrangements in developing B cells that combine gene segments into intact genes encoding the light and heavy chains. The rearrangements producing heavy-chain genes and T-cell receptor genes are similar. The light and heavy chain genes are transcribed into precursor mRNAs, which are processed into finished mRNAs, which are translated on ribosomes into the antibody polypeptides (Figure 43.4).
- The antibody-mediated immune response has two general phases: T-cell activation, and B-cell activation and antibody production. T-cell activation begins when a dendritic cell engulfs a pathogen and produces antigens, making the cell an antigen-presenting cell (APC). The APC secretes interleukins, which activate the T cell. The T cell then secretes cytokines, which stimulate the T cell to proliferate, producing a clone of cells. The clonal cells differentiate into helper T cells (Figures 43.3, 43.6, and 43.8).
- B-cell receptors (BCRs) on B cells recognize antigens on a pathogen and engulf it. The B cells then display the antigens. The TCR on a helper T cell activated by the same antigen binds to the antigen on the B cell. Interleukins from the T cell stimulate the B cell to produce a clone of cells with identical BCRs. The clonal cells differentiate into plasma cells, which secrete antibodies specific for the antigen, and memory B cells, which provide immunological memory of the antigen encounter (Figures 43.3, 43.8, and 43.9).
- Clonal expansion is the process of selecting a lymphocyte specifically for cloning when it encounters an antigen from among a randomly generated, large population of lymphocytes with receptors that specifically recognize the antigen (Figure 43.10).
- Antibodies clear the body of antigens by neutralizing or agglutinating them, or by aiding the innate immune response (Figure 43.11).
- In immunological memory, the first encounter of an antigen elicits a primary immune response and later exposure to the same antigen elicits a rapid secondary response with a greater production of antibodies (Figure 43.12).
- Active immunity is the production of antibodies in the body in response to an antigen. Passive immunity is the acquisition of antibodies by direct transfer from another person.
- In cell-mediated immunity, cytotoxic T cells recognize and bind to antigens displayed on the surfaces of infected body cells, or to cancer cells. They then kill the infected body cell (Figure 43.13).
- Antibodies are widely used in research to identify, locate, and determine the functions of molecules in biological systems.
- Monoclonal antibodies are made by isolating fully active B cells from a test animal, fusing them with cancer cells to produce hy-

bridomas, and using single hybridomas to start clones of cells, all of which make highly specific antibodies against the same epitope of an antigen (Figure 43.14).

Animation: Antibody structure

Animation: Gene rearrangements

Animation: Clonal selection of a B cell

Animation: Antibody-mediated response

Animation: Cell-mediated response

43.4 Malfunctions and Failures of the Immune System

- In immunological tolerance, molecules present in an individual at birth normally do not elicit an immune response.
- In some people, the immune system malfunctions and reacts against the body's own proteins or cells, producing autoimmune disease.
- The first exposure to an allergen sensitizes an individual by leading to the production of memory B and T cells, which cause a greatly intensified response at the next and subsequent exposures.
- Most allergies result when antigens act as allergens by stimulating B cells to produce IgE antibodies, which leads to the release of histamine. Histamine produces the symptoms characteristic of allergies (Figure 43.15).

Animation: HIV replication cycle

43.5 Defenses in Other Animals

- Antibodies, complement proteins, and other molecules with defensive functions have been identified in all vertebrates.
- Invertebrates rely on nonspecific defenses, including surface barriers, phagocytes, and antimicrobial molecules.

Questions

Self-Test Questions

1. Which of the following most directly affects a cell harboring a virus?
   a. $CD8^+$ T cells that bind class I MHC proteins holding viral antigen
   b. $CD4^+$ T cells that bind free viruses in the blood
   c. B cells secreting perforin
   d. antibodies that bind the viruses with their constant ends
   e. natural killer cells secreting antiviral antibodies
2. Components of the inflammatory response include all *except*:
   a. macrophages.
   b. neutrophils.
   c. B cells.
   d. mast cells.
   e. eosinophils.
3. When a person resists infection by a pathogen after being vaccinated against it, this is the result of:
   a. innate immunity.
   b. immunological memory.
   c. a response with defensins.
   d. an autoimmune reaction.
   e. an allergy.
4. One characteristic of a B cell is that it:
   a. has the same structure in both invertebrates and vertebrates.
   b. recognizes antigens held on class I MHC proteins.
   c. binds viral infected cells and directly kills them.
   d. makes many different BCRs on its surface.
   e. has a BCR on its surface, which is the IgM molecule.
5. Antibodies:
   a. are each composed of four heavy and four light chains.
   b. display a variable end, which determines the antibody's location in the body.
   c. belonging to the IgE group are the major antibody class in the blood.
   d. found in large numbers in the mucous membranes belong to class IgG.
   e. function primarily to identify and bind antigens free in body fluids.
6. The generation of antibody diversity includes the:
   a. joining of V to C to J segments to make a functional light chain gene.
   b. choice from several different types of C segments to make a functional light chain gene.
   c. deletion of the J segment to make a functional light chain gene.
   d. joining of V to J to C segments to make a functional light chain gene.
   e. initial generation of IgG followed later by IgM on a given cell.
7. An APC:
   a. can be a $CD8^+$ T cell.
   b. derives from a phagocytic cell and is lymphocyte-stimulating.
   c. secretes antibodies.
   d. cannot be a B cell.
   e. cannot stimulate helper T cells.
8. Antibodies function to:
   a. deactivate the complement system.
   b. neutralize natural killer cells.
   c. clump bacteria and viruses for easy phagocytosis by macrophages.
   d. eliminate the chance for a secondary response.
   e. kill viruses inside of cells.
9. After Jen punctured her hand with a muddy nail, in the emergency room she received both a vaccine and someone else's antibodies against tetanus toxin. The immunity conferred here is:
   a. both active and passive.
   b. active only.
   c. passive only.
   d. first active; later passive.
   e. innate.
10. Medicine attempts to enhance the immune response when treating:
    a. organ transplant recipients.
    b. anaphylactic shock.
    c. rheumatoid arthritis.
    d. HIV infection.
    e. Type I diabetes.

Questions for Discussion

1. HIV wreaks havoc with the immune system by attacking helper T cells and macrophages. Would the impact be altered if the virus attacked only macrophages? Explain.

2. Given what you know about how foreign invaders trigger immune responses, explain why mutated forms of viruses, which have altered surface proteins, pose a monitoring problem for memory cells.
3. Cats, dogs, and humans may develop myasthenia gravis, an autoimmune disease in which antibodies develop against acetylcholine receptors in the synapses between neurons and skeletal muscle fibers. Based on what you know of the biochemistry of muscle contraction (see Section 41.1), explain why people with this disease typically experience severe fatigue with even small levels of exertion, drooping of facial muscles, and trouble keeping their eyelids open.

Experimental Analysis

Space, the final frontier! Indeed, but being in space has some problems. Astronauts in space show a decline in their ability to mount an immune response and, consequently, develop a decreased resistance to infection. Two potentially important differences in physiology in space versus on Earth are more fluid flowing to the head and a lack of weight-bearing on the lower limbs. Could they be involved somehow in the deleterious effect on the immune system? Design an experiment to be done on Earth to answer this question.

Evolution Link

Defensins are found in a wide range of organisms, including plants as well as animals. What are the evolutionary implications of this observation?

How Would You Vote?

Drugs are available that can extend the life of patients with AIDS, but their high cost is more than people in most developing countries can afford to pay. Should the federal government offer incentives to companies to discount the drugs for developing countries? What about AIDS patients at home? Who should pay for their drugs? Go to www.thomsonedu.com/login to investigate both sides of the issue and then vote.