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Chapter 15

Innate and Adaptive Immunity

The immune system has evolved to defend against bacteria, viruses, and other foreign substances. Through recognition of molecular patterns, the immune system can distinguish itself from foreign substances and can discriminate potentially harmful from non-harmful agents. It also defends against abnormal cells and molecules that periodically develop. Although the immune response normally is protective, it also can produce undesirable effects such as when the response is excessive, as in allergies, or when it recognizes self-tissue as foreign, as in autoimmune disease. This chapter is divided into three parts: (1) introduction to the immune system, (2) innate immunity, (3) adaptive immunity, and (4) developmental aspects of the immune system.

Introduction to the Immune System

The term *immunity* has come to mean protection from disease and, more specifically, infectious disease. The collective, coordinated response of the cells and molecules of the immune system is called the *immune response.* Although the relationship between microbes and infectious diseases dates far back in history, it has only been within the last 30 to 40 years that an understanding of the cellular and biochemical mechanisms involved in the immune response has begun to emerge. Advances in cell culture techniques, immunochemistry, recombinant deoxyribonucleic acid (DNA) technology, and the creation of genetically altered animals, such as "transgenic" and "knockout" mice, have transformed immunology from a largely descriptive science to one of immune phenomena that can be explained in structural and biochemical terms.

Innate and Adaptive Immunity

There are two host defenses that cooperate to protect the body—the early, rapid responses of innate immunity, and the very effective but later responses of adaptive immunity. As the first line of defense, *innate* (also called *natural*

or *native*) *immunity* consists of the physical, chemical, molecular, and cellular defenses that are in place before infection and can function immediately as an effective barrier to microbes. *Adaptive* (also called *specific* or *acquired*) *immunity* is the second major immune defense, responding less rapidly than innate immunity but more effectively. Adaptive immunity uses focused recognition of each unique type of foreign agent followed, in days, by an amplified and effective response.

The major components of innate immunity are the skin and mucous membranes, phagocytic leukocytes (mainly neutrophils and macrophages), specialized lymphocytes (the natural killer cells), and several plasma proteins, including the proteins of the complement system (Fig. 15-1). The innate immune system is able to distinguish self from nonself and is able to recognize and react against various classes of microbial agents. The response of the innate immune system is rapid, usually within minutes to hours, and prevents the establishment of infection and deeper tissue penetration of microorganisms. The effector responses used by the innate immune system to eliminate the microbes are very similar for different classes of microorganisms. Although most innate responses are very effective in controlling and destroying the invading agent, pathogenic microbes have evolved several approaches to evade innate defenses. The microorganisms not controlled by innate immunity are usually controlled by the more specific approaches of adaptive immunity.

The adaptive immune system consists of two groups of lymphocytes and their products, including antibodies (see Fig. 15-1). Whereas the cells of the innate immune system recognize structures shared by classes of microorganisms, the cells of the adaptive immune system are capable of recognizing numerous microbial and noninfectious substances and developing a unique specific immune response for each substance. Substances that elicit adaptive immune responses are called *antigens*. A memory of the substance is also developed so that a repeat exposure to the same microbe or agent produces a quicker and more vigorous response.

There are two types of adaptive immune responses: humoral and cell-mediated immunity. *Humoral immunity* is mediated by molecules called *antibodies* that are produced by cells called *B lymphocytes*. Antibodies are secreted into the circulation and mucosal fluid, where they neutralize or eliminate extracellular microbes and microbial toxins. One of the important functions of

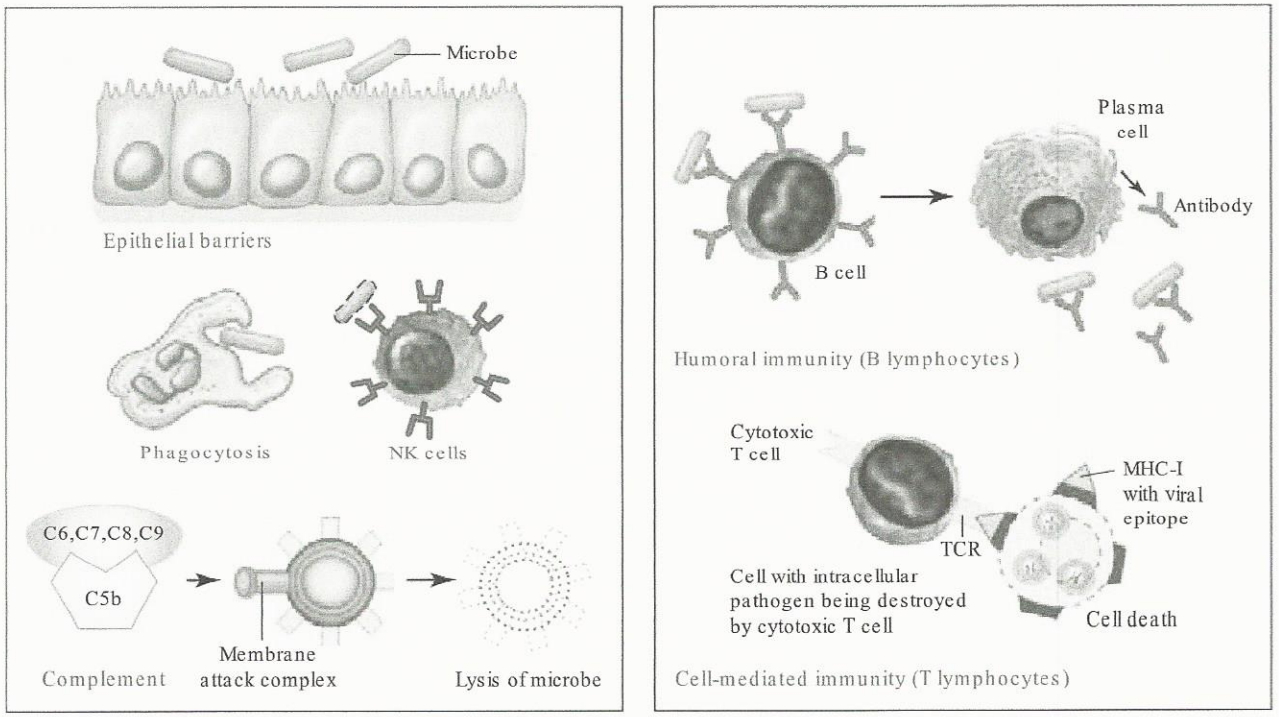

FIGURE 15-1. Mechanisms of innate and adaptive immunity. **(A)** The major effectors of the innate immune system include the immediately available epithelial barriers, phagocytic leukocytes, natural killer (NK) cells, and complement system. These effectors are in place before an encounter with an infectious agent and provide rapid protection against infection. **(B)** Adaptive immunity develops later than innate immunity, is acquired through previous experience with a foreign agent, and is mediated by T and B lymphocytes and their products. Humoral immunity is provided by B lymphocytes that differentiate into antibody-producing plasma cells that interact with and protect against microbes that are present in the blood or on mucosal surfaces. Cell-mediated immunity is provided by cytotoxic T cells that destroy cells infected with intracellular pathogens. MHC-1, major histocompatibility complex-1; TCR, T-cell receptor.

humoral immunity is to stop microbes that are present on mucosal surfaces and in the blood from gaining access to and colonizing body tissues. *Cell-mediated immunity,* which defends against intracellular microbes such as viruses, is provided by cells called *T lymphocytes.* Some T lymphocytes activate phagocytes to destroy microbes that have been engulfed, whereas others kill any type of host cell that is harboring microbes.

Recent studies have shown that essential, cooperative interactions exist between innate and adaptive immunity. Innate immunity communicates to lymphocytes involved in adaptive immunity the characteristics of the pathogen and information about its intracellular or extracellular location. The innate immune response also stimulates and influences the nature of adaptive immune responses. At the effector stage of immunity, the adaptive immune response amplifies and increases its efficiency by recruitment and activation of additional phagocytes and molecules of the innate immune system. Both innate and adaptive immunity destroy the invading agent by using the effector responses of phagocytosis and the complement system. Thus, immunity is truly an interactive, cooperative effort.

Cells of the Immune System

All of the cellular elements of the blood, including the red blood cells, platelets, and white blood cells, derive from the hematopoietic stem cells in the bone marrow (see Chapter 11). As these stem cells differentiate, they give rise to cells with more limited developmental potential, including the immediate progenitors of the two main categories of white blood cells, the myeloid and lymphoid lineages. The common myeloid progenitor is the precursor of most of the phagocytic cells of the innate immune system, and the lymphoid lineage consists of the lymphocytes of the adaptive immune system and natural killer cells of innate immunity. The general properties of these cells are presented in this section, whereas their specific functions in relation to innate or adaptive immunity are discussed in those sections of the chapter.

Myeloid Lineage Phagocytic Cells

The common myeloid progenitor is the precursor of the monocytes/macrophages, granulocytes, and dendritic cells of the innate immune system. These three cell types make up the phagocytic cells of the immune system.

Monocytes/Macrophages. Macrophages are part of the monocytic phagocyte system, a family of phagocytic cells. They are resident in almost all tissues and are the mature form of monocytes, which circulate in the blood and continually migrate into tissues, where they differentiate into macrophages. Macrophages are relatively long-lived cells and perform several different functions during the innate and adaptive immune responses. One function is to engulf and kill invading microorganisms. In this phagocytic role they are an important first-line defense in innate immunity, and they dispose of pathogens and infected cells targeted for disposal by an adaptive immune response.

Although their primary role is in phagocytosis, macrophages also function as *antigen-presenting cells* of the adaptive immune response. That is, they process and present molecules of foreign antigens to the lymphocytes involved in adaptive immunity. Macrophages also help induce inflammation, and they secrete signaling proteins that activate other immune cells and recruit them into an immune response. In addition to these immune-system roles, macrophages act as general scavenger cells in the body, clearing dead cells and cell debris.

Granulocytes. The granulocytes are so called because they have densely staining granules in the cytoplasm. There are three types of granulocytes—neutrophils, eosinophils, and basophils—which are distinguished by the staining properties of their granules. Compared to the macrophages, they are relatively short-lived, surviving only a few days, and are produced in increased numbers during an immune response. Neutrophils, which are named for their neutral-staining granules, are the most numerous of the granulocytes and the most important cell in innate immunity. They take up a variety of microorganisms by phagocytosis and efficiently destroy them using degradative enzymes and other antimicrobial substances stored in their cytoplasmic granules. The protective functions of the basophils, which stain blue, and eosinophils, which stain red, are less well understood. They are thought to be an important defense against parasites, which are too large to be ingested by macrophages and neutrophils. They are also involved in allergic reactions, in which their effects are damaging and not protective (see Chapter 16).

Dendritic Cells. The dendritic cells are the third class of phagocytic cells of the immune system. They have long fingerlike processes, which give them their name. Most dendritic cells are found as immature cells under epithelial tissue and in most organs, where they are poised to capture foreign agents and transport them to peripheral lymphoid organs. Once activated, they undergo a complex maturation process as they migrate to the regional lymph nodes.

Like macrophages, dendritic cells function as key antigen-presenting cells that initiate adaptive immune responses by processing and presenting molecules of foreign antigens to B and T lymphocytes. Both macrophages and dendritic cells also release several communication molecules that direct the nature of adaptive immune responses. Thus, they serve as important intermediaries between innate and adaptive immunity.

Lymphocytes and Natural Killer Cells

The common lymphoid progenitor in the bone marrow gives rise to two types of antigen-specific lymphocytes—the B and T lymphocytes of the adaptive immune system—and a third type of lymphocyte, the natural killer cell, that does not respond to specific antigens but is considered part of the innate immune system. The B and T lymphocytes are the only cells that produce specific receptors for antigen and thus are the key mediators of adaptive immunity. A naive lymphocyte is a mature

B or T lymphocyte that has not previously encountered antigen or is not the progeny of an antigen-stimulated mature lymphocyte.

B lymphocytes (B cells) are the only cells capable of producing antibodies; therefore, they are the cells that mediate humoral immunity. B cells use membrane-bound antibodies to recognize a wide variety of proteins, polysaccharides, lipids, and small chemicals. These antigens may be expressed on microbial surfaces or they may be in soluble forms (toxins). In response to antigen and other signals, B cells differentiate into plasma cells which produce antibody. The secreted antibodies enter the circulation and mucosal fluids and bind to microbes before they have a chance to colonize body tissues.

T lymphocytes (T cells) are responsible for cell-mediated immunity. The antigen receptors of most T lymphocytes only recognize peptide fragments of protein antigens that are bound to specialized peptide display molecules called *major histocompatibility complex (MHC) molecules* on the surface of antigen-presenting cells. Among T lymphocytes are a subset of T cells called *helper T cells* that help B lymphocytes produce antibodies and help phagocytic cells destroy ingested pathogens, and another subset called *cytotoxic T cells* that kill or lyse intracellular microbes.

Although all lymphocytes are morphologically similar, they vary in terms of lineage, cell membrane molecules and receptors, function, and response to antigen. These cells are often distinguished by surface proteins. The standard nomenclature for these proteins is the CD (clusters of differentiation) numeric designation ($CD4^+$, $CD8^+$), which is used to delineate surface proteins that define a particular cell type or stage of cell differentiation and are recognized by a "cluster" of antibodies.

The CD classification is now widely used in clinical medicine and experimental immunology. In human immunodeficiency virus (HIV) infection, for example, a decline or rise in the $CD4^+$ helper T-cell count is used to follow the progression of the disease and response to treatment. Further investigation of the CD molecules has shown that they are not merely phenotypic markers of cell type but are themselves involved in a variety of lymphocyte functions, including promotion of cell-to-cell adhesion and transduction of signals that lead to lymphocyte activation.

The third type of lymphocyte, the natural killer (NK) cell is part of the innate immune system and may be the first line of defense against viral infections. The NK cell also has the ability to recognize and kill tumor cells, abnormal body cells, and cells infected with *intracellular pathogens,* such as viruses and intracellular bacteria.

Organs and Tissues of the Immune System

The cells of the immune system are present in large numbers in the central and peripheral lymphoid organs. These organs and tissues are widely distributed in the body and provide different, but often overlapping, functions (Fig. **15-2**). The lymphoid organs are connected by networks of lymph channels, blood vessels, and capillaries. The immune cells continuously circulate through the various tissues and organs to seek out and destroy foreign material.

Central Lymphoid Tissues

The central lymphoid tissues, the bone marrow and thymus gland, provide the environment for immune cell production and maturation (see Chapter 11). The specialized microenvironment of the bone marrow provides signals both for the development of lymphocyte progenitors from the hematopoietic stem cells and for the subsequent differentiation of B cells.

T-cell progenitors migrate from the bone marrow to the thymus where the process of maturation occurs. The thymus is an elongated, bilobed structure located in the neck region of the chest above the heart. The function of the thymus is central to the development of the immune system because it generates mature, immunocompetent T lymphocytes expressing appropriate receptors. The thymus is fully formed and functional at birth. It persists

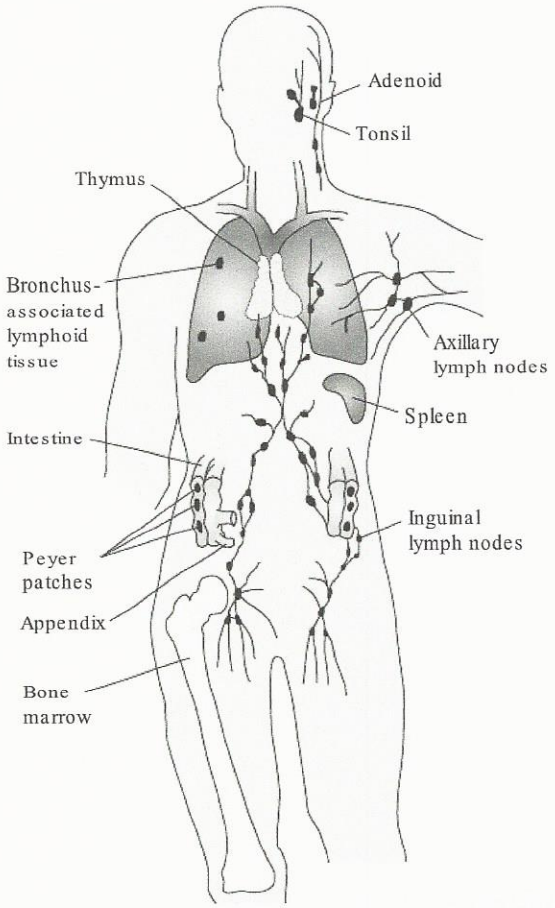

FIGURE 15-2. Central and peripheral lymphoid organs and tissues.

as a large organ until about the time of puberty, when T-cell development and proliferation are reduced and the thymus begins slowly regressing and is replaced by adipose tissue. Nevertheless, some thymus tissue persists and can be restimulated under conditions that demand rapid T-cell proliferation.

Precursor T (pre-T) cells enter the thymus as functionally and phenotypically immature T cells. They undergo cycles of proliferation and selection as they move from the cortical to medullary compartments of the thymus. Rapid cell multiplication, maturation, and selection occur in the cortex under the influence of the microenvironment, thymic hormones, and cytokines. As the T cells multiply and mature, they acquire T-cell receptors, surface markers that distinguish among the different types of T cells, and antigens that distinguish them from nonself. Only those T cells able to recognize foreign antigens and distinguish self from nonself are allowed to mature and leave the thymus. This process is called *thymic selection*. The thymus must be extremely thorough in eliminating self-reactive cells to ensure that autoimmune reactivity and disease do not result. Mature, immunocompetent T-helper and T-cytotoxic cells leave the thymus in 2 to 3 days and enter the peripheral lymphoid tissues through the bloodstream.

The process of B-cell maturation, which is similar to that of T-cell maturation, occurs in the bone marrow. Here, the B cells multiply and acquire immunoglobulin (Ig) signaling molecules and cell markers that distinguish them from nonself. As with T cells, only those B cells that are able to distinguish self from nonself are allowed to mature and leave the bone marrow.

Peripheral Lymphoid Tissues

The peripheral lymphoid structures, which consist of the lymph nodes, the spleen, and other secondary lymphoid tissues, function to concentrate antigen, aid in processing of antigen, and promote the cellular interactions necessary for development of adaptive immune responses.

Lymph Nodes. The vessels of the lymphatic system remove protein-rich fluid, called *lymph*, from the intercellular spaces and return it to the circulation (see the lymphatic system, Chapter 17). Before lymph is returned to the blood, it passes through lymph nodes, which are highly organized lymphoid organs with two distinct functions. First, they filter foreign material from lymph before it enters the bloodstream. Lymph nodes are located at points of convergence of lymphatic vessels, with aggregates of lymph nodes processing lymph from discrete anatomic sites, including the axillae and groin, and along the great vessels of the neck, thorax, and abdomen (see Fig. **15-2**). Second, they serve as centers for proliferation and response of immune cells.

Each lymph node is a small, bean-shaped, encapsulated organ (Fig. 15-3). Lymph enters the node through afferent vessels that penetrate the capsule, and leaves through efferent vessels located in the deep indentation

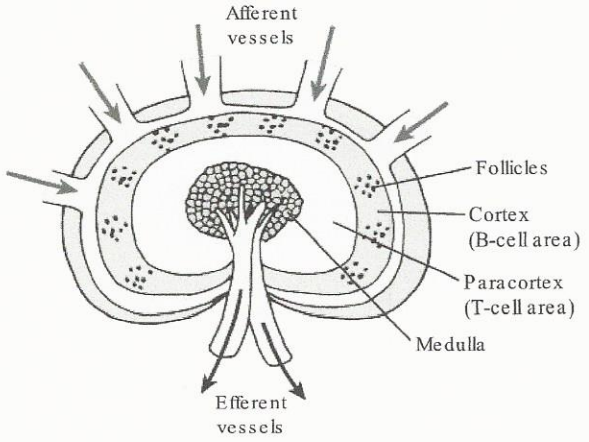

FIGURE 15-3. Structural features of a lymph node. Lymphocytes and macrophages flow slowly through the node, which allows for trapping and interactions of antigens and immune cells.

of the hilus. Lymphocytes and macrophages flow slowly through the node, which allows trapping and interaction of antigen and immune cells. As lymph passes through the lymph nodes, antigen-presenting cells in the nodes are able to sample the antigens that enter through the epithelia. In addition, microbes that bypass the epithelial barriers of the innate immune system are captured by resident dendritic cells and transported to draining lymph nodes.

A lymph node is divided into several specialized areas: an outer cortex, a paracortex, and an inner medulla. B lymphocytes are more abundant in the follicles located in the outer cortex. The T lymphocytes proliferate on antigenic stimulation and migrate to the follicles, where they interact with B lymphocytes. These activated follicles become germinal centers, containing macrophages, follicular dendritic cells, and maturing T and B cells. Activated B cells then migrate to the medulla, where they complete their maturation into plasma cells. These cells stay localized in the lymph node but release large quantities of antibodies into the circulation.

Spleen. The spleen is a large, ovoid secondary lymphoid organ located high in the left abdominal cavity. The spleen filters antigens from the blood and is important in the response to systemic infections. The spleen is composed of red and white pulp. The red pulp is well supplied with arteries and is the area where senescent and injured red blood cells are removed. The white pulp contains concentrated areas of B and T lymphocytes permeated by macrophages and dendritic cells. A sequence of activation events similar to that seen in the lymph nodes occurs in the spleen.

Other Secondary Lymphoid Tissues. Other secondary lymphoid tissues include the *mucosa-associated lymphoid tissues* (MALT). These nonencapsulated clusters of lymphoid tissues are located around

membranes lining the respiratory, digestive, and urogenital tracts. These gateways into the body must harbor the immune cells needed to respond to a large and diverse population of microorganisms. In some tissues, the lymphocytes congregate in loose clusters, but in other tissues such as the tonsils, Peyer patches in the intestine, and the appendix, organized structures are evident (see Fig. **15-2**). These tissues contain all the necessary cell components (i.e., T cells, B cells, macrophages, and dendritic cells) for an immune response. Because of the continuous stimulation of the lymphocytes in these tissues by microorganisms constantly entering the body, large numbers of plasma cells are evident. Immunity at the mucosal layers helps to exclude many pathogens and thus protects the vulnerable internal organs.

Cytokines That Mediate and Regulate Immunity

Although cells of both the innate and adaptive immune systems communicate critical information by cell-to-cell contact, many interactions and effector responses depend on the secretion of short-acting soluble molecules called *cytokines*. The sources and properties of the main cytokines that participate in innate and adaptive immunity are summarized in Table 15-1.

General Properties of Cytokines

Cytokines are low–molecular-weight regulatory proteins that are produced by cells of the innate and adaptive immune systems and that mediate many of the actions of these cells. The names of specific types of cytokines were derived from the biologic properties first ascribed to them. For example, *interleukins* (ILs) were found to be made by leukocytes and to act on leukocytes, and *interferons* (IFNs) were found to interfere with virus multiplication.

Although cytokines have many diverse actions, all share several important properties. Most cytokines are released at cell-to-cell interfaces, where they bind to specific receptors on the membrane surface of their target cells. All cytokines are secreted in a brief, self-limited manner. They are not usually stored as preformed molecules and their synthesis is limited to new gene transcription resulting from cellular activation. The short half-life of cytokines ensures that excessive immune responses and systemic activation do not occur.

The actions of cytokines are often pleiotropic and redundant. *Pleiotropism* refers to the ability of a cytokine to act on different cell types. For example, IL-2, initially discovered as a T-cell growth factor, is also known to affect the growth of B cells and NK cells. Interferon-γ is the key macrophage-activating cytokine that functions in both innate and adaptive immune responses. Although pleiotropism allows cytokines to mediate diverse effects, it greatly limits their use for therapeutic purposes because of numerous unwanted side effects. *Redundancy* refers to the ability of different cytokines to stimulate the same or overlapping biologic functions. Because of this redundancy, antagonists against a single cytokine may not have functional consequences because other cytokines may compensate.

Not only are the actions of cytokines pleiotropic and redundant, but the same cytokines may be produced by several different cell types. For example, IL-1 can be produced by virtually all leukocytes, endothelial cells, and fibroblasts. Cytokines often influence the synthesis and actions of other cytokines. The ability of one cytokine to stimulate the production of others often leads to cascades in which the second and third cytokines may mediate the biologic effects of the first. Cytokines may also serve as antagonists to inhibit the action of another cytokine, or in some cases they may produce additive or greater than anticipated effects.

Cytokine actions may be local or systemic. Most cytokines act close to where they are produced, acting on the same cell that secreted the cytokine (autocrine mechanism), or they may influence the activity of nearby cells (paracrine mechanism). When produced in large amounts, cytokines may enter the bloodstream and exert their action on distant cells in an endocrine manner; the best examples are IL-1 and tumor necrosis factor-α (TNF-α), which produce the systemic acute-phase response during inflammation.

Chemokines

Chemokines are cytokines that stimulate the migration and activation of immune and inflammatory cells. There are two major subclasses, termed *CC chemokines* and *CXC chemokines,* which are distinguished by their amino acid sequence. The largest family, the CC chemokines, attracts mononuclear leukocytes to sites of chronic inflammation. The CXC chemokines attract neutrophils to sites of acute inflammation.

Chemokines are implicated in a number of acute and chronic diseases, including atherosclerosis, rheumatoid arthritis, inflammatory bowel disease (Crohn disease and ulcerative colitis), allergic asthma and chronic bronchitis, multiple sclerosis, systemic lupus erythematosus, and HIV infection. To enter target cells, HIV type 1 requires two distinct elements: the CD4 recognition molecule of the helper T cell and either the CXCR4 or CCR5 chemokine. The targeting of T cells and monocytes allows HIV-1 access to sanctuary sites throughout the body and also cripples the $CD4^+$ T-helper cell that orchestrates antiviral immunity (discussed in Chapter 16).

Colony-Stimulating Factors

Colony-stimulating factors (CSFs) are cytokines that stimulate bone marrow pluripotent stem and progenitor or precursor cells to produce large numbers of platelets, erythrocytes, lymphocytes, neutrophils, monocytes, eosinophils, basophils, and dendritic cells. The CSFs were named according to the type of target cell on which they act (see Table 15-1). Granulocyte-monocyte colony-stimulating factor (GM-CSF) acts on