Interest in HLA molecules was spurred by the realization, in the 1960s and 1970s, that **a number of autoimmune and other diseases are associated with the inheritance of particular HLA alleles.** These associations are discussed when the pathogenesis of autoimmune diseases is considered later in the chapter.

Cytokines: Messenger Molecules of the Immune System

The induction and regulation of immune responses involve multiple interactions among lymphocytes, dendritic cells, macrophages, other inflammatory cells (e.g., neutrophils), and endothelial cells. Some of these interactions depend on cell-to-cell contact; however, **many cellular interactions and functions of leukocytes are mediated by secreted proteins called *cytokines.*** Molecularly defined cytokines are called *interleukins*, because they mediate communications between leukocytes. Most cytokines have a wide spectrum of effects, and some are produced by several different cell types. The majority of these cytokines act on the cells that produce them (*autocrine* actions) or on neighboring cells (*paracrine*) and rarely at a distance (*endocrine*).

Cytokines contribute to different types of immune responses.

- In innate immune responses, cytokines are produced rapidly after encounter with microbes and other stimuli, and function to induce inflammation and inhibit virus replication. These cytokines include TNF, IL-1, IL-12, type I IFNs, IFN-γ, and chemokines (Chapter 3). Their major sources are macrophages, dendritic cells, and NK cells, but endothelial and epithelial cells can also produce them.
- In adaptive immune responses, cytokines are produced principally by CD4+ T lymphocytes activated by antigen and other signals, and function to promote lymphocyte proliferation and differentiation and to activate effector cells. The main ones in this group are IL-2, IL-4, IL-5, IL-17, and IFN-γ; their roles in immune responses are described later. Some cytokines serve mainly to limit and terminate immune responses; these include TGF-β and IL-10.
- Some cytokines stimulate hematopoiesis and are called *colony-stimulating factors* because they are assayed by their ability to stimulate formation of blood cell colonies from bone marrow progenitors (Chapter 13). Their functions are to increase leukocyte numbers during immune and inflammatory responses, and to replace leukocytes that are consumed during such responses. They are produced by marrow stromal cells, T lymphocytes, macrophages, and other cells. Examples include the colony-stimulating factors (CSFs) such as GM-CSF, and IL-7.

The knowledge gained about cytokines has numerous practical therapeutic applications. Inhibiting cytokine production or actions is an approach for controlling the harmful effects of inflammation and tissue-damaging immune reactions. Patients with rheumatoid arthritis often show dramatic responses to TNF antagonists, an elegant example of rationally designed and molecularly targeted therapy. Many other cytokine antagonists are now approved for the treatment of various inflammatory disorders. Conversely, administration of cytokines is used to boost reactions that are normally dependent on these proteins, such as hematopoiesis and defense against some viruses. An important therapeutic application of cytokines is to mobilize and recruit stem cells from bone marrow to peripheral blood; the cells are then collected from the blood for stem cell transplantation.

Overview of Lymphocyte Activation and Immune Responses

All adaptive immune responses develop in steps, consisting of: antigen recognition, activation of specific lymphocytes to proliferate and differentiate into effector and memory cells, elimination of the antigen, and decline of the response, with memory cells being the long-lived survivors. The major events in each step are summarized later; these general principles apply to protective responses against microbes as well as pathologic responses that injure the host.

Display and Recognition of Antigens

Microbes and other foreign antigens can enter anywhere in the body. It is obviously impossible for lymphocytes of every specificity to patrol every possible portal of antigen entry. In fact, antigens are captured and concentrated in lymphoid organs through which lymphocytes circulate, thus increasing the likelihood of lymphocytes finding the antigen they recognize. Microbes and their protein antigens are captured by dendritic cells that are resident in epithelia and tissues. These cells carry their antigenic cargo to draining lymph nodes (Fig. 6-10). Here the antigens are processed and displayed complexed with MHC molecules on the cell surface, where the antigens are recognized by T cells.

B lymphocytes use their antigen receptors (membrane-bound antibody molecules) to recognize antigens of many different chemical types, including proteins, polysaccharides, and lipids.

Even before the antigens of a microbe are recognized by T and B lymphocytes, the microbe elicits an innate immune response through recognition by pattern recognition receptors; this encounter is the first line of defense and also serves to activate adaptive immunity. In the case of immunization with a protein antigen, microbial mimics, called *adjuvants*, are given with the antigen and these stimulate innate immune responses. During the innate response the microbe or adjuvant activates antigen-presenting cells to express molecules called *costimulators* and to secrete cytokines that stimulate the proliferation and differentiation of T lymphocytes. The principal costimulators for T cells are the B7 proteins (CD80 and CD86) that are expressed on antigen-presenting cells and are recognized by the CD28 receptor on naive T cells. Thus, antigen ("signal 1") and costimulatory molecules produced during innate immune responses to microbes ("signal 2") function cooperatively to activate antigen-specific lymphocytes (Fig. 6-5). The requirement for microbe-triggered signal 2 ensures that the adaptive immune response is induced by microbes and not by harmless substances. In immune responses to tumors and transplants, "signal 2" may be provided by substances