The products of activated macrophages eliminate injurious agents such as microbes and initiate the process of repair, but are also responsible for much of the tissue injury in chronic inflammation. Several functions of macrophages are central to the development and persistence of chronic inflammation and the accompanying tissue injury.

- Macrophages, like the other type of phagocyte, the neutrophils, **ingest and eliminate microbes and dead tissues.**
- Macrophages **initiate the process of tissue repair** and are involved in scar formation and fibrosis. These processes are discussed later in the chapter.
- Macrophages **secrete mediators of inflammation,** such as cytokines (TNF, IL-1, chemokines, and others) and eicosanoids. Thus, macrophages are central to the initiation and propagation of inflammatory reactions.
- Macrophages **display antigens to T lymphocytes and respond to signals from T cells,** thus setting up a feedback loop that is essential for defense against many microbes by cell-mediated immune responses. These interactions are described further in the discussion of the role of lymphocytes in chronic inflammation, below, and in more detail in Chapter 6 where cell-mediated immunity is considered.

Their impressive arsenal of mediators makes macrophages powerful allies in the body's defense against unwanted invaders, but the same weaponry can also induce considerable tissue destruction when macrophages are inappropriately or excessively activated. It is because of these activities of macrophages that tissue destruction is one of the hallmarks of chronic inflammation.

In some instances, if the irritant is eliminated, macrophages eventually disappear (either dying off or making their way into the lymphatics and lymph nodes). In others, macrophage accumulation persists, as a result of continuous recruitment from the circulation and local proliferation at the site of inflammation.

Role of Lymphocytes

Microbes and other environmental antigens activate T and B lymphocytes, which amplify and propagate chronic inflammation. Although the major function of these lymphocytes is as the mediators of adaptive immunity, which provides defense against infectious pathogens (Chapter 6), these cells are often present in chronic inflammation and when they are activated, the inflammation tends to be persistent and severe. Some of the strongest chronic inflammatory reactions, such as granulomatous inflammation, described later, are dependent on lymphocyte responses. Lymphocytes may be the dominant population in the chronic inflammation seen in autoimmune and other hypersensitivity diseases.

Antigen-stimulated (effector and memory) T and B lymphocytes use various adhesion molecule pairs (selectins, integrins and their ligands) and chemokines to migrate into inflammatory sites. Cytokines from activated macrophages, mainly TNF, IL-1, and chemokines, promote leukocyte recruitment, setting the stage for persistence of the inflammatory response.

By virtue of their ability to secrete cytokines, CD4+ T lymphocytes promote inflammation and influence the nature of the inflammatory reaction. These T cells greatly amplify the early inflammatory reaction that is induced by recognition of microbes and dead cells as part of innate immunity. There are three subsets of CD4+ T cells that secrete different types of cytokines and elicit different types of inflammation.

- T_H1 cells produce the cytokine IFN-γ, which activates macrophages by the classical pathway.
- T_H2 cells secrete IL-4, IL-5, and IL-13, which recruit and activate eosinophils and are responsible for the alternative pathway of macrophage activation.
- T_H17 cells secrete IL-17 and other cytokines, which induce the secretion of chemokines responsible for recruiting neutrophils (and monocytes) into the reaction.

Both T_H1 and T_H17 cells are involved in defense against many types of bacteria and viruses and in autoimmune diseases. T_H2 cells are important in defense against helminthic parasites and in allergic inflammation. These T cell subsets and their functions are described in more detail in Chapter 6.

Lymphocytes and macrophages interact in a bidirectional way, and these interactions play an important role in propagating chronic inflammation (Fig. 3-21). Macrophages display antigens to T cells, express membrane molecules (called costimulators), and produce cytokines (IL-12 and others) that stimulate T-cell responses (Chapter 6). Activated T lymphocytes, in turn, produce cytokines, described earlier, which recruit and activate macrophages, promoting more antigen presentation and cytokine secretion. The result is a cycle of cellular reactions that fuel and sustain chronic inflammation.

Activated B lymphocytes and antibody-producing plasma cells are often present at sites of chronic inflammation. The antibodies may be specific for persistent foreign or self antigens in the inflammatory site or against altered tissue components. However, the specificity and even the importance of antibodies in most chronic inflammatory disorders are unclear.

In some chronic inflammatory reactions, the accumulated lymphocytes, antigen-presenting cells, and plasma cells cluster together to form lymphoid tissues resembling lymph nodes. These are called *tertiary lymphoid organs*; this type of *lymphoid organogenesis* is often seen in the synovium of patients with long-standing rheumatoid arthritis and in the thyroid in Hashimoto thyroiditis. It has been postulated that the local formation of lymphoid organs may perpetuate the immune reaction, but the significance of these structures is not established.

Other Cells in Chronic Inflammation

Other cell types may be prominent in chronic inflammation induced by particular stimuli.

- **Eosinophils** are abundant in immune reactions mediated by IgE and in parasitic infections (Fig. 3-22). Their recruitment is driven by adhesion molecules similar to those used by neutrophils, and by specific chemokines (e.g., eotaxin) derived from leukocytes and epithelial cells. Eosinophils have granules that contain *major basic protein*, a highly cationic protein that is toxic to parasites but also causes lysis of mammalian epithelial cells. This