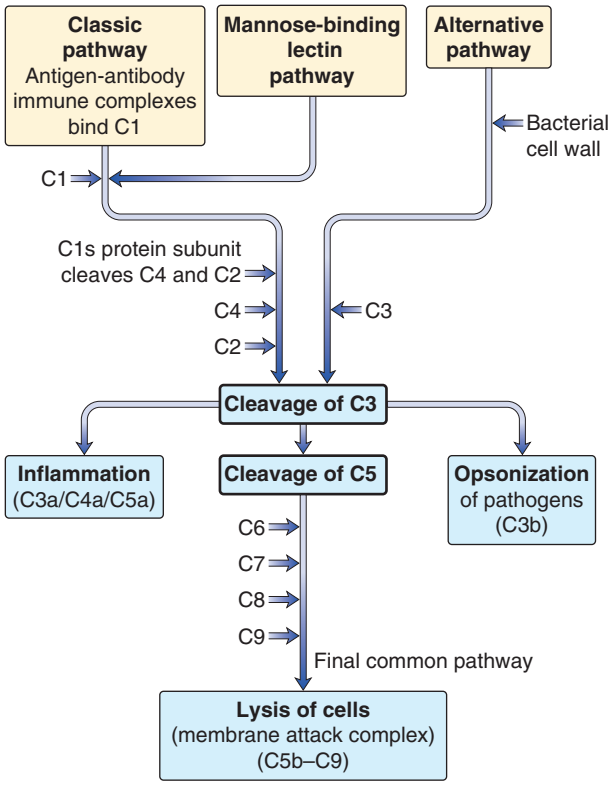

FIGURE 86-1 The complement pathway and other effector functions. (From Kumar P, Clark M, editors: Kumar and Clark's clinical medicine, ed 8, London, 2012, Elsevier.)

by chemotactic factors, including formyl peptides derived from bacteria, complement C3a and C5a, IL-8, interferon, and leukotrienes, particularly leukotriene B_4. Neutrophils migrate from the endovascular space into inflammatory tissue through a complicated integrin-regulated process that includes receptors on neutrophils and endothelial cells. Activated neutrophils then migrate down a chemoattractive (i.e., chemokine) gradient toward the site of inflammation.

Neutrophils are killing machines containing granules that have up to 100 different antimicrobial molecules. The contents of granules are released intracellularly into phagosomes after phagocytosis of a pathogen or released extracellularly in the vicinity of pathogens. Phagocytosis is greatly enhanced by opsonization (i.e., antibody and complement binding) of pathogens. The major microbicidal mechanism of neutrophils is the superoxide burst (i.e., production of superoxide anion catalyzed by NADPH oxidase) and then the dismutation to hydrogen peroxide. Many other granule molecules, such as cathepsins, elastases, defensins, and collagenase contribute to the killing process. Similar mechanisms exist in other phagocytes such as macrophages.

Eosinophils, which are found more in tissue than the circulation, are primarily important in host defenses against multicellular parasites such as parasitic worms. Growth and differentiation of eosinophils is promoted by IL-5. Eosinophils are activated and recruited by a variety of mediators, including complement factors and leukotrienes. Eosinophil granules contain specific cationic proteins that are toxic to parasites. Eosinophils also play key roles in the pathogenesis of allergic reactions and diseases such as asthma.

Basophils in blood and mast cells in tissue contain granules with histamine. They can be activated by complement factors and antigen-IgE binding on the surface of mast cells. Histamine is a short-acting, low-molecular-weight amine that acts through four different histamine receptors. Its actions include bronchoconstriction and bronchial smooth muscle contraction, itching, pain, vasodilation, and increased vascular permeability. Histamine also plays a role in gastric acid secretion, motion sickness, and sleep suppression. Commonly used antihistamines counter these effects.

Blood monocytes are produced in the bone marrow and circulate for several days in the blood. They then migrate into tissues, where they phagocytize pathogens and debris and kill microorganisms when activated by bacterial products such as lipopolysaccharide (LPS), interferon-γ, and other cytokines.

The properties and function of macrophages depend on the tissue. Alveolar macrophages in the lung are continuously exposed to airborne particles and pathogens, whereas microglia in the brain have a very different environment and function. Macrophages clear cellular debris after acute inflammation, and thus are the janitors of peripheral tissue. Macrophages produce a variety of cytokines important in the inflammatory process, including IL-1, TNF-α, IL-6, IL-15, and leukocyte growth factors.

Fever during inflammation and infection results from cytokines such as IL-1 and TNF-α that are released by macrophages into the circulation. These molecules increase the level of prostaglandins in the hypothalamus, which elevates the normal temperature set point. This stimulates thermoregulatory mechanisms to elevate the core body temperature.

Macrophages play a central role in granuloma formation. For example, macrophages are critical in controlling difficult-to-kill acid-fast mycobacteria such as *M. tuberculosis* or fungi by walling off viable organisms in granulomas. Macrophages also present antigen derived from microbial pathogens to T cells, helping to initiate the adoptive immune response. Cells of the myeloid lineage can control the immune response and are known as myeloid-derived suppressor cells.

Dendritic cells are derived from myeloid or lymphocytic precursors. Dendritic cells are found primarily in tissues where pathogens are likely to enter the body, such as the skin, gastrointestinal tract, spleen, and respiratory tract. These cells have branchlike cytoplasmic extensions (for which they are named), and they phagocytize pathogens in a manner similar to macrophages. They are the major antigen-presenting cells (APCs) in the body.

Natural killer (NK) cells are T lymphocytes that kill abnormal cells, including virus-infected cells and certain tumor cells. They do not require antigen sensitization for the production of perforin, a pore-forming protein with lethal effects. They are part of the first line of defense against viral infections while adaptive immunity is developing.

Adaptive Immunity

The adaptive immune response produces exquisitely specific, protective mechanisms against microbial pathogens (see Table 86-1). The specific response can be recalled rapidly by memory B and T cells years after infection if the particular