produced. Several adhesion molecules present in the intercellular junctions between endothelial cells are involved in the migration of leukocytes. These molecules include a member of the immunoglobulin superfamily called *CD31* or *PECAM-1* (platelet endothelial cell adhesion molecule). After traversing the endothelium, leukocytes pierce the basement membrane, probably by secreting collagenases, and enter the extravascular tissue. The cells then migrate toward the chemotactic gradient created by chemokines and other chemoattractants and accumulate in the extravascular site.

The most telling proof of the importance of leukocyte adhesion molecules is the existence of genetic deficiencies in these molecules that result in recurrent bacterial infections as a consequence of impaired leukocyte adhesion and defective inflammation. These leukocyte adhesion deficiencies are described in Chapter 6.

Chemotaxis of Leukocytes

After exiting the circulation, leukocytes move in the tissues toward the site of injury by a process called *chemotaxis*, which is defined as locomotion along a chemical gradient. Both exogenous and endogenous substances can act as chemoattractants. The most common exogenous agents are *bacterial products*, including peptides that possess an *N*-formylmethionine terminal amino acid and some lipids. Endogenous chemoattractants include several chemical mediators (described later): (1) *cytokines*, particularly those of the chemokine family (e.g., IL-8); (2) *components of the complement system, particularly C5a*; and (3) *arachidonic acid (AA) metabolites, mainly leukotriene B_4 (LTB_4)*. All these chemotactic agents bind to specific seven-transmembrane G protein-coupled receptors on the surface of leukocytes. Signals initiated from these receptors result in activation of second messengers that increase cytosolic calcium and activate small guanosine triphosphatases of the Rac/Rho/cdc42 family as well as numerous kinases. These signals induce polymerization of actin, resulting in increased amounts of polymerized actin at the leading edge of the cell and localization of myosin filaments at the back. The leukocyte moves by extending filopodia that pull the back of the cell in the direction of extension, much as an automobile with front-wheel drive is pulled by the wheels in front (Fig. 3-5). The net result is that leukocytes migrate toward the inflammatory stimulus in the direction of the locally produced chemoattractants.

The nature of the leukocyte infiltrate varies with the age of the inflammatory response and the type of stimulus. In most forms of acute inflammation neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours and are replaced by monocytes in 24 to 48 hours (Fig. 3-6). There are several reasons for the early preponderance of neutrophils: they are more numerous in the blood than other leukocytes, they respond more rapidly to chemokines, and they may attach more firmly to the adhesion molecules that are rapidly induced on endothelial cells, such as P- and E-selectins. After entering tissues, neutrophils are short-lived; they undergo apoptosis and disappear within 24 to 48 hours. Monocytes not only survive longer but may also proliferate in the tissues, and thus they become the dominant population in prolonged inflammatory reactions. There are, however, exceptions to this stereotypic pattern of cellular infiltration.

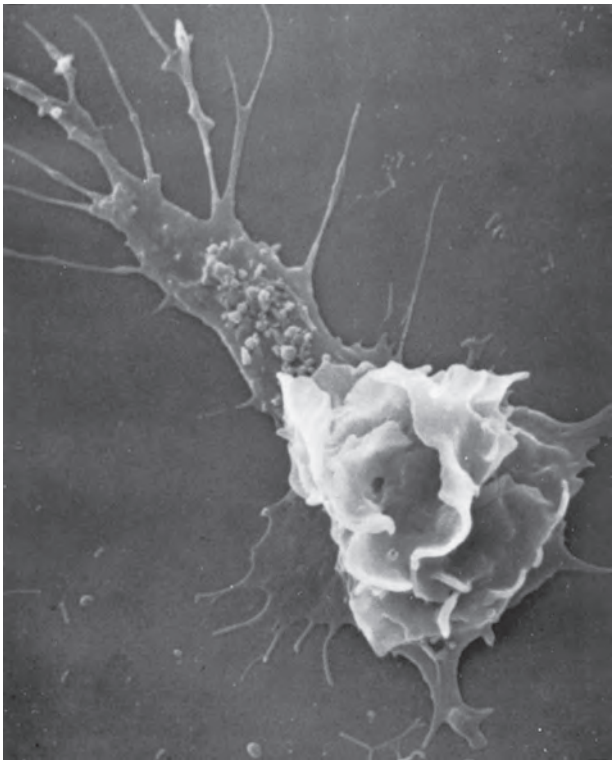

Figure 3-5 Scanning electron micrograph of a moving leukocyte in culture showing a filopodium *(upper left)* and a trailing tail. (Courtesy Dr. Morris J. Karnovsky, Harvard Medical School, Boston, Mass.)

In certain infections—for example, those produced by *Pseudomonas* bacteria—the cellular infiltrate is dominated by continuously recruited neutrophils for several days; in viral infections, lymphocytes may be the first cells to arrive; some hypersensitivity reactions are dominated by activated lymphocytes, macrophages, and plasma cells (reflecting the immune response); and in allergic reactions, eosinophils may be the main cell type.

The molecular understanding of leukocyte recruitment and migration has provided a large number of potential therapeutic targets for controlling harmful inflammation. Agents that block TNF, one of the major cytokines in leukocyte recruitment, are among the most successful therapeutics ever developed for chronic inflammatory diseases, and antagonists of leukocyte integrins are approved for inflammatory diseases or are being tested in clinical trials. Predictably, these antagonists not only have the desired effect of controlling the inflammation but can also compromise the ability of treated patients to defend themselves against microbes, which, of course, is the physiologic function of the inflammatory response.

KEY CONCEPTS

Leukocyte Recruitment to Sites of Inflammation

- Leukocytes are recruited from the blood into the extravascular tissue where infectious pathogens or damaged tissues may be located, migrate to the site of infection or tissue injury, and are activated to perform their functions.
- Leukocyte recruitment is a multistep process consisting of loose attachment to and rolling on endothelium (mediated