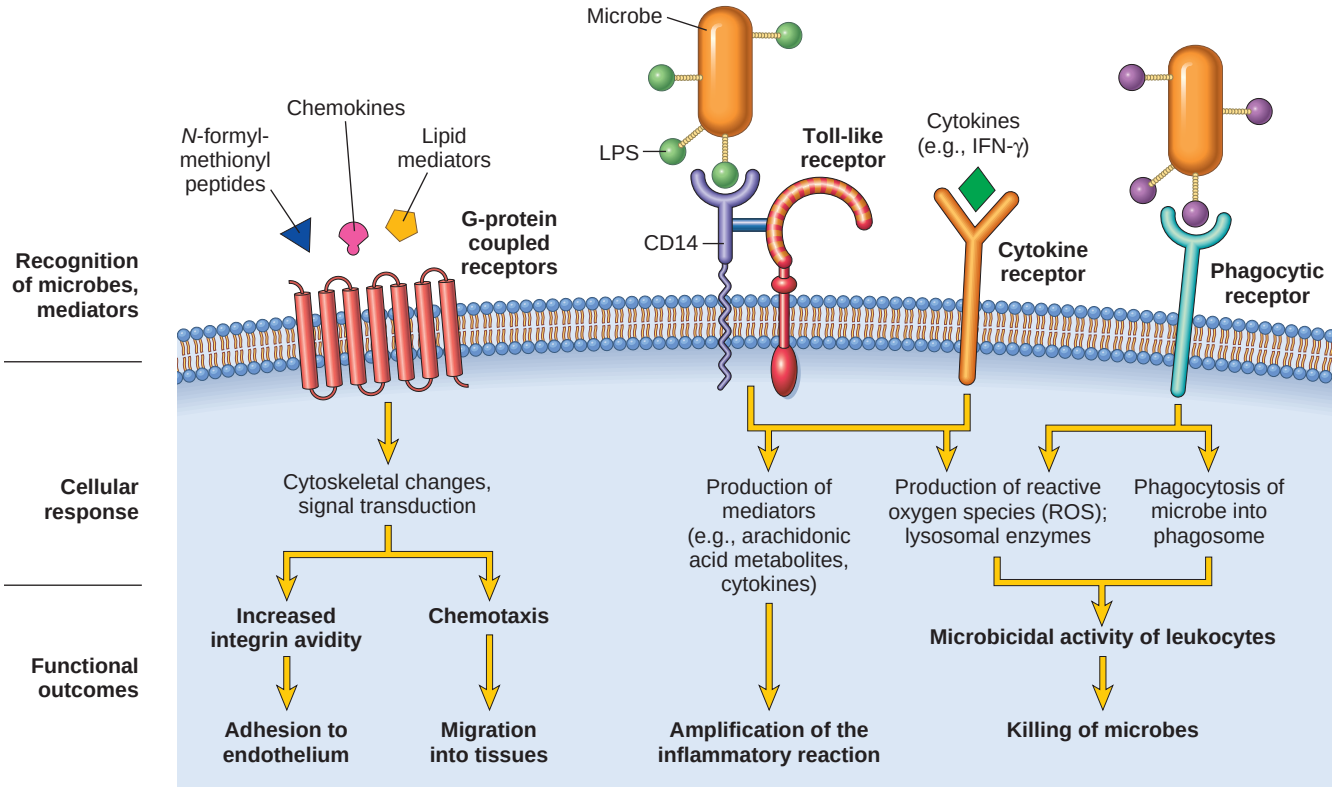

Figure 3-7 Leukocyte activation. Different classes of cell surface receptors of leukocytes recognize different stimuli. The receptors initiate responses that mediate the functions of the leukocytes. Only some receptors are depicted (see text for details). LPS first binds to a circulating LPS-binding protein (not shown). IFN-γ, Interferon-γ; LPS, lipopolysaccharide.

The process of phagocytosis is complex and involves the integration of many receptor-initiated signals that lead to membrane remodeling and cytoskeletal changes. Phagocytosis is dependent on polymerization of actin filaments; it is, therefore, not surprising that the signals that trigger phagocytosis are many of the same that are involved in chemotaxis.

Intracellular Destruction of Microbes and Debris

Killing of microbes is accomplished by reactive oxygen species (ROS, also called *reactive oxygen intermediates*) and reactive nitrogen species, mainly derived from nitric oxide (NO), and these as well as lysosomal enzymes destroy phagocytosed debris (Fig. 3-8). This is the final step in the elimination of infectious agents and necrotic cells. The killing and degradation of microbes and dead cell debris within neutrophils and macrophages occur most efficiently after activation of the phagocytes. All these killing mechanisms are normally sequestered in lysosomes, to which phagocytosed materials are brought. Thus, potentially harmful substances are segregated from the cell's cytoplasm and nucleus to avoid damage to the phagocyte while it is performing its normal function.

Reactive Oxygen Species. ROS are produced by the rapid assembly and activation of a multicomponent oxidase, NADPH oxidase (also called phagocyte oxidase), which oxidizes NADPH (reduced nicotinamide-adenine dinucleotide phosphate) and, in the process, reduces oxygen to superoxide anion ($O_2^{\bullet}$). In neutrophils, this oxidative reaction is triggered by activating signals and accompanies phagocytosis, and is called the *respiratory burst*. Phagocyte oxidase is an enzyme complex consisting of at least seven proteins. In resting neutrophils, different components of the enzyme are located in the plasma membrane and the cytoplasm. In response to activating stimuli, the cytosolic protein components translocate to the phagosomal membrane, where they assemble and form the functional enzyme complex. Thus, the *ROS are produced within the lysosome and phagolysosome*, where they can act on ingested particles without damaging the host cell. $O_2^{\bullet}$ is then converted into hydrogen peroxide (H_2O_2), mostly by spontaneous dismutation. H_2O_2 is not able to efficiently kill microbes by itself. However, the azurophilic granules of neutrophils contain the enzyme *myeloperoxidase* (MPO), which, in the presence of a halide such as Cl^-, converts H_2O_2 to hypochlorite (OCl^-, the active ingredient in household bleach). The latter is a potent antimicrobial agent that destroys microbes by *halogenation* (in which the halide is bound covalently to cellular constituents) or by *oxidation* of proteins and lipids (lipid peroxidation). The H_2O_2-MPO-halide system is the most efficient bactericidal system of neutrophils. Nevertheless, inherited deficiency of MPO by itself leads to minimal increase in susceptibility to infection, emphasizing the redundancy of microbicidal mechanisms in leukocytes. H_2O_2 is also converted to hydroxyl radical ($^{\bullet}OH$), another powerful destructive agent. As discussed in Chapter 2, these oxygen-derived free radicals bind to and modify cellular lipids, proteins, and nucleic acids, and thus destroy cells such as microbes.