- *Monocytes* and *neutrophils* are phagocytes in the blood that can rapidly be recruited to any site of infection; monocytes that enter the tissues and mature are called *macrophages*. All tissues contain resident macrophages, the professional phagocytes of the body. These cells not only sense the presence of microbes and other offending agents, but also ingest (phagocytose) these invaders and destroy them. Because macrophages are the dominant cells of chronic inflammation, we described them in more detail in Chapter 3 in the discussion of chronic inflammation.
- *Dendritic cells* are a specialized cell population present in epithelia, lymphoid organs, and most tissues. They capture protein antigens and display peptides for recognition by T lymphocytes. In addition to their antigen presenting function, dendritic cells are endowed with a rich collection of receptors that sense microbes and cell damage and stimulate the secretion of cytokines, mediators that play critical roles in inflammation and anti-viral defense. Thus, dendritic cells are involved in the initiation of innate immune responses, but, unlike macrophages, they are not key participants in the destruction of microbes and other offending agents.
- *Natural killer cells* provide early protection against many viruses and intracellular bacteria; their properties and functions are described later.
- Several other cell types can sense and react to microbes. These include *mast cells*, which are capable of producing many mediators of inflammation (discussed later), and even epithelial and endothelial cells.
- It has recently been recognized that cells with the appearance of lymphocytes but with features more like the cells of innate immunity may contribute to the early defense against microbes. These *innate lymphoid cells* are described later, when the properties and functions of lymphocytes are discussed.
- In addition to these cells, several soluble proteins play important roles in innate immunity. The proteins of the *complement system*, which were described in Chapter 3, are plasma proteins that are activated by microbes using the alternative and lectin pathways in innate immune responses; in adaptive immunity it is activated by antibodies using the classical pathway. Other circulating proteins of innate immunity are mannose-binding lectin and C-reactive protein, both of which coat microbes and promote phagocytosis. Lung surfactant is also a component of innate immunity, providing protection against inhaled microbes.

Cellular Receptors for Microbes, Products of Damaged Cells, and Foreign Substances

Cells that participate in innate immunity are capable of recognizing certain microbial components that are shared among related microbes and are often essential for infectivity (and thus cannot be mutated to allow the microbes to evade the defense mechanisms). These microbial structures are called *pathogen-associated molecular patterns*. Leukocytes also recognize molecules released by injured and necrotic cells, which are called *damage-associated molecular patterns*. Collectively, the cellular receptors that recognize these molecules are often called *pattern recognition receptors*.

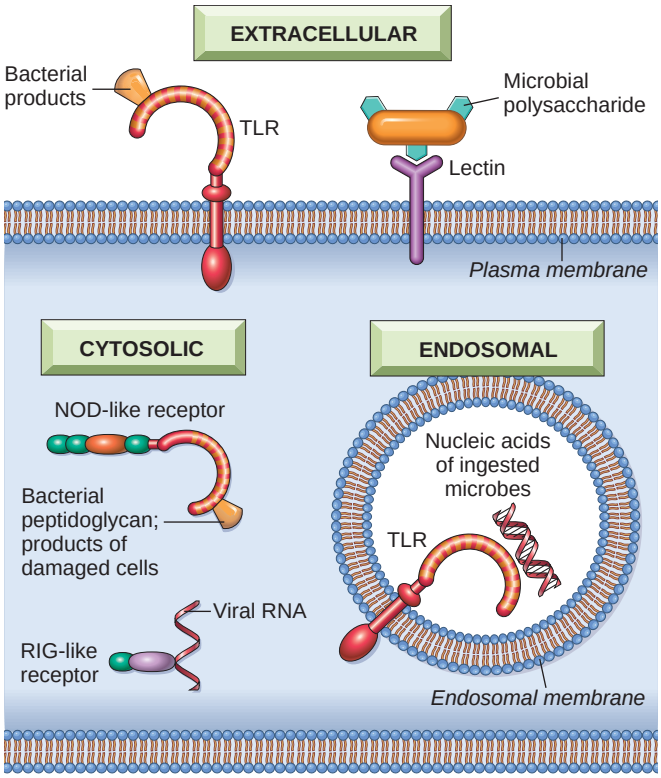

Figure 6-2 Cellular receptors for microbes and products of cell injury. Phagocytes, dendritic cells, and many types of epithelial cells express different classes of receptors that sense the presence of microbes and dead cells. Toll-like receptors (TLRs) located in different cellular compartments, as well as other cytoplasmic and plasma membrane receptors, recognize products of different classes of microbes. The four major classes of innate immune receptors are TLRs, NOD-like receptors in the cytosol (NLRs), C-type lectin receptors (CLRs), and RIG-like receptors for viral nucleic acids (RLRs).

Pattern recognition receptors are located in all the cellular compartments where microbes may be present: plasma membrane receptors detect extracellular microbes, endosomal receptors detect ingested microbes, and cytosolic receptors detect microbes in the cytoplasm (Fig. 6-2). Several classes of these receptors have been identified.

Toll-Like Receptors. The best known of the pattern recognition receptors are the Toll-like receptors (TLRs), whose founding member, *Toll*, was discovered in *Drosophila*. A family of related proteins was later shown to be essential for host defense against microbes. There are 10 TLRs in mammals, and each recognizes a different set of microbial molecules. The TLRs are present in the plasma membrane and endosomal vesicles (Fig. 6-2). All these receptors signal by a common pathway that culminates in the activation of two sets of transcription factors: (1) *NF-κB*, which stimulates the synthesis and secretion of cytokines and the expression of adhesion molecules, both of which are critical for the recruitment and activation of leukocytes (Chapter 3), and (2) *interferon regulatory factors (IRFs)*, which stimulate the production of the antiviral cytokines, type I interferons. Germline loss-of-function mutations affecting TLRs and their signaling pathways are associated with rare but serious immunodeficiency syndromes, described later in the chapter.