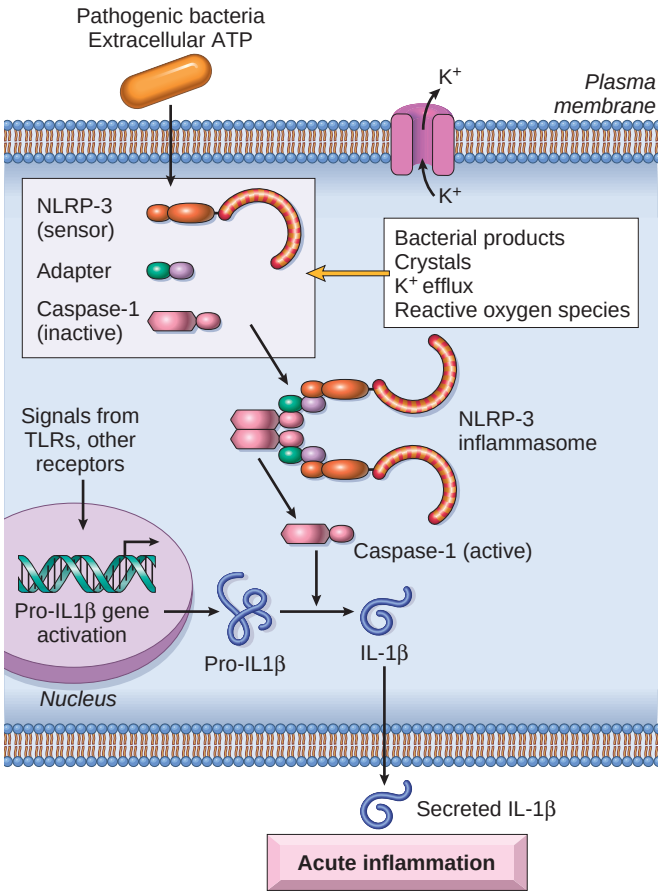

Figure 6-3 The inflammasome. The inflammasome is a protein complex that recognizes products of dead cells and some microbes and induces the secretion of biologically active interleukin 1. The inflammasome consists of a sensor protein (a leucine-rich protein called NLRP3), an adapter, and the enzyme caspase-1, which is converted from an inactive to an active form.

NOD-Like Receptors and the Inflammasome. NOD-like receptors (NLRs) are cytosolic receptors named after the founding member NOD-2. They recognize a wide variety of substances, including products of necrotic cells (e.g., uric acid and released ATP), ion disturbances (e.g., loss of K^+), and some microbial products. How this family of sensors is capable of detecting so many, quite diverse, signs of danger or damage is not known. Several of the NLRs signal via a cytosolic multiprotein complex called the *inflammasome*, which activates an enzyme (caspase-1) that cleaves a precursor form of the cytokine interleukin-1 (IL-1) to generate the biologically active form (Fig. 6-3). As is discussed later, IL-1 is a mediator of inflammation that recruits leukocytes and induces fever. Gain-of-function mutations in one of the NLRs result in periodic fever syndromes, called *autoinflammatory syndromes* (to be distinguished from autoimmune diseases, which result from T and B lymphocyte reactions against self antigens). The autoinflammatory syndromes respond very well to treatment with IL-1 antagonists. The NLR-inflammasome pathway may also play a role in many common disorders. For example, recognition of urate crystals by a class of NLRs underlies the inflammation associated with gout. These receptors may also be capable of detecting lipids and cholesterol crystals that are deposited in abnormally large amounts in tissues, and the resulting inflammation may contribute to obesity-associated type 2 diabetes and atherosclerosis, respectively.

Other Receptors for Microbial Products. *C-type lectin receptors* (CLRs) expressed on the plasma membrane of macrophages and dendritic cells detect fungal glycans and elicit inflammatory reactions to fungi. *RIG-like receptors* (RLRs), named after the founding member RIG-I, are located in the cytosol of most cell types and detect nucleic acids of viruses that replicate in the cytoplasm of infected cells. These receptors stimulate the production of antiviral cytokines. *G protein–coupled receptors* on neutrophils, macrophages, and most other types of leukocytes recognize short bacterial peptides containing *N*-formylmethionyl residues. Because all bacterial proteins and few mammalian proteins (only those synthesized within mitochondria) are initiated by *N*-formylmethionine, this receptor enables neutrophils to detect bacterial proteins and stimulate chemotactic responses of the cells. *Mannose receptors* recognize microbial sugars (which often contain terminal mannose residues, unlike mammalian glycoproteins) and induce phagocytosis of the microbes.

Reactions of Innate Immunity

The innate immune system provides host defense by two main reactions.

- *Inflammation*. Cytokines and products of complement activation, as well as other mediators, are produced during innate immune reactions and trigger the vascular and cellular components of inflammation. The recruited leukocytes destroy microbes and ingest and eliminate damaged cells. This reaction is described in Chapter 3.
- *Antiviral defense.* Type I interferons produced in response to viruses act on infected and uninfected cells and activate enzymes that degrade viral nucleic acids and inhibit viral replication, inducing what has been called an *antiviral state*.
- In addition to these defensive functions, innate immunity provides the danger signals that stimulate the subsequent more powerful adaptive immune response. The nature of some of these signals is described later.

Innate immunity, unlike adaptive immunity, does not have memory or fine antigen specificity. It is estimated that innate immunity uses about 100 different receptors to recognize 1,000 molecular patterns. In contrast, adaptive immunity uses two types of receptors (antibodies and T-cell receptors, described later), each with millions of variations, to recognize millions of antigens.

Adaptive Immunity

The adaptive immune system consists of lymphocytes and their products, including antibodies. The lymphocytes of adaptive immunity use highly diverse receptors to recognize a vast array of foreign substances. In the remainder of this introductory section we focus on lymphocytes and the reactions of the adaptive immune system.