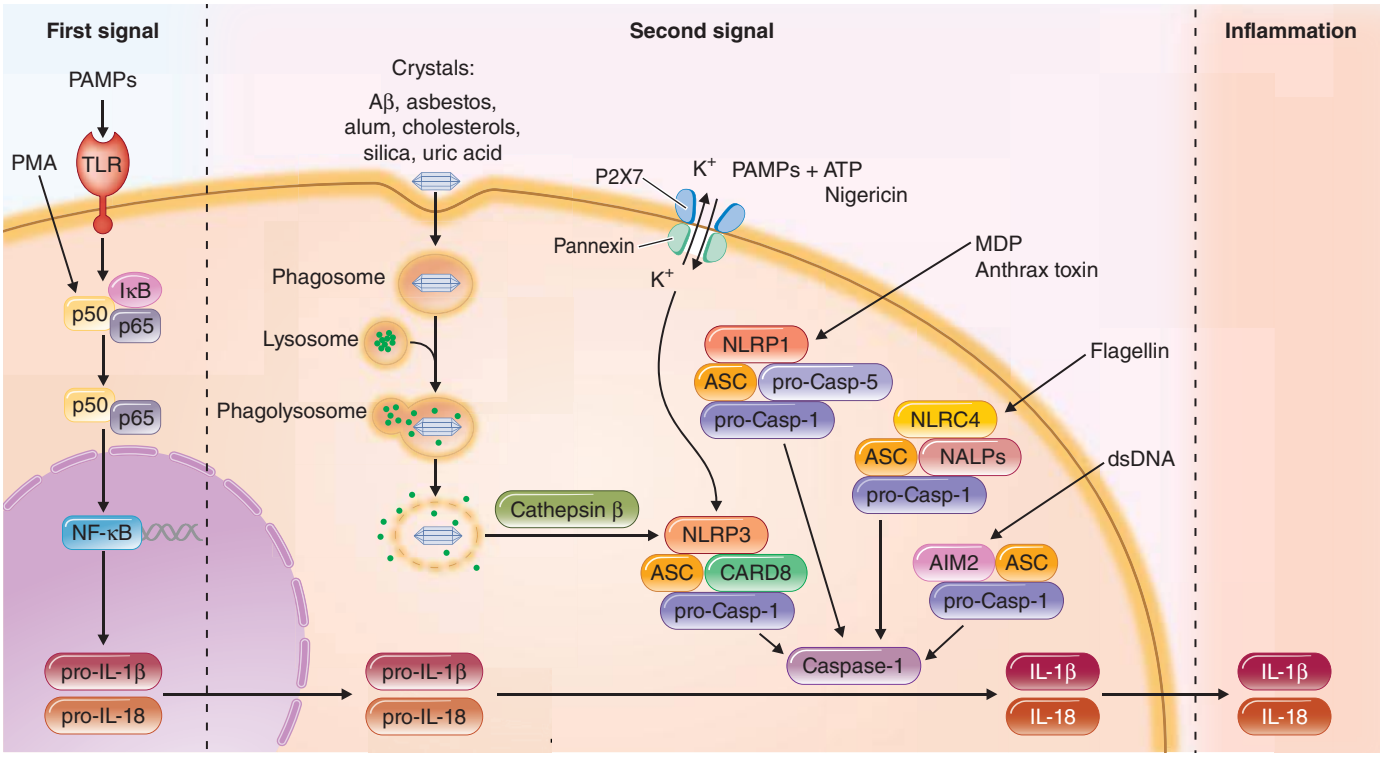

FIGURE 145e-4 **Inflammasomes**. The nucleotide-binding oligomerization domain-like receptor (NLR) family of proteins is involved in the regulation of innate immune responses. These proteins sense pathogen-associated molecular patterns (PAMPs) in the cytosol as well as the host-derived signals known as damage-associated molecular patterns (DAMPs). Certain NLRs induce the assembly of large caspase-1-activating complexes called *inflammasomes*. Activation of caspase-1 through autoproteolytic maturation leads to the processing and secretion of the proinflammatory cytokines interleukin 1β (IL-1β) and IL-18. So far, four inflammasomes have been identified and defined by the NLR protein that they contain: the NLRP1/NALP1b inflammasome; the NLRC4/IPAF inflammasome; the NLRP3/NALP3 inflammasome; and the AIM2 (absent in melanoma 2)–containing inflammasome. Aβ, amyloid β; ASC, apoptosis-associated speck-like protein containing CARD; ATP, adenosine 5′-triphosphate; CARD8, caspase recruitment domain–containing protein 8; IκB, inhibitor of κB; IPAF, interleukin-converting enzyme protease-activating factor; MDP, muramyl dipeptide; NF-κB, nuclear factor κB; P2X7, purinergic *P2X7* (receptor); PMA, phorbol myristate acetate; TLR, Toll-like receptor. (*Pathway diagram reproduced with permission from Invivogen [www.invivogen.com/review-inflammasome].)*

plasminogen and host matrix metalloproteases, then combine to degrade the extracellular matrix and promote microbial spread. Some bacteria (e.g., brucellae) can be carried from a mucosal site to a distant site by phagocytic cells that ingest but fail to kill the bacteria.

Fungal pathogens almost always take advantage of host immunocompromise to spread hematogenously to deeper tissues. The AIDS epidemic has resoundingly illustrated this principle: the immunodeficiency of many HIV-infected patients permits the development of life-threatening fungal infections of the lung, blood, and brain. Other than the capsule of *C. neoformans*, specific fungal antigens involved in tissue invasion are not well characterized. Both fungal pathogens and protozoal pathogens (e.g., *Plasmodium* species and *E. histolytica*) undergo morphologic changes to spread within a host. *C. albicans* undertakes a yeast-hyphal transformation wherein the hyphal forms are found where the fungus is infiltrating the mucosal barrier of tissues, while the yeast form grows on epithelial cell surfaces as well as on the tips of hyphae that have infiltrated tissues. Malarial parasites grow in liver cells as merozoites and are released into the blood to invade erythrocytes and become trophozoites. *E. histolytica* is found as both a cyst and a trophozoite in the intestinal lumen, through which this pathogen enters the host, but only the trophozoite form can spread systemically to cause amebic liver abscesses. Other protozoal pathogens, such as *T. gondii*, *Giardia lamblia*, and *Cryptosporidium*, also undergo extensive morphologic changes after initial infection to spread to other tissues.

Tissue Tropism The propensity of certain microbes to cause disease by infecting specific tissues has been known since the early days of bacteriology, yet the molecular basis for this propensity is understood somewhat better for viral pathogens than for other agents of infectious disease. Specific receptor-ligand interactions clearly underlie the ability of certain viruses to enter cells within tissues and disrupt normal tissue function, but the mere presence of a receptor for a virus on a target tissue is not sufficient for tissue tropism. Factors in the cell, route of viral entry, viral capacity to penetrate into cells, viral genetic elements that regulate gene expression, and pathways of viral spread in a tissue all affect tissue tropism. Some viral genes are best transcribed in specific target cells, such as hepatitis B genes in liver cells and Epstein-Barr virus genes in B lymphocytes. The route of inoculation of poliovirus determines its neurotropism, although the molecular basis for this circumstance is not understood.

Compared with viral tissue tropism, the tissue tropism of bacterial and parasitic infections has not been as clearly elucidated, but studies of *Neisseria* species have provided insights. Both *N. gonorrhoeae*, which colonizes and infects the human genital tract, and *N. meningitidis*, which principally colonizes the human oropharynx but can spread to the brain, produce type IV pili (Tfp) that mediate adherence to host tissues. In the case of *N. gonorrhoeae*, the Tfp bind to a glucosamine-galactose-containing adhesin on the surface of cervical and urethral cells; in the case of *N. meningitidis*, the Tfp bind to cells in the human meninges and thus cross the blood-brain barrier. *N. meningitidis* expresses a capsular polysaccharide, while *N. gonorrhoeae* does not; however, there is no indication that this property plays a role in the different tissue tropisms displayed by these two bacterial species. *N. gonorrhoeae* can use cytidine monophosphate *N*-acetylneuraminic acid from host tissues to add *N*-acetylneuraminic acid (sialic acid) to its lipooligosaccharide O side chain, and this alteration appears to make the organism resistant to host defenses. Lactate, present at high levels on genital mucosal surfaces, stimulates sialylation of gonococcal lipooligosaccharide. Bacteria with sialic acid sugars in their capsules,