The type 1 IFNs bind to the IFN-α receptor composed of two protein chains, IFNAR1 and IFNAR2. Humans produce three type 1 IFNs: IFN-α, IFN-β, and IFN-γ. These molecules activate another class of proteins known as the signal transducer and activator of transcription (STAT) complexes. The STAT factors are important in regulating immune system genes and thus play a critical role in responding to microbial infections.

Another intracellular complex of proteins found to be a major factor in the host cell response to infection is the *inflammasome* **(Fig. 145e-4)**, in which inflammatory cytokines IL-1 and IL-18 are changed from their precursor to their active forms prior to secretion by the cysteine protease caspase-1. Within the inflammasome are additional proteins that are members of the nucleotide binding and oligomerization domain (NOD)–like receptor (NLR) family. Like the TLRs, NOD proteins sense the presence of the conserved microbial factors released inside a cell. Recognition of these PAMPs by NLRs leads to caspase-1 activation and to secretion of active IL-1 and IL-18 by an unknown mechanism. Studies of mice indicate that as many as four inflammasomes with different components are formed: the IPAF inflammasome, the NALP1 inflammasome, the cryopyrin/NALP3 inflammasome, and an inflammasome triggered by *Francisella tularensis* infection (Fig. 145e-4). The components depend on the type of stimulus driving inflammasome formation and activation.

A recent addition to the identified intracellular components responding to microbial infection is *autophagy*, initially described as an intracellular process for degradation and recycling of cellular components for reuse. Now it is clear that autophagy constitutes an early defense mechanism in which, after ingestion, microbial pathogens either within vacuoles or in the cytoplasm are delivered to lysosomal compartments for degradation. Avoidance of this process is critical if pathogens are to cause disease and can be achieved by multiple mechanisms, such as inhibition of proteins within the autophagic vacuole by shigellae, recruitment of host proteins to mask *Listeria monocytogenes*, and inhibition of formation of the vacuole by *L. pneumophila*.

ADDITIONAL INTERACTIONS OF MICROBIAL PATHOGENS AND PHAGOCYTES Other ways that microbial pathogens avoid destruction by phagocytes include production of factors that are toxic to these cells or that interfere with their chemotactic and ingestion function. Hemolysins, leukocidins, and the like are microbial proteins that can kill phagocytes that are attempting to ingest organisms elaborating these substances. For example, *S. aureus* elaborates a family of bicomponent leukocidins that bind to host receptors such as the HIV co-receptor CCR5 (which is also used by the LukE/D toxin) or—in the case of the Panton-Valentine leukocidin—the receptor of the C5a component of activated complement (which is used by LukF/S). Streptolysin O made by *S. pyogenes* binds to cholesterol in phagocyte membranes and initiates a process of internal degranulation, with the release of normally granule-sequestered toxic components into the phagocyte's cytoplasm. *E. histolytica*, an intestinal protozoan that causes amebic dysentery, can disrupt phagocyte membranes after direct contact via the release of protozoal phospholipase A and pore-forming peptides.

MICROBIAL SURVIVAL INSIDE PHAGOCYTES Many important microbial pathogens use a variety of strategies to survive inside phagocytes (particularly macrophages) after ingestion. Inhibition of fusion of the phagocytic vacuole (the phagosome) containing the ingested microbe with the lysosomal granules containing antimicrobial substances (the lysosome) allows *Mycobacterium tuberculosis*, *S. enterica* serovar Typhi, and *Toxoplasma gondii* to survive inside macrophages. Some organisms, such as *L. monocytogenes*, escape into the phagocyte's cytoplasm to grow and eventually spread to other cells. Resistance to killing within the macrophage and subsequent growth are critical to successful infection by herpes-type viruses, measles virus, poxviruses, *Salmonella*, *Yersinia*, *Legionella*, *Mycobacterium*, *Trypanosoma*, *Nocardia*, *Histoplasma*, *Toxoplasma*, and *Rickettsia*. *Salmonella* species use a master regulatory system—in which the *PhoP*/*PhoQ* genes control other genes—to enter and survive within cells, with intracellular survival entailing structural changes in the cell envelope LPS.

TISSUE INVASION AND TISSUE TROPISM

Tissue Invasion Most viral pathogens cause disease by growth at skin or mucosal entry sites, but some pathogens spread from the initial site to deeper tissues. Virus can spread via the nerves (rabies virus) or plasma (picornaviruses) or within migratory blood cells (poliovirus, Epstein-Barr virus, and many others). Specific viral genes determine where and how individual viral strains can spread.

Bacteria may invade deeper layers of mucosal tissue via intracellular uptake by epithelial cells, traversal of epithelial cell junctions, or penetration through denuded epithelial surfaces. Among virulent *Shigella* strains and invasive strains of *E. coli*, outer-membrane proteins are critical to epithelial cell invasion and bacterial multiplication. *Neisseria* and *Haemophilus* species penetrate mucosal cells by poorly understood mechanisms before dissemination into the bloodstream. Staphylococci and streptococci elaborate a variety of extracellular enzymes, such as hyaluronidase, lipases, nucleases, and hemolysins, that are probably important in breaking down cellular and matrix structures and allowing the bacteria access to deeper tissues and blood. For example, staphylococcal α-hemolysin binds to a receptor, A-disintegrin and metalloprotease 10 (ADAM-10), to cause endothelial cell damage and disruption of vascular barrier function—events that are likely critical for systemic spread of *S. aureus* from an initial infectious site. Organisms that colonize the gastrointestinal tract can often translocate through the mucosa into the blood and, under circumstances in which host defenses are inadequate, cause bacteremia. *Yersinia enterocolitica* can invade the mucosa through the activity of the invasin protein. The complex milieu of the basement membrane–containing structures, such as laminin and collagen, that anchor epithelial cells to mucosal surfaces must often be breached. Numerous organisms express factors known as MSCRAMMs (microbial surface components recognizing adhesive matrix molecules). These MSCRAMMS promote bacterial attachment to factors in the host extracellular matrix, such as laminin, collagen, and fibronectin. Additional microbial proteases, along with the host's own surface-bound

(TAK1-binding protein 1/2). This signaling complex associates with the ubiquitin-conjugating enzyme Ubc13 and the Ubc-like protein UEV1A to catalyze the formation of a polyubiquitin chain on TRAF6. Polyubiquitination of TRAF6 activates TAK1, which, along with TAB1/2 (a protein that binds to lysine residue 63 in polyubiquitin chains via a conserved zinc-finger domain), phosphorylates the inducible kinase complex: IKKα, IKKβ, and IKKγ. IKKγ is also called NEMO (nuclear factor κB [NF-κB] essential modulator). This large complex phosphorylates the inhibitory component of NF-κB, IκBα, resulting in release of IκBα from NF-κB. Phosphorylated (PP) IκB is then ubiquitinated (ub) and degraded, and the two components of NF-κB, p50 or Rel and p65, translocate to the nucleus, where they bind to regulatory transcriptional sites on target genes, many of which encode inflammatory proteins. In addition to inducing NF-κB nuclear translocation, the TAK1/TAB1/2 complex activates MAP kinase transducers such as MKK 4/7 and MKK 3/6, which can lead to nuclear translocation of transcription factors such as AP1. TLR4 can also activate NF-κB nuclear translocation via the MyD88-independent TRIF (TIR domain–containing adapter-inducing IFN-β) and TRAM (TRIF-related adapter molecule) cofactors. Intracellular TLRs 3, 7, 8, and 9 also use MyD88 and TRIF to activate IFN response factors 3 and 7 (IRF-3 and IRF-7), which also function as transcriptional factors in the nucleus. ATP, adenosine 5′-triphosphate; ECSIT, evolutionarily conserved signaling intermediate in Toll pathways; FADD, Fas-associated protein with death domain; JNK, c-Jun N-terminal kinase; MAVS, mitochondrial antiviral signaling protein; MEKK-1, MAP/ERK kinase kinase 1; p38 MAPK, p38 mitogen-activated protein kinase; RIG-1, retinoic acid–inducible gene 1; TBK1, TANK-binding kinase 1. (*Pathway diagram reproduced courtesy of Cell Signaling Technology, Inc. [www.cellsignal.com].*)