Leading Edge
Review

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The Inflammasomes

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Inflammasomes are molecular platforms activated upon cellular infection or stress that trigger the maturation of proinflammatory cytokines such as interleukin-1β to engage innate immune defenses. Strong associations between dysregulated inflammasome activity and human heritable and acquired inflammatory diseases highlight the importance this pathway in tailoring immune responses. Here, we comprehensively review mechanisms directing normal inflammasome function and its dysregulation in disease. Agonists and activation mechanisms of the NLRP1, NLRP3, IPAF, and AIM2 inflammasomes are discussed. Regulatory mechanisms that potentiate or limit inflammasome activation are examined, as well as emerging links between the inflammasome and pyroptosis and autophagy.

Traditionally, innate immunity has been viewed as the first line of defense discriminating "self" (e.g., host proteins) from "nonself" (e.g., microorganisms). However, emerging literature suggests that innate immunity actually serves as a sophisticated system for sensing signals of "danger," such as pathogenic microbes or host-derived signals of cellular stress, while remaining unresponsive to nondangerous motifs, such as normal host molecules, dietary antigens, or commensal gut flora. The notion that innate immunity functions as a danger sentinel has similarities to Matzinger's "danger hypothesis," proposed for adaptive immune responses (Matzinger, 1994). Such a model for recognizing situations of host danger allows for coordinate activation of immune system antimicrobial and tissue repair functions in response to infection or injury, while avoiding collateral damage in situations in which harmless nonself is present.

The innate immune system engages an array of germline-encoded pattern-recognition receptors (PRRs) to detect invariant microbial motifs. PRRs are expressed by cells at the front line of defense against infection, including macrophages, monocytes, dendritic cells, neutrophils, and epithelial cells, as well as cells of the adaptive immune system. PRRs include the membrane-bound Toll-like receptors (TLRs) and C-type lectins (CTLs), which scan the extracellular milieu and endosomal compartments for pathogen-associated molecular patterns (PAMPs). Intracellular nucleic-acid sensing PRRs cooperate to provide cytosolic surveillance, including the RNA-sensing RIG-like helicases (RLHs), RIG-I and MDA5, and the DNA sensors, DAI and AIM2. The outcome of PAMP recognition by PRRs depends upon the nature of both the responding cell and the invading microbe. However, signal transduction from these receptors converges on a common set of signaling modules, often including the activation of the NF-κB and AP-1 transcription factors that drive proinflammatory cytokine/chemokine production and members of the IRF transcription factor family that mediate type I interferon (IFN)-dependent antiviral responses. A further set of intracellular PRRs, distinct from those described above, are the NOD-like receptors (NLRs) that recognize PAMPs, as well as host-derived danger signals (danger-associated molecular patterns, DAMPs). Microbial detection by PRRs such as TLRs is reviewed elsewhere (see Review by O. Takeuchi and S. Akira et al. on page 805 of this issue). This Review focuses on those PRRs that assemble into high-molecular weight, caspase-1-activating platforms called "inflammasomes" that control maturation and secretion of interleukins such as IL-1β and IL-18, whose potent proinflammatory activities direct host responses to infection and injury.

The NLR Family

The NLRs are comprised of 22 human genes and many more mouse genes because of gene expansion since the last common ancestor. The NLR family is characterized by the presence of a central nucleotide-binding and oligomerization (NACHT) domain, which is commonly flanked by C-terminal leucine-rich repeats (LRRs) and N-terminal caspase recruitment (CARD) or pyrin (PYD) domains. LRRs are believed to function in ligand sensing and autoregulation, whereas CARD and PYD domains mediate homotypic protein-protein interactions for downstream signaling. The NACHT domain, which is the only domain common to all NLR family members, enables activation of the signaling complex via ATP-dependent oligomerization. Phylogenetic analysis of NLR family NACHT domains reveals 3 distinct subfamilies within the NLR family: the NODs (NOD1-2, NOD3/NLRC3, NOD4/NLRC5, NOD5/NLRX1, CIITA), the NLRPs (NLRP1-14, also called NALPs) and the IPAF subfamily, consisting of IPAF (NLRC4) and NAIP (Figure 1A). The phylogenetic relationships between subfamily members (Figure 1A) are also supported by similarities in domain structures (Figure 1B). This is particularly clear for the NLRPs, which all contain PYD, NACHT, and LRR domains, with the exception of NLRP10, which lacks LRRs. This Review uses the most common NLR family nomenclature; however, an alternative nomenclature based on NLR family member domain structure was proposed (Ting et al., 2008), and a full list of alternative gene names for NLRP1, NLRP3, and IPAF are given in Table S1 available online.

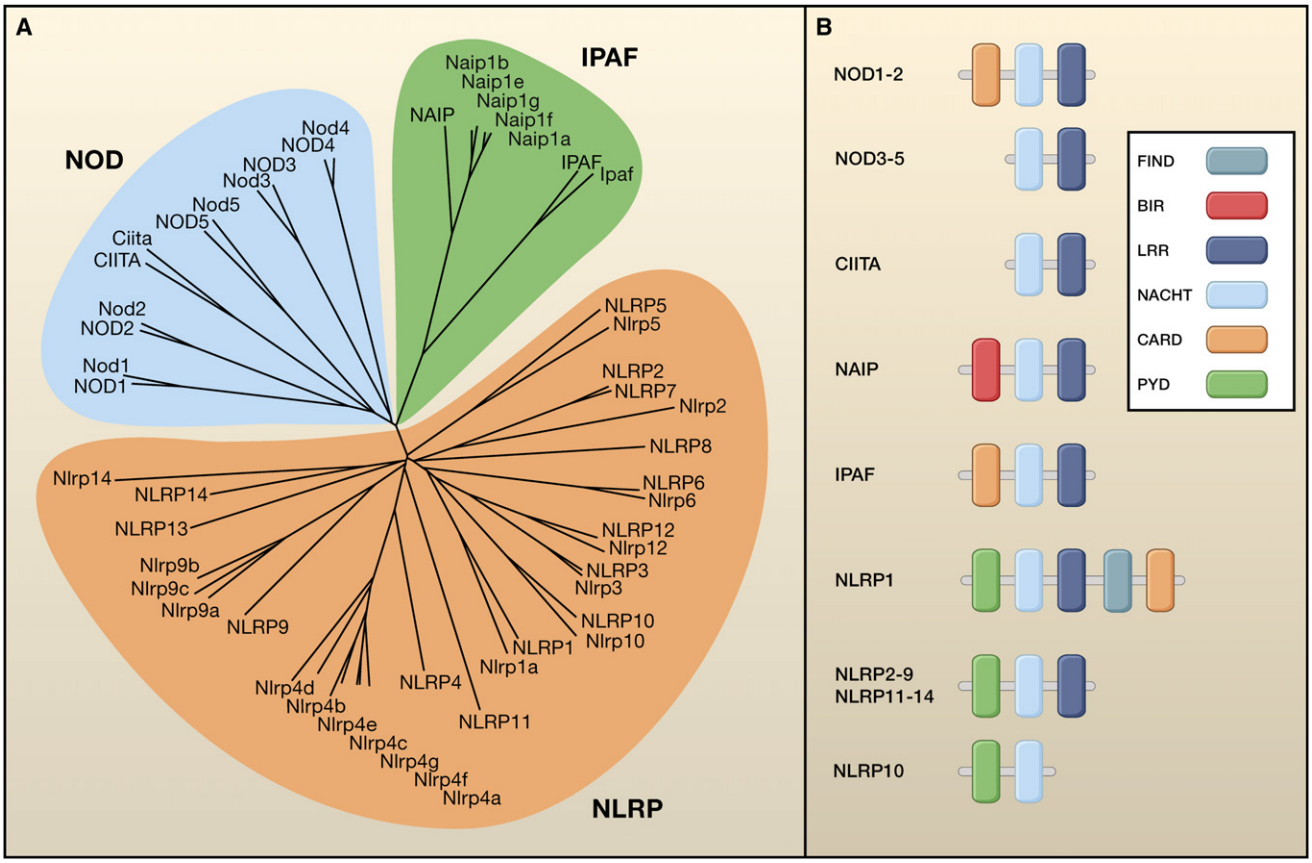

Figure 1. Human and Mouse NLR Family Members

(A) Phylogenetic relationships between NACHT domains of each human (uppercase) and mouse (lowercase) NLR (NOD-like receptor) protein show 3 distinct subfamilies within the NLRs: the NOD, NLRP, and IPAF subfamilies.

(B) Domain structures for human NLRs reveal commonalities within the subfamilies. Domains are classified according to the NCBI domain annotation tool for the longest human protein product, with the exception of the FIIND domain that was identified independently of NCBI (Tschopp et al., 2003). It should be noted that CIITA is often annotated as harboring a CARD domain, because a splice variant expressed in dendritic cells contains a domain with homology to CARD domains (Nickerson et al., 2001); however, the translated transcript variant is not classified as containing a classical CARD domain by typical approaches (NCBI conserved domains, Simple Modular Architecture Research Tool [SMART]). Likewise, these domain prediction approaches do not classify NOD3 and NOD4 as CARD-containing and experimental evidence for a CARD domain function has yet to be reported. Domains: BIR, baculoviral inhibition of apoptosis protein repeat domain; CARD, caspase recruitment domain; FIIND, domain with function to find; LRR, leucine-rich repeat; NACHT, nucleotide-binding and oligomerization domain; PYD, pyrin domain.

The class II transactivator (CIITA) was the first NLR to be characterized, and is a key regulator of class II MHC genes that is mutated in bare lymphocyte syndrome (Steimle et al., 1993). The transcriptional coactivator factor function of CIITA appears to be distinct among NLRs, as no other NLRs have been shown to exert transcriptional regulator activity or other nuclear functions. Other members of the NLR family are generally considered to perform cytoplasmic surveillance for PAMPs or DAMPs. NOD1 and NOD2 both recognize breakdown products of bacterial cell walls (mesodiaminopimelic acid and muramyl dipeptide [MDP], respectively) and, upon ligand sensing, oligomerize and recruit RIP2 via CARD-CARD interactions. Assembly of NOD1 and NOD2 signalosomes ultimately culminates in the activation of the NF-κB transcription factor, which drives proinflammatory gene regulation (reviewed in Kufer et al., 2006). Mutations in NOD2 are associated with human inflammatory diseases such as Crohn's disease and Blau syndrome (Hugot et al., 2001; Miceli-Richard et al., 2001; Ogura et al., 2001). The functions of NOD3 and NOD4 await clarification. The function of NOD5 (NLRX1) is a matter of debate; recent reports position NOD5 within the mitochondrial matrix, or, alternatively, as recruited to the outer mitochondrial membrane, and propose functions in either suppressing MAVS-dependent antiviral pathways or promoting the generation of reactive oxygen species (ROS) (Arnoult et al., 2009; Moore et al., 2008; Tattoli et al., 2008). Many of the remaining NLR family members are poorly characterized at present; however, we describe below the function of those NLR family members that regulate caspase-1 activity through inflammasome formation.

Inflammasomes: Platforms for Caspase-1 Activation and IL-1β Maturation

Caspases are cysteine proteases that initiate or execute cellular programs, leading to inflammation or cell death. They are

synthesized as inactive zymogens, and their potent cellular activities are tightly controlled by proteolytic activation. Caspases are categorized as either proinflammatory or proapoptotic, depending upon their participation in these cellular programs. The proinflammatory caspases are comprised of caspase-1, -11 and -12 in mouse and caspase-1, -4, and -5 in human (Martinon and Tschopp, 2007). Caspase-12 is mutated to encode a nonfunctional protein in most human populations (Xue et al., 2006). Of the proinflammatory caspases, caspase-1 is the most fully characterized. Its catalytic activity is tightly regulated by signal-dependent autoactivation within multiprotein complexes called "inflammasomes" that mediate caspase-1-dependent processing of cytokines such as IL-1β (Martinon et al., 2002).

IL-1β is an important proinflammatory mediator that is generated at sites of injury or immunological challenge to coordinate programs as diverse as cellular recruitment to a site of infection or injury and the regulation of sleep, appetite, and body temperature (see Review by C.A. Dinarello on page 935 of this issue). IL-1β activity is rigorously controlled by expression, maturation, and secretion; proinflammatory stimuli induce expression of the inactive IL-1β proform, but cytokine maturation and release are controlled by inflammasomes. An endogenous IL-1 receptor antagonist (IL-1RA) also regulates IL-1β action. Most reports characterizing inflammasomes have focused on cells of the myeloid lineage, such as macrophages or dendritic cells; however, cells outside the myeloid compartment can activate inflammasomes. For example, keratinocyte exposure to skin irritants or ultraviolet B (UVB) irradiation triggers NLRP3 inflammasome activation (Feldmeyer et al., 2007; Watanabe et al., 2007).

Inflammasomes are assembled by self-oligomerizing scaffold proteins. A number of NLR family member have been reported to exhibit inflammasome activity in vitro; however, few NLR family members have clear physiological functions in vivo. NLRP1, NLRP3, and IPAF are danger sentinels that self-oligomerize via homotypic NACHT domain interactions to form high-molecular weight complexes (probably hexamers or heptamers) that trigger caspase-1 autoactivation. The HIN-200 family member, AIM2, also mediates inflammasome assembly. Inflammasome components and activation mechanisms depend on the nature of the individual protein scaffolds (Figure 2). Domain structure conservation between NLRPs (Figure 1B) suggests that uncharacterized family members may also mediate or regulate inflammasome activation.

The NLRP3 Inflammasome

The NLRP3 inflammasome is currently the most fully characterized inflammasome and consists of the NLRP3 scaffold, the ASC (PYCARD) adaptor, and caspase-1. NLRP3 is activated upon exposure to whole pathogens, as well as a number of structurally diverse PAMPs, DAMPs, and environmental irritants (Table S1). Whole pathogens demonstrated to activate the NLRP3 inflammasome include the fungi *Candida albicans* and *Saccharomyces cerevisiae* that signal to the inflammasome via Syk (Gross et al., 2009), bacteria that produce pore-forming toxins, including *Listeria monocytogenes* and *Staphylococcus aureus* (Mariathasan et al., 2006), and viruses such as Sendai virus, adenovirus, and influenza virus (Kanneganti et al., 2006; Muruve et al., 2008). In some cases, the individual microbial components (PAMPs, virulence factors) that activate the inflammasome have been identified (for instance, the alpha-toxin of *S. aureus*; Craven et al., 2009).

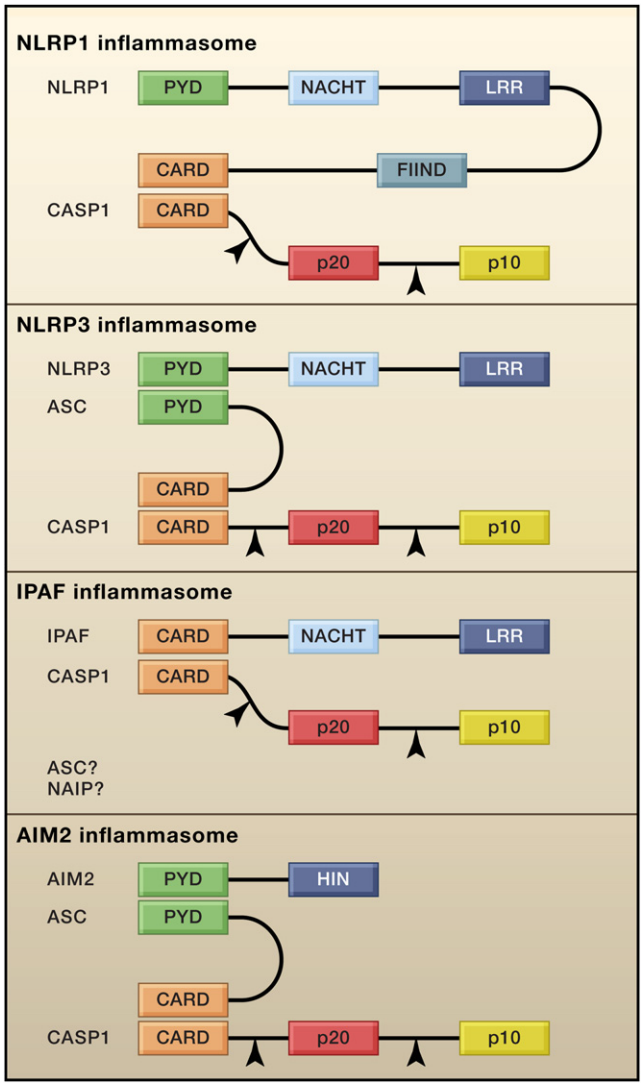

Figure 2. Minimal NLRP1, NLRP3, IPAF, and AIM2 Inflammasomes

For simplicity, the unoligomerized inflammasome complexes are depicted. Removal of the CARD domain and processing of the caspase domain of caspase-1 by autocleavage at the indicated sites results in the formation of the active caspase-1 p10/p20 tetramer. It should be noted that although human NLRP1 contains a PYD, mouse NLRP1 proteins do not harbor functional PYDs. Human NLRP1 can also recruit a second caspase, caspase-5, to the complex (not shown). Maximal caspase-1 activation in response to IPAF agonists can require ASC or NAIP, depending on the stimulus. The interaction of these proteins with the IPAF inflammasome activation is currently unclear. Domains: CARD, caspase recruitment domain; FIIND, domain with function to find; HIN, HIN-200/IF120x domain; LRR, leucine-rich repeat; NACHT, nucleotide-binding and oligomerization domain; PYD, pyrin domain.

The unexpected finding that the NLRP3 inflammasome can be activated by host-derived molecules forms part of an emerging literature supporting a model in which the innate immune system detects endogenous indicators of cellular danger or stress,

a hypothesis with similarities to the "danger model" proposed for adaptive immune responses in place of the more simplistic self/nonself recognition model (Matzinger, 1994). A number of host-derived molecules indicative of injury activate the NLRP3 inflammasome, including extracellular ATP (Mariathasan et al., 2006) and hyaluronan (Yamasaki et al., 2009) that are released by injured cells. Fibrillar amyloid-β peptide, the major component of Alzheimer's disease brain plaques, also activates the NLRP3 inflammasome (Halle et al., 2008). The NLRP3 inflammasome also detects signs of metabolic stress, including elevated extracellular glucose (Zhou et al., 2010) such as that occurring in metabolic syndrome, and monosodium urate (MSU) crystals that form as a consequence of hyperuricemia in the autoinflammatory disease gout (Martinon et al., 2006). Uric acid can also be released during cell injury, and uric acid-dependent pathways in this context also activate the inflammasome (Gasse et al., 2009; Griffith et al., 2009). Additionally, the NLRP3 inflammasome drives inflammation in response to a number of environmental irritants, including silica (Cassel et al., 2008; Dostert et al., 2008; Hornung et al., 2008), asbestos (Cassel et al., 2008; Dostert et al., 2008), UVB irradiation (Feldmeyer et al., 2007), and skin irritants such as trinitrophenylchloride, trinitrochlorobenzene, and dinitrofluorobenzene (Sutterwala et al., 2006; Watanabe et al., 2007). NLRP3 inflammasome activation in response to these insults has been linked to pathology associated with silicosis, asbestosis, sunburn, and contact hypersensitivity reactions, respectively.

Models for NLRP3 Activation

Prior to agonist treatment, the NLRP3 LRR domains are thought to mediate autoinhibition in a manner similar to that described for IPAF (Poyet et al., 2001). This may be mediated by the SGT1 and HSP90 chaperones that appear to hold NLRP3 in an inactive, but signal-competent state; these chaperones also interact with IPAF (Mayor et al., 2007). Upon NLRP3 activation, NLRP3 oligomerization leads to PYD domain clustering and presentation for homotypic interaction with the PYD- and CARD-containing adaptor ASC, whose CARD domain in turn recruits the CARD of procaspase-1. Procaspase-1 clustering permits autocleavage and formation of the active caspase-1 p10/p20 tetramer, which then processes cytokine proforms such as IL-1β to generate the active molecules. Mature IL-1β is secreted alongside caspase-1 by an unconventional protein secretion pathway that is currently unclear.

Mechanisms leading to NLRP3 inflammasome activation are intensely debated. Three models that may not be exclusive are widely supported in the literature (Figure 3). Extracellular ATP stimulates the purogenic P2X7 ATP-gated ion channel (Kahlenberg and Dubyak, 2004), triggering K+ efflux and inducing gradual recruitment of the pannexin-1 membrane pore (Kanneganti et al., 2007). The first model posits that pore formation allows extracellular NLRP3 agonists to access the cytosol and directly activate NLRP3 (Kanneganti et al., 2007). However, the structural diversity within NLRP3 agonists argues against direct interaction between NLRP3 and all of its activators.

A second model was proposed for activators that form crystalline or particulate structures, such as MSU, silica, asbestos, amyloid-β, and alum, wherein engulfment of these agonists by phagocytes leads to lysosomal damage, resulting in cytosolic

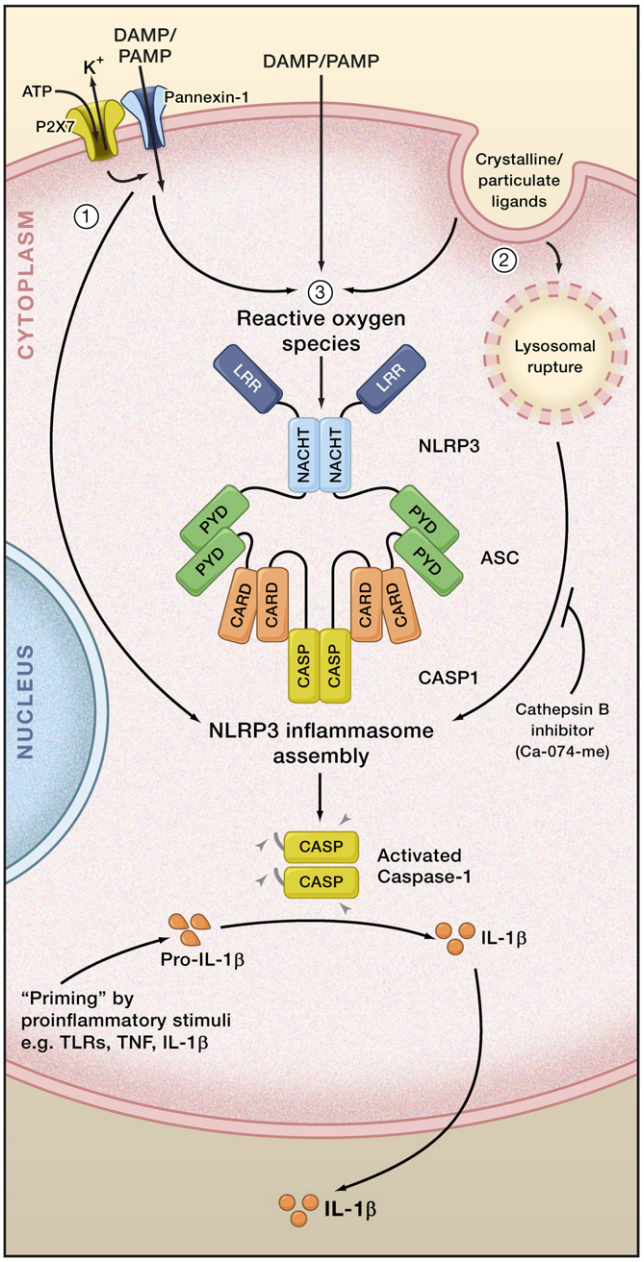

Figure 3. NLRP3 Inflammasome Activation

Three major models for NLRP3 inflammasome activation are favored in the field, which may not be exclusive: (1) The NLRP3 agonist, ATP, triggers P2X7-dependent pore formation by the pannexin-1 hemichannel, allowing extracellular NLRP3 agonists to enter the cytosol and directly engage NLRP3. (2) Crystalline or particulate NLRP3 agonists are engulfed, and their physical characteristics lead to lysosomal rupture. The NLRP3 inflammasome senses lysosomal content in the cytoplasm, for example, via cathepsin-B-dependent processing of a direct NLRP3 ligand. (3) All danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), including ATP and particulate/crystalline activators, trigger the generation of reactive oxygen species (ROS). A ROS-dependent pathway triggers NLRP3 inflammasome complex formation. Caspase-1 clustering induces autoactivation and caspase-1-dependent maturation and secretion of proinflammatory cytokines, such as interleukin-1β (IL-1β) and IL-18.

release of lysosomal contents that are somehow sensed by the NLRP3 inflammasome (Halle et al., 2008; Hornung et al., 2008). A role for the lysosomal protease, cathepsin B, in activation of a direct NLRP3 ligand was suggested in this model (Halle et al., 2008; Hornung et al., 2008). However, cathepsin B-deficient macrophages exhibit normal caspase-1 activation and IL-1β maturation in response to particulate NLRP3 agonists (Dostert et al., 2009), implicating off-target effects of the cathepsin B inhibitor, as was recently suggested for NLRP1 (Newman et al., 2009).

Under the third model, all NLRP3 agonists trigger the generation of ROS, and this common pathway engages the NLRP3 inflammasome (Cassel et al., 2008; Cruz et al., 2007; Dostert et al., 2008). The production of ROS represents one of the most evolutionarily conserved pathways of response to infection or injury; for example, a gradient of ROS is the apical signal directing wound healing in zebrafish (Niethammer et al., 2009), and ROS are antimicrobial effectors in plants (Bolwell, 1999). In support of this model, all NLRP3 agonists tested, including ATP and particulate activators, induce ROS and ROS blockade by chemical scavengers suppresses inflammasome activation (Cassel et al., 2008; Cruz et al., 2007; Dostert et al., 2008; Gross et al., 2009; Pétrilli et al., 2007; Shio et al., 2009).

The source of ROS is currently unclear, but one or several NADPH oxidases are implicated, as suppression of the common p22 subunit inhibits inflammasome activation (Dostert et al., 2008); alternatively, ROS may be of mitochondrial origin. Mechanisms directing ROS-dependent NLRP3 inflammasome activation remain to be characterized in detail; however, a recent report implicates a ROS-sensitive NLRP3 ligand, thioredoxin-interacting protein (TXNIP/VDUP1), in NLRP3 activation (Zhou et al., 2010).

Despite strong evidence for the ROS model, a number of aspects of this model require resolution. For example, some ROS-inducing agents (such as cytokines) do not engage the NLRP3 inflammasome, suggesting that while necessary, ROS alone is insufficient for triggering NLRP3 activity. Alternatively, a very specific ROS location or nature may be required. Additionally, superoxide directly inhibits caspase-1 activity by modifying redox-sensitive cysteines (Meissner et al., 2008); whether such a mechanism provides temporal- or dose-dependent negative feedback to limit caspase-1 function triggered by a ROS-dependent NLRP3 pathway requires clarification. The manner by which cytoplasmic K+ concentration modulates NLRP3 activity is also currently unclear. Macrophages cultured in medium containing a high concentration of K+ show decreased capacity for NLRP3-dependent caspase-1 activation in response to a range of agonists, suggesting that K+ efflux is necessary upstream of NLRP3 activation (Dostert et al., 2008; Fernandes-Alnemri et al., 2007; Franchi et al., 2007a; Gross et al., 2009; Pétrilli et al., 2007; Shio et al., 2009). Future studies are required to determine whether ionic flux and ROS pathways are inter-regulated or independently required for NLRP3 activation.

The NLRP1 Inflammasome

The NLRP1 inflammasome was the first to be described. Human *NLRP1* has three orthologs in mouse (*Nlrp1a-c*, Figure 1) that are highly polymorphic between inbred mouse strains (Boyden and Dietrich, 2006). Strain variation in the mouse *Nlrp1b* locus appears to underlie susceptibility to *Bacillus anthracis* lethal toxin (LeTx), as macrophages from susceptible, but not resistant, mouse strains activate caspase-1 after LeTx exposure (Boyden and Dietrich, 2006). The NLRP1 inflammasome can also be activated by MDP (Faustin et al., 2007).

As a consequence of domain structure differences between NLRP1 and NLRP3, the minimal components of the NLRP1 inflammasome are somewhat different to its NLRP3 counterpart (Figure 2). NLRP1 contains a C-terminal extension that harbors a CARD domain, which can interact directly with procaspase-1 and bypass the requirement for ASC, although ASC inclusion in the complex augmented human NLRP1 inflammasome activity (Faustin et al., 2007). Unlike human NLRP1, murine NLRP1 orthologs lack functional PYD domains and are predicted to be unable to interact with ASC. Indeed, ASC is dispensable for caspase-1 activation by NLRP1b in mouse macrophages (Hsu et al., 2008). In addition to caspase-1, NLRP1 also interacts with caspase-5, which may contribute to IL-1β processing in human cells (Martinon et al., 2002). The exact mechanisms of NLRP1 activation remain obscure, but, as for NLRP3, K+ efflux appears to be essential (Fink et al., 2008; Wickliffe et al., 2008).

The IPAF Inflammasome

The IPAF inflammasome is activated by gram-negative bacteria possessing type III or IV secretion systems, such as *Salmonella typhimurium, Shigella flexneri, Legionella pneumophila*, and *Pseudomonas aeruginosa* (Amer et al., 2006; Franchi et al., 2007b; Mariathasan et al., 2004; Miao et al., 2008; Sutterwala et al., 2007; Suzuki et al., 2007). As IPAF contains a CARD domain, it could be expected to interact directly with procaspase-1, which is indeed the case (Figure 2) (Poyet et al., 2001). Maximal caspase-1 activation in response to *S. typhimurium*, *S. flexneri*, and *P. aeruginosa* requires the ASC adaptor (Franchi et al., 2007b; Mariathasan et al., 2004; Suzuki et al., 2007). The role for ASC in the IPAF inflammasome remains unclear; it is presumed that these proteins do not interact directly as IPAF does not contain a PYD domain. It is possible that IPAF collaborates with a PYD-containing protein (such as an NLRP) for responses to these pathogens. ASC is dispensable for IPAF-dependent caspase-1 activation in response to *L. pneumophila* (Case et al., 2009), but protection against this pathogen appears to require IPAF collaboration with another NLR family member, NAIP (Ren et al., 2006; Zamboni et al., 2006). IPAF-dependent caspase-1 activation is accompanied by rapid cell death (Fink and Cookson, 2006). Interestingly, the pathways downstream of IPAF appear to be independently regulated; maximal caspase-1 activation by the IPAF inflammasome requires ASC, but IPAF-dependent cell death is independent of ASC upon macrophage infection with *S. flexneri* (Suzuki et al., 2007; Suzuki and Núñez, 2008) and *P. aeruginosa* (Sutterwala et al., 2007).

The exact mechanisms directing IPAF inflammasome activation and the participation of ASC and NAIP in this process remain elusive. The LRR domain of IPAF is likely to autorepress in the absence of ligand, as removal of the LRR domain from IPAF results in a spontaneously active mutant (Poyet et al., 2001). The IPAF inflammasome is activated by cytosolic flagellin (Miao et al., 2007). It is likely that other PAMPs modulate IPAF function, as *P. aeruginosa* appears to activate IPAF through flagellin-dependent and -independent pathways (Miao et al.,

2008; Sutterwala et al., 2007), and nonflagellated bacteria such as *S. flexneri* trigger IPAF inflammasome activity (Suzuki et al., 2007). IPAF activation depends upon virulence factor injection into the cytosol via bacterial type III and IV secretion systems (Ren et al., 2006; Sun et al., 2007; Suzuki et al., 2007). Cytosolic localization of flagellin by other means (liposomes, expression systems) is sufficient for IPAF-dependent caspase-1 activation, suggesting that the sole function of bacterial secretion systems in IPAF activation is cytoplasmic injection of bacterial components (Franchi et al., 2006; Lightfield et al., 2008; Miao et al., 2006). Unlike NLRP3, IPAF inflammasome activity is not inhibited by high extracellular K+, suggesting that IPAF is not a sensor for ionic flux (Pétrilli et al., 2007). Direct interaction between IPAF and an activating ligand has not been demonstrated, so it is possible that IPAF senses a common pathway induced by cytosolic PAMPs, analogous to the ROS pathway proposed for NLRP3.

The AIM2 Inflammasome

The recent identification of the HIN-200 family member, AIM2, as a cytosolic double-stranded DNA (dsDNA) sensor that induces caspase-1-dependent IL-1β maturation is an important advance in the inflammasome field (Bürckstümmer et al., 2009; Fernandes-Alnemri et al., 2009; Hornung et al., 2009; Roberts et al., 2009). It is the first identification of a non-NLR family member forming an inflammasome scaffold, and oligomerization of the complex is suggested to be mediated not by a central oligomerization domain within the inflammasome scaffold protein (as for the NLR NACHT domain) but by clustering upon multiple binding sites in the ligand, dsDNA, to which AIM2 binds via its C-terminal HIN domain (Bürckstümmer et al., 2009; Fernandes-Alnemri et al., 2009; Hornung et al., 2009). The AIM2 inflammasome is composed of AIM2, ASC, and caspase-1. AIM2 contains a PYD domain that, as for NLRP3, interacts with ASC via homotypic PYD-PYD interactions, allowing the ASC CARD domain to recruit procaspase-1 to the complex (Figure 2). As for other inflammasomes, upon autoactivation, caspase-1 directs proinflammatory cytokine maturation and secretion (such as IL-1β and IL-18). Ligand requirements for AIM2 are quite permissive, as cytosolic dsDNA from virus, bacteria, or the host itself can activate the AIM2 inflammasome (Hornung et al., 2009; Muruve et al., 2008). Further studies are required to firmly establish the physiological relevance of this pathway, but AIM2 is proposed to function in cytosolic surveillance for DNA viruses and may contribute to autoimmune responses against self-DNA in systemic lupus erythematosus.

Regulation of Inflammasome Activity and IL-1β Secretion

TLRs and Other Proinflammatory Signaling Pathways

Both inflammasome activity and pro-IL-1β availability are highly influenced by integration with proinflammatory signaling pathways such as those triggered by TLR ligation. For this reason, experimental protocols examining inflammasome activation commonly include "priming" with a TLR agonist (such as lipopolysaccharide, LPS) or a proinflammatory cytokine (such as tumor necrosis factor, TNF). Most importantly, although inflammasome-dependent caspase-1 activation can be observed in the absence of priming, IL-1β secretion is minimal, because most cells do not constitutively express pro-IL-1β. Pro-IL-1β is potently induced by proinflammatory signals such as LPS or TNF that activate the NF-κB transcription factor and allow *IL-1β* promoter activation (Hiscott et al., 1993). Although the primary function of priming in experimental protocols is to induce pro-IL-1β, it also potentiates NLRP3 inflammasome activity through NF-κB-dependent induction of NLRP3, which may be a limiting component of the complex (Bauernfeind et al., 2009). Whether other inflammasomes are similarly subject to synergy from priming signals has yet to be determined. The IFN-inducible nature of AIM2 (DeYoung et al., 1997) suggests that it could also be primed in such a manner by TLR agonists that induce autocrine type I IFN or indeed by IFNs themselves.

A recent report suggests that inflammasome activity is modulated by antiviral pathways (Poeck et al., 2010). RIG-I ligation by vesicular stomatitis virus or synthetic RNA triggered caspase-1 activity and IL-1β maturation, in a manner independent of the MAVS and CARD9 adaptors that mediate RIG-I-dependent transcriptional responses (e.g., NF-κB and IFN pathways). The exact mechanisms directing RIG-I-dependent caspase-1 activation are currently unclear. RIG-I-dependent caspase-1 cleavage is ASC dependent but occurs independently of NLRP3, suggesting either that RIG-I can form its own inflammasome or that it regulates the activity of a known or uncharacterized NLRP3-independent inflammasome. Antiviral pathways triggered by the related RIG-I-like helicase, MDA5, also modulate caspase-1 cleavage; MDA5 collaborates with NLRP3 for inflammasome responses to encephalomyocarditis virus (Poeck et al., 2010). In this case, augmented NLRP3 inflammasome activity may be mediated at least partially through MDA5-dependent "priming" of inflammasome activity, for instance by sensitizing cells to NLRP3 agonists via NLRP3 induction.

Negative Regulation of Inflammasome Activation

The importance of the inflammasome in controlling infection is highlighted by microbial evolution of inflammasome inhibitors. These include viral PYD proteins and various bacterial virulence factors that inhibit caspase-1 activation. Such factors are reviewed extensively elsewhere (Martinon et al., 2009). A number of host mechanisms also suppress inflammasome activation and presumably function to inhibit the extent of potentially dangerous immune activation.

Most recently, mouse $CD4^+$ effector and memory T cells were demonstrated to suppress NLRP1 and NLRP3, but not IPAF, inflammasome-mediated caspase-1 activity and IL-1β secretion (Guarda et al., 2009). Inhibition is dependent on cell-cell contact and is mediated by signaling by specific TNF family ligands (Guarda et al., 2009). Such an inhibitory pathway is likely to aid in "switching off" innate immune responses once the adaptive arm of the immune system is engaged.

A number of CARD- and PYD-containing proteins have been proposed to suppress inflammasome activity by blocking inflammasome component recruitment. Such PYD-containing proteins include pyrin, POP1 (PYDC1), and POP2 (PYDC2). The biological relevance of POP1- and POP2-dependent inflammasome inhibition is difficult to assess, as these genes are only present in primates. Conversely, modulation of inflammasome activity by pyrin has clear physiological relevance, as human pyrin mutations are responsible for familial Mediterranean fever

(The International FMF Consortium, 1997); however, the underlying disease-driving mechanisms await clarification. Pryin may inhibit inflammasome activation by sequestering ASC (Chae et al., 2003), or, alternatively, pyrin may itself form an inflammasome (Yu et al., 2006). Further evidence for an important regulatory function for pyrin comes from a pyrin-interacting protein, PSTPIP1, mutations in which are associated with elevated IL-1β in the autoinflammatory disease, pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) (Shoham et al., 2003; Wise et al., 2002). CARD-containing proteins, such as human COP, INCA, iceberg, and caspase-12, are suggested to suppress inflammasome activation by preventing caspase-1 recruitment. Caspase-12 is proposed to function as a decoy inhibitor of caspase-1 (Saleh et al., 2006), but caspase-12 is nonfunctional in most human populations (Xue et al., 2006). As for POPs 1 and 2, COP, INCA, and iceberg do not have nonprimate orthologs. The evolution of a raft of potential inflammasome inhibitors in humans suggests strong selection pressure for control over inflammasome activation.

The antiapoptotic proteins Bcl-2 and Bcl-xL inhibit the inflammasome. These proteins interact with NLRP1 and suppress NLRP1-dependent caspase-1 activation and IL-1β secretion (Bruey et al., 2007), potentially by inhibiting ATP binding to the NLRP1 NACHT domain, a necessary step for NACHT domain oligomerization (Faustin et al., 2009).

Activated caspase-1 is secreted alongside mature IL-1β after inflammasome activation. It is possible that caspase-1 has extracellular functions; however, given its potent intracellular functions and the almost undetectable levels of activated caspase-1 within stimulated cells in most experimental settings, it is tempting to speculate that rapid caspase-1 release after activation represents an important regulatory mechanism to limit the activity of cytosolic caspase-1.

Inflammasome Activation Promotes Pyroptosis

Inflammasome-dependent caspase-1 activity can result in a highly inflammatory form of cell death known as pyroptosis in myeloid cells (Bergsbaken et al., 2009). Pyroptosis occurs most frequently upon infection with intracellular pathogens (Case et al., 2009; Fink et al., 2008; Suzuki et al., 2007) and is likely to form part of the antimicrobial response. Pyroptosis is caspase-1 dependent by definition and occurs independently of proapoptotic caspases (Bergsbaken et al., 2009). Although pyroptosis is considered to be a form of programmed cell death, it is distinct from the immunologically silent cell death presented by apoptosis. Pyroptosis is accompanied by plasma membrane rupture, water influx, cellular swelling, osmotic lysis, and release of proinflammatory cellular content (Fink and Cookson, 2006). Pyroptosis is also accompanied by DNA cleavage and nuclear condensation that is distinct from DNA laddering characteristic of apoptosis, as the nuclear integrity is not compromised (Fink and Cookson, 2006; Molofsky et al., 2006). Caspase-1-dependent inactivation of metabolic enzymes (Shao et al., 2007) is likely to limit the cellular energy supply during pyroptosis.

The regulation of pyroptosis is not well defined; however, the extent of pyroptosis appears to increase with increasing inflammasome stimulation, tempting speculation that pyroptosis may occur when cytoprotection by autophagy (see below) or mechanisms suppressing cytosolic caspase-1 action (e.g., secretion) become overwhelmed. Whether pyroptosis plays a pathological role in genetic autoinflammatory diseases that yield more active inflammasome pathways (discussed below) has yet to be determined.

Reciprocal Regulation of Inflammasome Activation and Autophagic Pathways

Autophagy is a cytoprotective process by which the cell sequesters damaged proteins, organelles, or pathogens in a double-membrane compartment, the autophagosome, targets this cellular material for degradation in the lysosome, and recycles the constituent molecules (Deretic and Levine, 2009). Autophagy occurs under normal physiological conditions but can be upregulated by cellular stress such as starvation, proinflammatory signaling (e.g., IFNγ), or bacterial infection (Deretic and Levine, 2009).

Recent reports reveal a complex interplay between inflammasome and autophagic pathways. Treatment with the TLR4 agonist, LPS, in the absence of contaminating ligands does not induce inflammasome activation in wild-type macrophages. However, blockade of autophagy by genetic ablation of the autophagy regulators Atg16L1 or Atg7 enables LPS-dependent inflammasome activation, suggesting that autophagy normally counters inflammasome activation by LPS (Saitoh et al., 2008). Although in this study, the nature of the inflammasome scaffold was not determined, LPS-induced inflammasome activation in Atg16L1-deficient cells is dependent on K+ efflux and ROS, suggestive of NLRP3 involvement. The mechanism underlying autophagy-dependent inflammasome inhibition is currently unclear. It has been suggested that autophagosomes may target inflammasomes for degradation (Harris et al., 2009). However, given that NLRP3 inflammasome activity is suppressed by ROS blockade (discussed above) and autophagy negatively regulates ROS generation (Bensaad et al., 2009; Dupont et al., 2009; Rouschop et al., 2009; Saitoh et al., 2008), it is possible that autophagic suppression of ROS indirectly inhibits inflammasome activity. Autophagy also appears to negatively regulate pyroptosis (Suzuki and Núñez, 2008). Interestingly, ROS derived from either the mitochondrial electron transport chain or NAPDH oxidases upregulates autophagy (Chen et al., 2009; Huang et al., 2009). Thus, ROS activation of autophagic machinery may represent a negative feedback mechanism to limit ROS-modulated caspase-1 activation while simultaneously removing ROS-damaged organelles and proteins and providing defense against intracellular pathogens. An additional layer of complexity in the links between inflammasomes and autophagy is suggested by a report that the inflammasome negatively regulates autophagy (Suzuki et al., 2007). This study found that caspase-1 deficiency promotes autophagy in macrophages infected with the IPAF agonist *S. flexneri*. Further research is required to clarify the complex reciprocal regulation of inflammasome and autophagic pathways.

Human Diseases Associated with Inflammasome Pathways

Elevated local or systemic IL-1β has been linked to a number of human hereditary or acquired diseases, and antagonists of

IL-1β or its receptor are proving successful treatments for a number of these diseases (Table S2). Most clinical trials to date have utilized daily injections of Anakinra, a recombinant form of the naturally occurring antagonist, IL-1RA. However, next-generation IL-1β antagonists are starting to become available; these include IL-1Trap, a decoy receptor with high affinity for IL-1 (Kalliolias and Liossis, 2008), and monoclonal antibodies that neutralize IL-1β. Clinical trials are currently assessing efficacy of Anakinra and next-generation IL-1β inhibitors for a wider range of diseases, including cryopyrin-associated periodic syndromes (CAPS), gout, and type II diabetes (T2D) (Hoffman, 2009; Lachmann et al., 2009a; Larsen et al., 2009; Larsen et al., 2007; Terkeltaub et al., 2009).

Cryopyrin-Associated Periodic Syndromes

The discovery that NLRP3 mutations are responsible for a set of rare autoinflammatory diseases known as CAPS has revolutionized the clinical management of these diseases. CAPS are heritable diseases characterized by recurrent fever and inflammation and are comprised of three autoinflammatory disorders that form a clinical continuum. These diseases, in order of increasing severity, are familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile cutaneous neurological articular syndrome (CINCA; also called neonatal-onset multisystem inflammatory disease, NOMID). Myeloid cells from these patients are hyperresponsive for IL-1β production (Agostini et al., 2004). In keeping with this, gene-targeted mice harboring equivalent mutations to those found in MWS or FCAS patients exhibit hyperactive NLRP3 inflammasomes leading to elevated IL-1β (Brydges et al., 2009; Meng et al., 2009). Patients with these diseases respond well to IL-1β antagonism by Anakinra (Goldbach-Mansky et al., 2006; Hawkins et al., 2004; Hawkins et al., 2003; Hoffman et al., 2004), next-generation IL-1β antagonists (Goldbach-Mansky et al., 2008; Hoffman, 2009; Hoffman et al., 2008; Lachmann et al., 2009b), and caspase-1 inhibition (Stack et al., 2005). Mutations in putative inflammasome regulators, pyrin and PSTPIP1, are also associated with human diseases related to CAPS (discussed above and in Table S2).

Gout

Gout is an autoinflammatory disease characterized by severe joint inflammation, resulting in arthropathy and considerable pain. Gout is strongly associated with metabolic disturbances leading to elevated blood uric acid levels (hyperuricemia) and the deposition of MSU crystals in joints (Talbott, 1940). Recent studies illuminate mechanisms underlying MSU-dependent joint inflammation. MSU is a potent activator of the NLRP3 inflammasome in vitro (Martinon et al., 2006), and MSU-dependent neutrophil recruitment is dependent on the ASC adaptor, caspase-1, and IL-1R in vivo (Martinon et al., 2006). A pathogenic role for inflammasome-regulated IL-1β in gout and the closely related disease pseudogout in humans is supported by the success of IL-1β antagonists in clinical trials (McGonagle et al., 2008; McGonagle et al., 2007; So et al., 2007; Terkeltaub et al., 2009).

Type II Diabetes

An emerging role for the NLRP3 inflammasome as a sensor of metabolic stress, as suggested by studies in gout, is reinforced by the success of IL-1 receptor antagonism in clinical trials for the treatment of T2D (Larsen et al., 2009; Larsen et al., 2007). Elevated IL-1β is a risk factor for the development of T2D (Spranger et al., 2003) and contributes to insulin resistance by antagonizing insulin signaling (Maedler et al., 2009). IL-1β also mediates the toxic effects of prolonged hyperglycaemia (glucotoxicity) in pancreatic islets, driving β cell destruction and dysregulating glucose-induced insulin secretion (Maedler et al., 2009). A recent study characterized IL-1β secretion in mouse pancreatic islets during chronic hyperglycaemia; high extracellular glucose triggers IL-1β secretion via the NLRP3 inflammasome (Zhou et al., 2010). Moreover, the NLRP3-binding protein, TXNIP, is itself heavily implicated in T2D, as a mediator of pancreatic β cell death and failing peripheral glucose uptake (Parikh et al., 2007; Shalev, 2008). Accordingly, TXNIP deficiency improves glucose tolerance and insulin sensitivity as compared to wild-type mice (Hui et al., 2008; Oka et al., 2009). Mechanisms by which inflammasome activation and elevated IL-1β may drive the progression from obesity to T2D are reviewed elsewhere in detail (Schroder et al., 2010).

Disease Associations of Other NLRPs

Mutations in NLRPs other than NLRP3 have been linked to human disease. NLRP12 mutations are associated with a fever syndrome resembling FCAS, called FACS2 (Jéru et al., 2008). The authors suggest that NLRP12 mutations in these patients disrupt the NF-κB inhibitory activity of the protein (Jéru et al., 2008); however, given the high homology between NLRP12 and NLRP3 (Figure 1) and the similarities in FCAS and FCAS2 patient symptoms, it is possible that inflammasome activity is dysregulated in these patients. Mutations in NLRP1 are associated with vitiligo-associated multiple autoimmune disease (Jin et al., 2007). NLRP2 mutation has been recently linked to a case of familial Beckwith-Wiedemann Syndrome, a fetal overgrowth and imprinting disorder (Meyer et al., 2009). NLRP7 mutations are associated with familial and recurrent hydatidiform moles, an abnormal pregnancy state in which placental villi are degenerated and the fertilized egg is nonviable (Murdoch et al., 2006). Disease-driving mechanisms engaged by mutation in these genes and the potential involvement of the inflammasome pathway await clarification.

Concluding Remarks

The past decade has witnessed great advances in our understanding of molecular mechanisms underlying innate immune system activation. In particular, the regulation of IL-1β maturation by the NLRP1, NLRP3, IPAF, and AIM2 inflammasomes is beginning to be characterized in detail. The potent activity of the inflammasome in directing innate immune responses is clearly demonstrated by a number of heritable and acquired diseases in which NLRP3 inflammasome activity is dysregulated, and the success with which many of these diseases can now be treated with antagonists of IL-1β or its receptor.

Despite these great advances, there remain a number of unresolved aspects of inflammasome biology. One of these is the nature of the endogenous signal leading to pro-IL-1β induction in these diseases. Proinflammatory cytokine signaling or PAMP recognition by PRRs are candidate signals, and in fact a recent study suggests that IL-1β provides its own priming signal in CAPS patients (Lachmann et al., 2009b). This may also be true

for other diseases, such as T2D and gout. The source of ROS that is generated in response to NLRP3-activating stimuli is also currently unclear. Another open question is the function of the uncharacterized NLRPs. Some of these have been demonstrated to modulate caspase-1 activity in vitro, but the ability of these NLRPs to form inflammasome scaffolds in vivo and the physiological situations triggering such activation remain obscure. Disease associations of a number of NLRPs suggest important roles in inflammatory or reproductive disease that should prove rich ground for future research.

SUPPLEMENTAL INFORMATION

Supplemental Information includes two tables and can be found with this article online at doi:10.1016/j.cell.2010.01.040.

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