Nucleotide-Binding Oligomerization Domain-Like Receptors: Intracellular Pattern Recognition Molecules for Pathogen Detection and Host Defense

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The nucleotide binding oligomerization domain-like receptor (NLR) family of pattern recognition molecules is involved in a diverse array of processes required for host immune responses against invading pathogens. Unlike TLRs that mediate extracellular recognition of microbes, several NLRs sense pathogens in the cytosol and upon activation induce host defense signaling pathways. Although TLRs and NLRs differ in their mode of pathogen recognition and function, they share similar domains for microbial sensing and cooperate to elicit immune responses against the pathogen. Genetic variation in several NLR genes is associated with the development of inflammatory disorders or increased susceptibility to microbial infection. Further understanding of NLRs should provide critical insight into the mechanisms of host defense and the pathogenesis of inflammatory diseases. The Journal of Immunology. 2006, 177: 3507–3513.

An effective immune response against microbial infection requires both the ability to sense the presence of the infectious agent, as well as the ability to destroy the pathogen. One way the immune system recognizes the presence of infection is through pathogen recognition molecules that detect the presence of unique microbial and viral components called pathogen-associated molecular patterns (PAMPs). These PAMPs include components of the bacterial cell wall (i.e., LPS, lipoteichoic acid, and peptidoglycan), specialized bacterial proteins (i.e., flagellin), as well as nucleic acid structures unique to bacteria and viruses (i.e., CpG DNA, dsRNA) (2). Three main families of pathogen recognition molecules cooperate in host defense and include TLRs, nucleotide-binding oligomerization domain (Nod)-like receptors (NLRs), and retinoid acid-inducible gene 1-like receptors (2). The detection of PAMPs by TLRs, NLRs, and retinoid acid-inducible gene 1-like receptors stimulates the activation of proinflammatory signaling pathways and caspas, as well as antiviral and bactericidal responses (2, 3). The coordination and cooperation of responses triggered by these pathogen sensors tailor the immune response to effectively abrogate the specific infection (2). Genetic mutations that cause alterations in these signaling pathways frequently result in inflammatory disease or immune disorders (4). Recent advances have been made in our understanding of the role of NLRs and their cooperation with TLRs in innate immunity and are the focus of this review.

NLR family of pathogen sensors

The NLR family (NLRs, also called Nod-leucine-rich repeats (LRRs), NACHT-LRRs, or CATEPILLER proteins) is composed of 23 cytosolic proteins characterized by the presence of a conserved Nod (3). The general domain structure of these proteins include an amino-terminal effector binding domain that consists of protein-protein interaction domains such as caspase recruitment domains (CARD), pyrin, or baculovirus inhibitor repeat domains, a central Nod that acts to oligomerize these proteins, and carboxyl-terminal LRRs that are required to detect specific PAMPs and is involved in autoregulation of NLR activity (3). These proteins have a remarkable structural similarity to plant disease resistance genes (R genes) and are thought to play key roles in pathogen defense through sensing bacteria and generating immune responses (5).

Recognition of microbes by NLRs

Nod1/CARD4 senses the presence of bacterial pathogens, such as Shigella flexneri (6), enteroinvasive Escherichia coli (7), Pseudomonas aeruginosa (8), and Helicobacter pylori (9, 10), through the recognition of peptidoglycan (PGN) molecules that contain meso-diaminopimelic acid (meso-DAP) (11). DAP is an unusual amino acid that is unique to PGN from most bacterial species and is involved in autoregulation of NLR activity (3). The general domain structure of these proteins include an amino-terminal effector binding domain that consists of protein-protein interaction domains such as caspase recruitment domains (CARD), pyrin, or baculovirus inhibitor repeat domains, a central Nod that acts to oligomerize these proteins, and carboxyl-terminal LRRs that are required to detect specific PAMPs and is involved in autoregulation of NLR activity (3). These proteins have a remarkable structural similarity to plant disease resistance genes (R genes) and are thought to play key roles in pathogen defense through sensing bacteria and generating immune responses (5).

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3 Abbreviations used in this paper: PAMP, pathogen-associated molecular pattern; Nod, nucleotide-binding oligomerization domain; CARD, caspase-recruitment domain; LRR, leucine-rich repeat; ASC, apoptosis-associated speck-like protein containing a CARD; MDP, muramyl dipeptide; NLR, Nod-like receptor; PGN, peptidoglycan; DAP, diaminopimelic acid; iE-DAP, N-(α-D-glutamyl-meso-DAP; IKK, IκB kinase; CD, Crohn’s disease; BS, Blau syndrome; PCAS, familial cold autoinflammatory syndrome.

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Analysis of synthetic compounds revealed that the dipeptide γ-D-glutamyl-meso-DAP (iE-DAP) is sufficient to trigger Nod1 activation (11, 13). However, these iE-DAP-containing PGN molecules must be delivered intracellularly through either invasion of the cytosol by intracellular bacteria, as in S. flexneri infection (6), or transport of these molecules through bacterial secretion systems, like the type IV secretion system of H. pylori (9).

Another NLR family member, Nod2/CARD15, also recognizes the presence of bacteria through sensing a component of PGN. Nod2 is activated by muramyl dipeptide (MDP), which is a conserved structure in virtually all types of PGN (12). Like iE-DAP, MDP must be delivered intracellularly either by bacteria that invade the cell or through other cellular uptake mechanisms to be detected by Nod2. However, in contrast to Nod1 that recognizes only a subset of microbes that contain the dipeptide iE-DAP, Nod2 functions as a general sensor of bacteria (12).

Ipaf/CLAN/CARD12 is critical for generating an immune response to Salmonella typhimurium and Legionella pneumophila through sensing a component of these bacteria distinct from PGN (14, 15). Recent studies have revealed that intracellular flagellin is the PAMP recognized by Ipaf independently of TLR5, which senses extracellular flagellin (16, 17). The recognition of flagellin by Ipaf upon infection with S. typhimurium or L. pneumophila is dependent on a functional bacterial secretion system (type III or type IV, respectively), suggesting that monomeric flagellin delivered to the host cytosol through these secretion systems activates Ipaf (16, 17).

Cryopyrin/PYPAF1/NALP3 not only detects the presence of microbes, but also mediates activation of the immune system in response to endogenous danger signals that are released by injured cells (18, 19). Several recent articles have demonstrated that Cryopyrin senses bacterial RNA, synthetic purine analogs R837 (imiquimod) and R848 (resiquimod), as well as the endogenous danger signals monosodium urate or calcium pyrophosphate dehydrate crystals (18, 19). Both R838 and R848 structurally resemble uric acid, suggesting that Cryopyrin senses purine-like structures. In addition, other results indicate that Cryopyrin regulates caspase-1 activation in response to factors that induce intracellular K⁺ efflux, such as certain toxins and high extracellular concentrations of ATP (20, 21).

Finally, the susceptibility of certain mouse strains to infection by specific bacteria has been shown to be dependent on other NLR family members. Mouse susceptibility to Bacillus anthracis lethal toxin-induced macrophage cell death is controlled by Nap1b, indicating that this NLR protein is involved in sensing lethal toxin (22). A mutation in the mouse NLR protein, Naip5, has been associated with host susceptibility to the intracellular pathogen L. pneumophila (23), suggesting that Naip5 functions as a cytosolic sensor of L. pneumophila. However, the specific component of L. pneumophila recognized by Naip5 remains to be identified.

Although there is compelling evidence that NLR proteins are activated by specific PAMPs, the mechanism involved remains unclear. Several studies have demonstrated that the LRRs of NLR proteins are required for PAMP sensing (24–26). However, there is no clear evidence that mammalian NLRs or their plant R protein homologs directly interact with their cognate microbial activators (5). This suggests that the sensing of microbial agonists by NLRs might be indirect through adaptor molecules or induced host factors that are recognized by NLRs. The identification of the molecular mechanism by which microbial agonists are sensed by NLRs remains an important challenge for future studies.

**Activation of NLR intracellular responses**

Molecular studies have revealed that stimulation of NLRs by microbial components results in the activation of two distinct proinflammatory intracellular responses. The current model of NLR activation is based on studies of one family member, the apoptosis regulator Apaf-1 (27), that revealed how this factor activates caspase-9 upon oligomerization.

Once activated, one group of NLRs, which includes Nod1 and Nod2, activates gene transcription through the NF-κB transcription factor and the MAPK signaling pathway. Stimulation of Nod1 or Nod2 by specific components of bacterial PGN causes the recruitment of a protein kinase RICK/RIP2/CARDIAK (Fig. 1). RICK has been demonstrated to be an essential component of both the Nod1 and Nod2 signaling pathways, since cells that do not express RICK are unable to activate an Nod1- or Nod2-mediated NF-κB response (28). The binding of RICK to Nod1 or Nod2 and its oligomerization activates downstream signaling pathways. One pathway activated is NF-κB through the recruitment of the IkB kinase (IKK) complex to RICK (29). RICK directly binds to IKKγ and activates the IKK complex through promoting the ubiquitinylation of IKKγ and stimulating the kinase activity of the two other components of the IKK complex, IKKα and IKKβ (29, 30). Activation of the IKK complex causes the phosphorylation and subsequent degradation of the NF-κB inhibitor IkBα (31). The activated NF-κB translocates to the nucleus where it binds to target gene promoters and stimulates gene transcription. In addition to the NF-κB pathway, MAPKs are activated in response to stimulation of Nod1 or Nod2 and result in the activation of the kinases p38, Erk, and Jnk (32). These two pathways are thought to work together to up-regulate the expression of proinflammatory molecules to stimulate both innate and adaptive immune responses (Fig. 1).

A second group of NLRs, which include Ipaf and Cryopyrin, respond to microbial components through proteolytic activation of caspase-1 to generate the proinflammatory cytokines IL-1β and IL-18 (Fig. 1). Caspase-1 is the prototypical member of a family of inflammatory caspases that includes caspase-4 and caspase-5 in humans and caspase-11 in mice (33). Caspase-1 is synthesized as an inactive zymogen that becomes activated by cleavage at aspartic residues to generate an enzymatically active heterodimer composed of a 10- and a 20-kDa chain (33). Cryopyrin and Ipaf can form multiprotein complexes termed “inflammasomes” that promote caspase-1 activation and subsequent processing of pro-IL-1β (34).

Recent studies have shown that Cryopyrin and Ipaf, as well as the adaptor ASC, are required for the activation of caspase-1 in response to microbial components and intracellular bacteria, a process that is TLR independent (16, 17, 19). ASC is essential for activation of caspase-1 in response to a broad range of PAMPs and intracellular pathogens, including S. typhimurium (14), L. monocytogenes (35), Francicella tularensis (36), and Staphylococcus aureus (21). In contrast, the functions of Ipaf and Cryopyrin are more restricted. Ipaf is required for caspase-1 activation induced by S.
Through the recognition of cytosolic flagellin, but dispensable for that triggered by *L. monocytogenes* or *F. tularensis* (14, 16, 17, 36). Cryopyrin appears to be important for caspase-1 activation after infection of macrophages with *L. monocytogenes* and *S. aureus* but not *S. typhimurium* (21). These results suggest that several NLRs may use the adaptor ASC to activate caspase-1 in response to bacterial infection.

**Functions of NLRs in the epithelium**

The functions of NLRs in the immune defenses of the epithelium are beginning to emerge. Several studies have implicated Nod1-dependent NF-κB activation in the induction of β-defensin and chemokine expression in response to *H. pylori* (9, 10), enteroinvasive *E. coli* (7), and *S. flexneri* infection (6) (Fig. 2A). Unlike airway epithelial surfaces, gastric and intestinal cells are largely deficient in TLR signaling and must rely on alternative systems, such as NLRs, for the detection of pathogens. *H. pylori* is an extracellular bacterium, but it injects muropeptides into gastric epithelial cells through its type IV secretion apparatus, providing a mechanism for the sensing of noninvasive bacteria intracellularly by host epithelial cells. Nod1 is required for the induction of β-defensin-2 in human gastric epithelial cells upon *H. pylori* infection (10). Since the mouse homolog of β-defensin-2 is also induced in vivo by *H. pylori* in a Nod1-dependent manner, this may explain the increased gastric colonization of cag-positive *H. pylori* strains in Nod1-null mice (9). In addition, induction of chemokine expression in epithelial cells after infection with enteroinvasive *E. coli* and *S. flexneri* is largely dependent on Nod1 (Fig. 2B) (6, 7). A role for Nod1 in early immune responses is supported by the finding that injection of mice with synthetic Nod1 activators induces high levels of CXCL1, CXCL2, and CCL2 and recruitment of neutrophils in vivo (37). Recognition of microbes inside host cells through Nod1 signals harmful infection by pathogenic bacteria in intestinal tissues and the activation of inflammatory immune responses.

Nod2 has been implicated in the expression of antimicrobial peptides in epithelial barriers. One such barrier includes Paneth cells, which are specialized intestinal cells located in the crypts of the small intestine, that secrete antimicrobial peptides such as α- and β-defensins (known as cryptdins in mice) (39). The Nod2-dependent regulation of α-defensins is consistent with the presence of Nod2 in Paneth cells (39), but this activity is intriguing in that there is no evidence that α-defensin expression is regulated via NF-κB-dependent pathways (39). In addition, production of human β-defensin-2 in keratinocytes of the skin was shown to be regulated by bacterial products in a Nod2-dependent manner (40). Interestingly, up-regulation of this gene was found to be dependent on NF-κB (40). Clearly, further work is needed to understand the role of Nod2 in the regulation of antimicrobial peptides at mucosal surfaces.
Stimulation of TLRs induces the production of pro-IL-1 leading to induction of the human iE-DAP-containing molecules into the host cytosol. Nod1 is then activated, *H. pylori* is dependent on the type IV secretion system of the bacterium that injects mokine genes and recruitment of neutrophils to the infection site.

Cooperation between NLRs and TLRs to control the secretion of IL-1β. Secretion of IL-1β is regulated by two distinct processes. Short-term stimulation of macrophages with TLR ligands including LPS, which is referred to as “priming,” is important for the initial production of pro-IL-1β. The second step involves activation of caspase-1, which is required for processing of pro-IL-1β into the biologically active mature IL-1β (33). Studies using macrophages deficient in MyD88, an essential adaptor for TLR signaling, revealed that MyD88 signaling is critical for the expression of pro-IL-1β via NF-κB activation, but is dispensable for caspase-1 activation in response to microbial stimuli (46). In the case of the NLR proteins, Ipaf and Cryopyrin play a critical role in caspase-1 activation independently of TLR signaling (16, 17, 19, 35), and, conversely, do not play a role in the activation of NF-κB and in the up-regulation of pro-IL-1β (14, 21). Thus, it appears that cooperative signaling occurs between NLRs and TLRs to control the secretion of IL-1β (Fig. 2D). Because both Ipaf and Cryopyrin can be activated by PAMPs that also activate TLRs (i.e., flagellin (16, 17) or microbial RNA (19)), it is hypothesized that secretion of IL-1β and other proinflammatory cytokines, whose expression is induced via TLR signaling (e.g., IL-6 or TNF-α), is coupled during bacterial infection. However, the requirement of a functional bacterial secretion system for caspase-1 activation in response to *S. typhimurium* infection (14, 16, 17) indicates that only virulent intracellular bacteria induce IL-1β secretion. These findings suggest that activation of cytosolic NLR proteins function to produce a more robust immune response to control invasive bacteria.

Prolonged exposure of macrophages to PAMPs (such as LPS) induces a state of cell tolerance to secondary TLR and bacterial challenge that is thought to protect the host from the harmful effects associated with overproduction of proinflammatory cytokines (47). Notably, macrophages tolerized with LPS secrete high levels of IL-1β which correlates with activation of Ipaf-dependent caspase-1 in response to *S. typhimurium* infection (17) (Fig. 2D). Cytosolic signaling and IL-1β secretion induced by bacteria might thus represent a mechanism to alert the immune system to the presence of invasive pathogens inside the macrophage.

**Cooperative signaling between NLR and TLR signaling**

Both MDP- and iE-DAP-containing molecules synergize with TLR ligands to induce the secretion of multiple cytokines and induction of costimulatory molecules in macrophages and dendritic cells (32, 41–43). Cooperation between MDP and LPS stimulation can be observed in whole animals where it enhances the severity of LPS-induced shock in a Nod2-dependent manner (32). This synergism between NLRs and TLRs could be explained by cross-induction of critical signaling molecules upon microbial stimulation (44, 45). The enhancement of TLR-mediated responses by Nod1 and Nod2 stimulatory molecules has been widely used to study Nod1 and Nod2 in mouse systems because, in contrast to human cells, mouse cells respond poorly to MDP and iE-DAP stimulation (32).

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several inflammatory or infectious diseases in human populations. Loss-of-function mutations in CIITA, an NLR family member, that result in MHC class II deficiency are responsible for the type II bare lymphocyte syndrome. CIITA mutations impair the transcriptional activity of CIITA, resulting in decreased MHC class II expression, immunodeficiency, and increased susceptibility to infection by a wide variety of pathogens (48).

Genetic variation in Nod2 is associated with susceptibility to several inflammatory diseases. Crohn’s disease (CD), a chronic inflammatory disorder of the intestinal wall, is associated with three common mutations (R702W, G908R, and L1007insC) involving amino acid residues near or within the LRRs of Nod2 (49, 50). Biochemical and functional studies in cell lines revealed that the human CD-associated Nod2 variants exhibit reduced or loss of activity when compared with the wild-type protein (24, 50). Similarly, the induction of TNF-α, IL-6, IL-10, and IL-1β by monocytes in response to MDP, but not to TLR agonists, is specifically impaired in patients and healthy individuals homozygous for the common Nod2 mutations (24, 51). The defective function of CD-associated Nod2 mutations is consistent with genetic studies that revealed that homozygosity for the common mutations is required for increased disease susceptibility (52), but is at odds with a study in mice showing that the L1007insC Nod2 mutation confers enhanced IL-1β secretion (53). The reason for the discrepancy between the human and mouse studies is unclear. The observation that the response to MDP is impaired in human cells homozygous for CD-associated Nod2 mutations suggests that a deficit in bacterial sensing triggers an abnormal inflammatory response to unclear bacteria or bacterial product in the intestinal tissue. Although several nonexcluding hypotheses have been proposed to explain the link between Nod2 mutations and CD, the precise mechanism(s) remains poorly understood. These mechanisms include reduced expression of α-defensins in Paneth cells, impaired production of inflammatory molecules by intestinal macrophages and/or dendritic cells, neutrophil dysfunction, and dysregulated TLR2 signaling (32, 54). The hypothesis that Nod2 mutations lead to decreased Paneth cell function is particularly attractive in that similar findings have been found in Nod2-deficient mice and CD patients (32, 55). However, there is no direct evidence that reduced production of α-defensins leads to impaired clearance of bacteria and intestinal inflammation. Clearly, further studies are needed to understand the link between Nod2 mutations and the development of CD.

The CD-associated Nod2 variants have been also linked to susceptibility to graft-vs-host disease and mortality in patients undergoing allogeneic bone marrow transplants (56, 57). These studies suggest that the interaction of Nod2 with intestinal flora can regulate, by mechanisms that remain unclear, the response of allogeneic T cells causing graft-vs-host disease.

Several missense mutations involving acid amino residues in the Nod domain of Nod2 cause two autosomal dominant disorders characterized by granulomatous inflammation at multiple organ tissues, called Blau syndrome (BS) and early-onset sarcoidosis (58, 59). In contrast to CD, the Nod2 mutations associated with BS and early-onset sarcoidosis exhibit enhanced activity (25), which is consistent with the dominant mode of inheritance of these diseases.

Several Nod1 polymorphisms have been associated with the development of atopic eczema and asthma, as well as with increased levels of serum IgE in several human populations (60, 61). The link between Nod1 and asthma is intriguing in that microbial exposure in childhood is known to protect against the development of disease (62). Thus, it is possible that cytosolic recognition of bacterial products via Nod1 in the skin and mucosal surfaces regulates directly or indirectly Th2 polarization and IgE levels.

Missense mutations in the CIAS1 gene, which encodes Cryopyrin, are the cause of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease. These diseases are characterized by spontaneous attacks of systemic inflammation without an apparent infectious or autoimmune etiology and represent a spectrum of related disorders of different severity, where FCAS patients are the least affected and neonatal-onset multisystem inflammatory disease patients the most severely affected (4). Notably, the mutations associated with these autoinflammatory syndromes localize to the Nod domain, suggesting that they affect the activation state of Cryopyrin (4, 25). Intriguingly, the R260W mutation associated with FCAS and Muckle-Wells syndrome corresponds to the R334W Nod2 mutation found in BS (25, 63). Consistent with these observations, functional studies revealed that the Cryopyrin mutants exhibit enhanced activity to induce IL-1β secretion (64). Furthermore, mononuclear cells from patients with autoinflammatory syndromes spontaneously secrete IL-1β and IL-18 (65). These observations suggest that the disease-associated mutations confer a state of constitutive activation to Cryopyrin, leading to increased caspase-1 activity. Notably, disease activity is greatly reduced after treatment with IL-1R antagonist in patients with these autoinflammatory syndromes, indicating a critical role for IL-1β in disease pathogenesis (66).

Conclusions

There is now conclusive evidence that several members of the NLR family play important roles in the immune response against invading pathogens and that NLR genetic variation causes or contributes to human disease. However, several questions remain, including the mechanism involved in microbial recognition through the LRRs of NLRs, the mechanism responsible for delivery of PAMPs to the cytosol, and a clearer understanding of the link between NLR and disease. Further studies including in-depth analyses of mutant mice deficient in NLR genes and further biochemical characterization of NLR signaling pathways are required to understand the function of NLRs in immune responses.

Disclosure

The authors have no financial conflict of interest.

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