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Inflammasomes in Myeloid Cells: Warriors within

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Abstract

The inflammasome is a large multimeric protein complex comprised of an effector protein that demonstrates a specificity for a variety of activators or ligands, an adaptor molecule and pro-caspase-1 which is converted to caspase-1 upon inflammasome activation. Inflammasomes are expressed primarily by myeloid cells and are located within the cell. The macromolecular inflammasome structure can be visualized by cryo-electron microscopy. This complex has been found to play a role in a variety of disease models in mice and several have been genetically linked to human diseases. In most cases, the effector protein is a member of the NLR (nucleotide-binding domain leucine rich repeat containing), or NOD (nucleotide oligomerization domain)-like receptor protein family. However, other effectors have also been described, with the most notable being AIM2 (absence in melanoma 2), which recognizes DNA to elicit inflammasome function. This chapter will focus on the role of the inflammasome in myeloid cells and its role in health and disease.

Introduction

Inflammation is the body's response to injury, pathogen exposure and irritants. Pattern recognition receptors allow our body to recognize a diverse array of patterns generated during exposure to these insults. In 2002, the Nucleotide-binding domain, Leucine-rich Repeat containing (NLR, also known as NOD-like receptor) gene family of pattern recognition receptors was discovered(1–3). While several members were already recognized at that point, reports of the entire NLR family provided a global view. In the past fifteen years of research, the physiological relevance of these genes has been revealed to include a diverse variety of functions. Gene mutations in some of the family members have been linked to autoinflammatory diseases in humans (Figure 1). This association of mutations in NLR genes to autoinflammatory diseases indicates critical functions in the regulation of immunity and inflammation.

There are 22 NLR genes in humans and 34 identified in mice, with each gene encoding a protein with a characteristic tripartite structure of central nucleotide binding domain (NBD), an N-terminal effector domain and a variable number of C-terminal leucine rich repeats (LRRs) (Figure 2)(4). Proteins with domain architecture similar to that of human NLRs exist in plants and in invertebrates such as sea urchins. These proteins are absent in nematodes and Drosophila, suggesting either convergent evolution between mammalian and plant NLRs or loss in invertebrates(5, 6). The effector domains of NLRs can be combinations of the

following domain types: acidic transactivation domain (AD), baculoviral inhibitory repeat (BIR)-like domain, caspase recruitment domain (CARD), pyrin domain or domain of unknown function (X) (Figure 2). The length of the LRR domains is highly variable. For example, an NLR may contain up to 30+ LRR domains(7). While each NLR has a unique capability to sense a variety of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), the exact mechanisms of NLR-ligand binding have only recently emerged for NOD2 and NLRC4/NAIP proteins. Initially NLRs were presumed to be expressed only in innate immune cells of monocyte/macrophage lineage. However, their ubiquitous expression throughout the human body is now widely accepted. Interestingly, different NLRs show distinct tissue, cellular and intracellular distributions, suggesting variable roles in different cell types(8). This chapter will focus on the role of NLRs in myeloid cells in the normal host as well as in dysregulated immune states of disease.

Activation of Inflammasome NLRs

Upon activation, several NLRs form multiprotein complexes called “inflammasomes”. These complexes consist of an NLR, an adapter molecule known as ASC (apoptosis-associated speck-like protein containing a CARD) and the inflammatory protease pro-caspase-1[4–5]. Even though the inflammasome mediated roles of NLRs have been extensively studied, there are several non-inflammasome mediated functions of NLRs including NF-κB regulation, MAPK activation, cytokine and chemokine production, IFN production, ribonuclease L activation and antimicrobial reactive oxygen species (ROS) production. The inflammasome forming NLRs will be discussed in detail here, while the readers are referred to other reviews for descriptions of the non-inflammasome forming NLRs(9–11).

A subset of NLRs (NLRP1, NLRP3, NLRP6, NLRP7, NLRC4, NLRC5 and NAIP2/5/6) has been reported to form inflammasomes. Each NLR with its activating signal, inflammasome components and disease association will be described here in some detail.

NLRP1

NLR family, Pyrin domain containing 1 or NLRP1 (formerly CARD7, DEFCAP, NALP1) was first characterized as a member of the CED-4 family of apoptotic proteins that are required to initiate programmed cell death(12–14). The first caspase-1 activating inflammasome to be identified consisted of NLRP1, ASC, caspase-1 and caspase-5(15). Overexpression of NLRP1 in mammalian cells led to apoptosis(12, 13). NLRP1 is a cytoplasmic protein that is highly expressed in peripheral blood lymphocytes(12). Initial studies on NLRP1 suggested that the NLRP1 inflammasome in humans consists of NLRP1, pro-caspase-1, caspase-5 and the adapter ASC(12, 13). It was later revealed that even though the presence of ASC may not be required for processing of pro-caspase-1 by the NLRP1 inflammasome, ASC does augment processing of pro-caspase-1(16).

There is one *NLRP1* gene in humans in contrast to three paralogs in mice, *Nlrp1a*, *Nlrp1b*, *Nlrp1c*(17). Interestingly, not all strains of mice express all isoforms. For example, some strains of inbred mice express different splice variants of *Nlrp1b,* while *Nlrp1a* is highly conserved(18). The NLRP1 protein in humans consists of an N terminal pyrin domain, a

central NBD-associated domain (NAD), LRRs, a function to find (FIIND) domain, and a C terminal CARD domain. Polymorphisms in the NLRP1 gene, in both the noncoding and coding sequences have been associated with the dermatologic autoimmune disease vitiligo(19–21). The NLRP1 haplotype associated with vitiligo and other autoimmune disorders leads to increased IL-1β processing. Several coding polymorphisms have also been associated with heightened risk for other autoimmune diseases such as Addison's disease and type 1 diabetes(22).

The mouse Nlrp1 paralogs vary in structure from the human protein such that Nlrp1a lacks the N terminal pyrin domain, Nlrp1b lacks both the pyrin and NAD domains and Nlrp1c lacks all but the NBD and LRR domains. Due to these differences, mouse and human NLRP1 appear to exhibit functional differences. Specifically, susceptible and resistant mouse *Nlrp1b* loci were genetically associated with *Bacillus anthracis* susceptibility(23, 24). Additionally, anthrax lethal toxin was found to activate mouse Nlrp1b and rat Nlrp1 inflammasome(25), resulting in caspase-1-dependent pyroptosis. Lethal toxin is composed of two proteins: protective antigen (PA) and lethal factor (LF), with PA binding to anthrax toxin receptors on host cells and subsequently translocating LF into the cytosol(26). LF was found to cause the proteolytic cleavage of rat Nlrp1 at the N-terminus, presumably by cleaving an inhibitory domain. Mutation of this cleavage site transformed a responsive allele to a nonresponsive allele and resulted in the abrogation of caspase-1 activation(27). In the mouse system, an engineered Nlrp1b that contained an artificial TEV protease cleavage site activated inflammasome in the presence of TEV(26). Interestingly, this cleavage site coincided with the cleavage site found in rat NLRP1, although dissimilar in sequence. Overall, this association of LF cleavage of Nlrp1b in the intact animal is less straightforward, in that Nlrp1b protein from both LF-responsive and - nonresponsive mouse strains were cleaved by LF(28).

In addition to pathogens, human NLRP1 inflammasome is activated by the peptidoglycan component muramyl dipeptide (MDP)(16). MDP stimulation of a macrophage cell line also leads to association of overexpressed NLRP1 with NOD2, leading to formation of a multi-protein complex consisting of NLRP1, NOD2 and caspase-1(25). These results suggest either the existence of an inflammasome containing NLRP1 plus NOD2 that is activated by MDP, or that MDP activates both NLRP1 and NOD2 inflammasomes. However, a mouse cell line deficient in *Nlrp1b* and lacking inflammasome activation by anthrax lethal toxin shows no defect in the assembly of NLRP1 inflammasome by MDP(29). While investigating the crystal structure of the LRR domain of NLRP1, Reubold et al. concluded that the LRR domain is not likely to contain the MDP-binding domain(30). Thus MDP may represent a species specific activator of NLRP1, considering the structural difference between human and rodent NLRP1.

NLRP1 has also been shown to mediate inflammasome activation in response to *Toxoplasma gondii* in a human monocytic cell line(31). This protein was later found to mediate host response to *Toxoplasma* in mice(32) but the process was not dependent on the cleavage site of Nlrp1b found in anthrax(23). Both Nlrp1b and Nlrp3 form inflammasomes that restrict Toxoplasma gondii infection via the production of IL-18(33). Finally, additional studies have

demonstrated that mouse *Nlrp1a* mediates inflammasome and pyroptosis function during LCMV infection and upon chemotherapy treatment(34).

Aside from response to microbial pathogen, NLRP1 is associated with several disease pathologies, including acute glaucoma, traumatic brain injury, acute lung injury, colitis and colitis-associated tumorigenesis(29, 35–37). Interestingly, a recent paper showed that Nlrp1 is also involved in metabolic disease, where it prevents obesity by the production of IL-18 which is known to prevent overeating(38). An inflammasome consisting of NLRP1, ASC, caspase-1, caspase-11 (the rodent ortholog of human caspase-5) and the X-linked inhibitor of apoptosis protein (XIAP) was shown to be present in rat spinal cord motor neurons, in protein co-immunoprecipitation and immunofluorescence experiments(39). Remarkably, therapeutic neutralization of ASC with an antibody was shown to improve histopathology after traumatic brain injury via reduction of immune responses(40). This finding is consistent with a report that ASC specks accumulate in the extracellular space after cells undergo pyroptosis to promote IL-1β maturation. Although phagocytosis of these specks was shown to induce lysosomal damage, stimulate soluble ASC nucleation and increase inflammation(41), “frustrated” phagocytosis has been noted as a consequence to injury (and inflammasome activation) found in various organs.

NLRP3

NLR family, Pyrin-domain containing 3 (*NLRP3*, also Cryopyrin, Nalp3, PYPAF1, CIAS1) was discovered in 2001, in a seminal report that mapped a causative NLRP3 mutation to rheumatologic autoinflammatory disorders, namely familial cold autoinflammatory syndrome (FCAS) and Muckle Wells syndrome (MWS)(42). In 2002, with the discovery of NOMID/CINCA (neonatal-onset multisystem inflammatory disease and Chronic infantile neurologic cutaneous and articular syndrome), FCAS and MWS were classified along with NOMID to form the cold associated periodic syndromes (CAPS)(43, 44). To date, the primary focus of inflammasome research has been anchored by NLRP3, which is a cytoplasmic protein that is primarily expressed in monocytes, macrophages, granulocytes, dendritic cells, epithelial cells and osteoblasts(45, 46). NLRP3 expression in myeloid cells is highly inducible(47). The protein is composed of 3 distinct domains: the N terminal pyrin domain, the central nucleotide binding domain (NBD), and the C terminal leucine-rich repeats (LRRs).

NLRP3 responds to a wide range of DAMPs and PAMPs, including bacterial and viral nucleic acids(48, 49), intracellular pathogens; ATP(50), uric acid(51, 52), β-amyloid(53), hyaluronan and heparin sulfate(54); silica(55–57), asbestos(56), cholesterol(58, 59) and alum crystals(57, 60); metabolites associated with type 2 diabetes such as ceramide, saturated fatty acids, islet amyloid peptides(61–63); hemozoin(64) byproduct from blood-feeding parasites that cause malaria; and cyclic dinucleotides (65). Activation of the NLRP3 inflammasome requires two signals and is controlled at transcriptional and post-translational levels (Figure 3). The first signal, also referred to as the priming signal, is the induction of the toll-like receptor (TLR)/nuclear factor (NF)-κB pathway to upregulate the expression of NLRP3(50)and pro-IL-1β(66). Signal 2 is transduced by various PAMPs and DAMPs to activate the functional NLRP3 inflammasome by initiating assembly of a multi-protein

complex consisting of NLRP3, the adaptor protein ASC, and pro-caspase-1(67). Association of NLRP3 with ASC is required for recruitment of pro-caspase-1(68). ASC utilizes its CARD domain to recruit pro-caspase-1 via homotypic CARD-CARD interactions. In the inflammasome complex, the inactive pro-caspase-1 undergoes autocatalytic cleavage to form active caspase-1. Caspase-1 in turn can cleave and activate multiple substrates ranging from chaperones, cytoskeletal and translation machinery, glycolysis and immune proteins such as the proinflammatory cytokines IL-1β and IL-18(69–71). While NLRP3 is known to respond to several PAMPs and DAMPs, evidence for direct binding of any ligand to NLRP3 remains indeterminate. One model is that NLRP3 activation is mediated via secondary intermediates such as potassium efflux(50), change in cell volume(72), calcium mobilization via the calcium channels TRPM2 or CASR(73–75), osmolarity changes(76), reactive oxygen species (ROS)(77) or mitochondrial DNA release(78, 79).

NLRP3 is associated with autoinflammatory, metabolic and autoimmune diseases(80–84)[80–84]. Autoinflammatory diseases will be discussed here. Autosomal dominant mutations in NLRP3 lead to three CAPS autoinflammatory syndromes in humans, ranging from the mild FCAS, to the intermediate MWS and the more severe NOMID/CINCA syndromes. Fever, urticaria-like rash and varying degrees of arthropathy and neurological manifestations are present in all three syndromes(43, 85–87). FCAS consists of the mildest symptoms including cold-induced urticaria and mild arthralgia. MWS is intermediate with non-cold induced spontaneous urticaria, sensorineural hearing loss, arthralgia, and in some cases renal amyloidosis. CINCA is the most severe with spontaneous urticaria, deforming arthropathy, sensorineural hearing loss, and chronic aseptic meningitis. All CAPS are characterized by increased levels of IL-1β in the absence of infection and can be successfully treated with inhibitors of IL-1β(88–90). Gain-of-function mutations of NLRP3 enhance IL-1β secretion even in the absence of a stimulus *in vitro*(15).

Major advances regarding NLRP3 inflammasome formation have been gleaned from elegant biochemical and cryo-electron microscopy (EM) studies. Biochemical studies showed that the pyrin domain is an evolutionary conserved structure that can cause ASC to form a prion-like filament, which then activates downstream effector caspases. Cryo-EM(91) results similarly support a model in which activated NLRP3 forms an oligomeric platform where the pyrin domain nucleates ASC via the latter's pyrin domain to form a filamentous structure. The CARD domain of ASC then interacts with the CARD domain of caspase-1 causing proximal caspase-1 to undergo auto-cleavage(92). As is noted below, in addition to NLRP3, AIM2 inflammasome activation by DNA binding also undergoes the same process.

NLRC4 and *NAIP*

NLR family, Caspase Recruitment domain containing 4 (NLRC4, also IPAF) is coupled to NAIP proteins (see later) that act as cytosolic receptors for PAMPs produced by flagellated pathogens, such as *Salmonella typhimurium*(68, 93) and *Legionella pneumophila*(94), and non-flagellated pathogens, such as *Shigella flexneri* and *Pseudomonas aeruginosa*(95). NLRC4 forms a homo-oligomeric inflammasome with caspase-1(68). The crystal structure of NLRC4 suggested that it remains in an autoinhibited state when unstimulated with ADP

bound to its central NBD. Disruption of this ADP-NBD interaction leads to constitutive activation of NLRC4(96).

NLRC4 is highly expressed in human brain, bone marrow and the THP-1 human monocytic cell line(97). Initial characterization of NLRC4 in human tissues and cell lines demonstrated its direct association with the CARD domain of pro-caspase-1 through CARD-CARD interactions(97, 98). This interaction can cause autocatalytic processing of pro-caspase-1 to caspase-1(97). A constitutively active NLRC4 causes autocatalytic processing of pro-caspase-1, generating caspase-1-dependent apoptosis in transfected cells(97). In macrophages, activation of the NLRC4 inflammasome by cytoplasmic flagellin leads to caspase-1 activation and IL-1β release(68, 93, 99). It is expected that NLRC4 interacts directly with pro-caspase-1 through CARD-CARD interactions. Although direct interaction of ASC with NLRC4 has not yet been demonstrated, *Asc*-deficient macrophages show defective caspase-1 activation and IL-1β release in response to *Salmonella*, *Shigella* and *Pseudomonas* infections, indicating that ASC can enhance the function of NLRC4(68, 95, 100).

NLR apoptosis-inhibitory proteins (NAIP, formerly called BIRC1, NLRB1) represent prime examples of NLRs that recognize their cognate ligands, which promotes NLRC4 recruitment to form a multimeric inflammasome complex(101–103). NAIP is expressed in peripheral blood mononuclear cells and macrophages. While the human genome has one *NAIP* gene that is functionally similar to murine *Naip1*(101, 104), there are 7 paralogs of NAIP in mice (Naip1-7), presumably to provide specificity of binding to a number of bacterial ligands.

Based on co-immunoprecipitation studies utilizing over-expressed *NAIP* and *NLRC4*, these two proteins were shown to associate, suggesting the potential for co-engagement in the same caspase-1 activating inflammasome(105). NAIP5 inflammasome activation has been reported in response to the C-terminus of flagellin after *Legionella pneumophila* infection(106). Transduction of macrophages with the C-terminal 35 amino acid fragment of flagellin leads to NAIP5-dependent cell death, while full length flagellin induces NAIP5-independent, NLRC4-dependent cell death and IL-1β release. Since NAIP5 does not have a caspase domain, it requires NLRC4 to activate pro-caspase-1. This suggests a mechanism for differential sensing of bacterial components where NAIP5 appears to possess NLRC4-dependent and -independent functions(106).

A recent study by Tenthorey et al. utilized a panel of chimeric NAIP molecules and identified the central NBD domain, rather than the expected LRR domain, to be associated with bacterial ligand binding(107). Moreover, ligand binding is essential for oligomerization of NAIP monomers into an inflammasome. In addition to NAIP5, NAIP6 can also recognize flagellin(102). In contrast, NAIP1 and 2 recognize bacterial type 3 secretory system needle protein and rod protein, respectively, but do not recognize flagellin. As a genetic test, mice with specific deletions in *Naip1* and *Naip2* provided biologic evidence for this specificity in mediating bacterial clearance(102, 108, 109).

Similar to NLRP3 and AIM2 (see below), cryo-EM has shed light on the assembly of the NLRC4/NAIP inflammasome. A contrasting model has emerged where ligand (PrgJ)-bound

NAIP is the initiating effector, but only one activated NAIP2 is necessary to cause the activation of NLRC4 protein that undergoes a dramatic conformational change in the exposure of its catalytic surface to activate another NLRC4, eventually forming a wheel-like configuration. This wheel-like platform associates with caspase-1 to cause the autocatalytic cleavage of caspase-1(110–112). In this model, ASC does not play a role since the CARD-CARD domain interaction necessary for the final activation step is mediated through NLRC4 and caspase-1.

NAIP and NLRC4 also have roles that are distinct from the inflammasome and myeloid cells. For example, epithelium-intrinsic functions of this protein pair are associated with restriction of *Salmonella* proliferation in the gut epithelium, independent of inflammasome products(113). NAIP/NLRC4 is also known to inhibit caspase-3 and caspase-7 mediated pathways(114). NAIP interacts with pro-caspase-9 via its BIR3 domain. This association prevents the autoproteolysis of caspase-9 in the apoptosome complex, preventing caspase-9-mediated cell death(115). The NBD and BIR domains of NAIP are required for inhibition of pro-caspase-9 autoproteolysis. Human NAIP is involved in bacterial sensing and inducing pyroptosis in human macrophages and epithelial cells(116).

In 1995, two groups reported deletion mutants of the *Naip* gene in patients with spinal muscular atrophy(117, 118). Since then, multiple reports in a number of countries have shown that deletions in *Naip* represent one of the most frequent and consistent genomic changes associated with spinal muscular dystrophy and positively correlates with clinical severity of this disease(119). The molecular basis for this disease association remains to be elucidated. More recently, a mutation in the NBD domain in NLRC4 was described that causes a gain-of-function phenotype that increases inflammasome activation and recurrent macrophage activation syndrome(120).

NLRP6

NLRP6 (formerly, PYPAF5) plays a role in impeding clearance of both Gram positive and negative bacterial infections. Overexpression of ASC with NLRP6 leads to enhanced caspase-1 activation(121), suggesting that it serves an inflammasome function. Structurally, NLRP6 resembles NLRP3, with an N-terminal pyrin domain, a central NOD domain and C-terminal LRRs. NLRP6 is expressed in myeloid cells such as granulocytes, dendritic cells and macrophages; is found in CD4 and CD8 T cells(122–126); and is activated during development by PPAR-γ in intestinal epithelium(127).

The majority of studies have found that NLRP6 protects against experimental colitis and colitis-associated tumorigenesis(125, 128) and its function in monocytes contributes to this protective outcome(129). However, divergent mechanisms have been proposed to account for this activity. An analysis of the association between NLRP6 and the microbiome suggests that *Nlrp6* deletion in mice causes dysbiosis attributed to reduced IL-18 which then causes expanded pathobiont bacteria Bacteroides (*Prevotellaceae*) and TM7 microbiota(128). Reciprocally, the presence of the microbiota enhances caspase-1 maturation that is dependent on NLRP6 control(130). However, other reports indicate alternative roles for NLRP6. It has been implicated in the control of intestinal epithelium renewal(126) to preserve the epithelial barrier as a checkpoint regulator of NF-κB/MAPK

pathways(124) or as a positive regulator of interferon-induced responses (i.e. ISGs) during viral infection(131). In addition, *NLRP6* deficiency has been found to cause defective autophagy in goblet cells and reduced mucus secretion, thus impeding pathogen clearance(132). A separate report also showed a similar dependency of goblet cell mucus secretion on NLRP6 and caspase-1/11, but not on IL-1/IL-18(133). Precisely how caspase-1/11 are involved is unclear.

NLRC5, NLRP7 and *NLRP12*

NLRC5, NLRP7 and NLRP12 represent three NLRs which have other functions, but also have been reported to mediate inflammasome function. While the reported function of NLRC5 is to regulate class I MHC gene transcription, studies in human macrophage lines or primary monocytic cells indicated that it also mediates inflammasome activation in a similar fashion as NLRP3 and associates with NLRP3(7). Similarly, rhinovirus induces NLRP3- and NLRC5-dependent inflammasome activation in bronchial cells(134). In *Nlrc5* deficient mice, Nlrp3 inflammasome is partially impaired, hinting at the intersection of these two factors(135).

NLRP7 consists of an N-terminal pyrin domain, followed by a NBD domain and C-terminal LRRs. Structural analysis of the pyrin domain from NLRP7 indicated that it possesses a six α-helix bundle death domain fold and forms a strong hydrophobic cluster upon pyrin-pyrin interactions(136). Khare et al. demonstrated the formation of a NLRP7-containing inflammasome in response to microbial lipopeptides in human macrophages(137). Activation of NLRP7 promoted ASC-dependent caspase-1 activation, IL-1β and IL-18 maturation and restriction of intracellular bacterial replication, but not caspase-1-independent secretion of the pro-inflammatory cytokines IL-6 and tumor necrosis factor-α. Radian et al. utilized the THP-1 monocytic cell line expressing a mutated Walker A motif to show defective NLRP7 inflammasome activation, thus suggesting that the NBD of NLRP7 is responsible for ATP binding and ATPase activity(138). This mutant cell line also showed defective IL-1β release and pyroptosis in response to acylated lipopeptides and *S. aureus* infection.

NLRP7 also has alternate functions outside of myeloid cells and is highly expressed in MI and MII oocytes. Mutations in the maternal gene *Nlrp7* are associated with biparental hydatidiform mole (HYDM1) in a number of patient cohorts which is characterized by abnormal growth of the placenta and lack of proper embryonic development(139). To identify the molecular mechanism associated with HYDM1, Singer et al. utilized a yeast two-hybrid screen against an ovarian library with NLRP7 as the bait. This approach led to the identification of the transcriptional repressor ZBTB16 as an interacting protein of NLRP7(140). This interaction was further verified in mammalian cells by immunoprecipitation and confocal microscopy; however, a clear mechanism for the molecular events leading to HYDM1 remains unknown.

NLRP12 (formerly called Monarch, PYPAF7, CLR19.3) was one of the first NLRs reported to be a negative regulator of inflammation via suppression of NF-κB signaling(141, 142). NLRP12 protein consists of an N-terminal pyrin domain, a central NBD, and a C-terminal domain composed of at least 12 LRRs(143). Initial studies of NLRP12 utilizing

overexpression systems suggested that it forms an inflammasome with ASC(144, 145). Additional research points to selective activation of the NLRP12 inflammasome by malaria and *Yersinia*(146, 147). However, aside from inflammasome activation, NLRP12 has prominent functions associated with inhibition of cytokine and inflammatory responses. At one level it induces proteasome-mediated degradation of NF-κB inducing kinase (NIK), leading to the suppression of the non-canonical NF-κB pathway and reduced expression of p52-dependent genes *Ccr4, Cxcl12* and *Cxcl13*(141). Two reports confirmed these data by using *Nlrp12*$^{-/-}$ mice in the azoxymethane chemically-induced colorectal cancer model with the inflammatory agent dextran sodium sulfate (AOM-DSS). These reports congruently found that ablation of NLRP12 increases NF-κB canonical and non-canonical pathways, increases ERK phosphorylation in innate immune cells as well as in non-hematopoietic cells in the tumor model, and enhances proinflammatory cytokines and chemokines typically known to promote tumorigenesis(148),(149). NLRP12 also attenuates host response to Salmonella(150); however, this activity may be pathogen specific, in that *Nlrp12*$^{-/-}$ mice exhibited normal host response to other bacteria(151).

Mutations in *Nlrp12* lead to Guadeloupe Variant Periodic Fever Syndrome. In this syndrome, the following alterations were identified: two missense mutations within the *Nlrp12* gene, nonsense mutation causing truncation within the NBD domain of the protein and deletion mutation leading to loss of the C-terminal LRRs. Both missense mutations caused reduced activity in the suppression of NF-κB signaling by NLRP12, while the NBD mutation caused a more significant impact on normal NLRP12-induced NF-κB signaling as compared to the LRR mutation. Since the symptoms are similar to FCAS, this syndrome is referred to as FCAS2. Individuals with this syndrome present with cold-induced heterogeneous symptoms including fever, arthralgia, myalgia, sensorineural hearing loss, aphthous ulcers and lymphadenopathy(152).

AIM2

In addition to inflammasome NLRs, AIM2 (Absent in Melanoma 2) is a DNA sensor that activates the inflammasome(153–156). AIM2, an interferon-inducible gene also known as PYHIN4, was identified while screening tumor suppressor genes associated with melanoma(157). The AIM2 protein consists of an N-terminal pyrin domain, mediating homotypic interactions with ASC, and a C-terminal HIN-200 domain for DNA binding. AIM2 can associate into ASC specks to form a novel inflammasome platform inducing activation of ASC-mediated apoptotic and pyroptotic cell death pathways during host response to bacterial DNA such as from *F. tularensis*(153, 155, 157–159).

The crystal structure characterization of AIM2 has provided insight into interactions important for AIM2 auto-inhibition and inflammasome assembly(160). AIM2 inflammasome-mediated and non-classical IL-1β secretion induced by LC-3 autophagy are linked via the microtubule-associated protein EB-1(161). AIM2 provides host defense against both cytosolic bacterial and viral pathogens, such as *Francisella tularensis*, *Listeria monocytogenes* and *Mycobacterium tuberculosis*(162–164). AIM2 also contributes to inflammation in response to bacterial infection in the brain(165). Alternatively, investigation has also shown AIM2 to impede cell survival pathways that promote tumor growth(166–

168). In the case of colorectal cancer, reduction or lack of expression of AIM2 is positively correlated with poor outcome(166). Two recent papers indicate that this role of AIM2 is inflammasome-independent and is due to the negative regulation by AIM2 of proliferative signals such as Akt and c-myc signaling(166, 168). AIM2 is also protective in the case of breast cancer where it prevents MCF-7 breast cancer cell growth *in vitro* and tumor growth *in vivo*(169).

Non-Canonical Inflammasomes

Aside from the activation of caspase-1 which is referred to as the canonical inflammasome pathway, a non-canonical pathway leading to caspase-11 maturation was first described by Kayagaki et al. who showed that this process is dependent on NLRP3 and ASC(170). Later, caspase-11 was shown to be activated by cytosolic LPS derived from Gram negative bacteria that reside in the cytosol, thereby engaging in the protection of mice against infection by other LPS producing bacteria(171, 172). Thus, while TLR4 mediates host response to extracellular LPS, the NLRP3-dependent caspase-11 pathway mediates host response to cytosolic LPS. The cytosolic presence of LPS is a crucial step, as *Salmonella* which reside in a vacuole does not elicit a caspase-11 response. In turn the expression of caspase-11 is activated by STAT1 downstream of type I or type II interferon. Others showed that caspase-11 is an intracellular receptor of LPS(173). However, caspase-11 also binds to endogenous ligand-oxidized phospholipids to elicit inflammasome-dependent activities(174). More recently, a caspase-11 substrate, gasdermin D, was identified by differential genetic screening strategies, to be important as an effector of pyroptosis and NLRP3-dependent inflammasome activation(175, 176).

In addition, to the above mentioned non-canonical pathway, an unconventional one step pathway of inflammasome activation exists in human monocytes in response to LPS alone. This pathway requires Syk activity and Ca^{2+} flux mediated by internalization of the CD14/TLR4 complex. Moreover, caspase-4 and caspase-5 have been shown to mediate IL-1α and IL-1β release from human monocytes after LPS stimulation(177).

Inflammasome NLRs in Cancers

In addition to the disease associations described above, the association of chronic inflammation with cancer is well established with chronic inflammation contributing to a tumor-promoting microenvironment. The following is not intended to be an exhaustive review of the field, but rather is presented to highlight the studies of NLRs and their roles in cancer. For example, the NLRP3 inflammasome remains the most investigated inflammasome with regard to cancer. Several groups have demonstrated the susceptibility of *Nlrp3* and *Casp1* deficient mice to dextran sulfate sodium (DSS)-induced colitis in a model of human ulcerative colitis. Defective inflammasome activation leads to loss of epithelial integrity, enhances leukocyte infiltration and increases chemokine expression in $Nlrp3^{-/-}$ and $Casp1^{-/-}$ mice, leading to increased mortality(178). These results were supported by Zaki et al., who showed NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer, with NLRP3 inflammasome-dependent IL-18 production protecting against colorectal tumorigenesis(179). Another group showed that the

suppressive impact of NLRP3 on colorectal cancer could be attributed to its enhancement of IL-18 which then activates natural killer cells(180). However, the protective or aggravating function of NLRP3 may be dependent on the severity of disease or factors in the local environment. The (181)NLRP3 inflammasome also appears to play a central role in the pathology of melanomas, gastric cancer and hepatocellular carcinoma(181). The NLRP3 inflammasome is constitutively expressed in human melanoma cells(182, 183). In the case of gastric cancer, *Mycoplasma hyorhinis* was shown to promote tumor development via NLRP3 inflammasome activation(184). Interestingly, IL-1β, but not IL-18, released from macrophages treated with *M. hyorhinis* promotes cell migration and invasion to exacerbate gastric cancer. The expression of NLRP3 inflammasome is down-regulated in hepatic parenchymal cells in hepatocellular carcinoma(185). Loss of NLRP3 inflammasome activation positively correlates with a higher pathological grade in hepatocellular carcinogenesis.

NLRP3 inflammasome activation has also been implicated in adaptive immune responses to cancer vaccines(186). The NLRP3 inflammasome is activated during chemotherapy. Dying tumor cells release ATP that is sensed by the $P2X_7$ receptors of dendritic cells leading to NLRP3 inflammasome activation. However when anti-tumor responses elicited by dendritic cell vaccination was tested, NLRP3 expression was found to be upregulated in tumor-associated myeloid derived suppressor cells (MDSCs), thus suppressing anti-tumor response(187). *Nlrp3*$^{-/-}$ mice have fewer MDSCs accumulating at the tumor site and increased survival upon dendritic cell vaccination. Since this research focused on different adaptive immune cell populations, the differences may be attributable to differences in tumor cell types, in vaccine formulation or in stimuli for NLRP3 inflammasome activation. Increased IL-1β secretion in the tumor microenvironment has also been linked to promotion of inflammation, early angiogenic response, as well as tumor induction and progression(188, 189).

Additional evidence has linked other inflammasomes to cancer. For instance, Hu et al. showed that regulation of inflammation-induced tumorigenesis is mediated by NLRC4 and caspase-1(190). In the AOM-DSS inflammation-induced colorectal cancer model, *Casp1*$^{-/-}$ and *Nlrc4*$^{-/-}$ mice exhibited increased tumor load and number per mice. Caspase-1 and NLRC4 are relatively highly expressed in both colonic epithelial cells and $CD45^+$ hematopoietic cells in the colon. In contrast, NLRP3 expression is primarily restricted to the hematopoietic compartment. These results concluded that an intrinsic epithelial cell effect exacerbates tumorigenesis in the absence of caspase-1 or NLRC4 activity.

Multiple associations of NAIP with cancers have been noted. NAIP expression is significantly elevated in malignantly transformed oral squamous cell carcinomas(191). The *Naip* allele is methylated in normal oral mucosa tissues. NAIP expression is increased in breast cancer(192) and is associated with an unfavorable prognosis. In the case of prostate cancer, several inhibitor of apoptosis protein members including NAIP are increased(193).

Linkage of NLRP6 to cancer has been derived from the study of mouse models of colon cancer. For example, Chen et al. established an association of NLRP6 with a colon cancer model, when they showed that *Nlrp6* deficient mice are more susceptible to DSS-induced

colitis and colitis-associated colon tumorigenesis as compared to wild type controls(125). NLRP6 controls epithelial self-renewal and colorectal carcinogenesis upon injury due to DSS.

Lastly, studies of the adaptor ASC have demonstrated a role in various types of cancers. ASC is overexpressed in several tumors, triggering apoptosis and formation of ASC specks. Studies have shown methylation-associated silencing of ASC across many cancer types(194). However, the mechanisms underlying regulation of ASC silencing or overexpression remain largely undetermined. ASC is inactivated in almost 40% of breast cancers(195). Yokoyama et al. supported these findings by showing ASC methylation present in colorectal cancer tissues(196). Histone deacetylation of the ASC gene is also seen in ovarian cancer. Additionally, aberrant methylation and inactivation of ASC has been seen in glioblastoma, prostate cancer, lung cancer, hepatocellular carcinoma and melanoma(197–199). Liu et al. identified a dual role of ASC in human melanoma tumorigenesis with ASC expression in metastatic melanoma down-regulated as compared to levels in primary melanoma(200). This reveals a complex role played by ASC in regulating cell proliferation. ASC may act as a potential modulator of inflammatory responses by coordinating the activity of NLRs and cytokine activating caspases in mammalian cells.

Inflammasome NLRs in Other Diseases

Above, we discussed the genetic and expression correlations of specific inflammasome genes to various diseases. Here, we intend to highlight where the inflammasome is implicated in other autoimmune and inflammatory diseases. In the case of Alzheimer's disease, caspase-1 expression was elevated in brain samples from Alzheimer's patients as well as from mice carrying mutations associated with familial Alzheimer's disease. Interestingly, mice lacking *Nlrp3* or *Casp1* showed less inflammasome activation and more protection from poor clinical outcomes associated with neuroinflammatory disease(201). It was found that phagocytosis of the β–amyloid protein by human microglia can activate the NLRP3 inflammasome and cause IL-1β release(53). This NLRP3 activation appears to be stimulated with lysosomal destabilization and subsequent release of cathepsin B caused by β-amyloid phagocytosis. The NLRP3 inflammasome also plays a significant role in the autoimmune demyelinating disease model of multiple sclerosis (MS) where experimental *Nlrp3*$^{-/-}$, *Casp1*$^{-/-}$ and *Il18*$^{-/-}$ mice displayed delayed demyelination(202, 203). Moreover, the efficacy of IFN-β in an EAE model of MS was dependent on NLRP3 activity(204). Lastly, observations point to a link between inflammasome and the autoimmune disease systemic lupus erythematosus (SLE). Leukocytes from SLE patients have increased AIM2 expression, even though there is no direct correlation between AIM2 expression and SLE disease activity(205). Similarly, in a mouse model of lupus, both IL-1β and IL-18 are important for disease progression, suggesting a possible inflammasome link(206).

Conclusions

The inflammasome has been a robust field of intensive investigation, uncovering significant revelations of an important family of regulators of health and disease. However, multiple questions remain unaddressed: the identity of ligands for several NLRs, the mechanism(s) of

ligand binding, the specific signaling pathways for regulation, cell-specific regulation of function in normal as well as in diseased hosts. Moreover, functions of NLRs beyond their roles in immunity remain largely unexplored. Discoveries emerging from investigating NLR biology promise to provide key insights into key pathways regulating immunity, inflammation and homeostasis.

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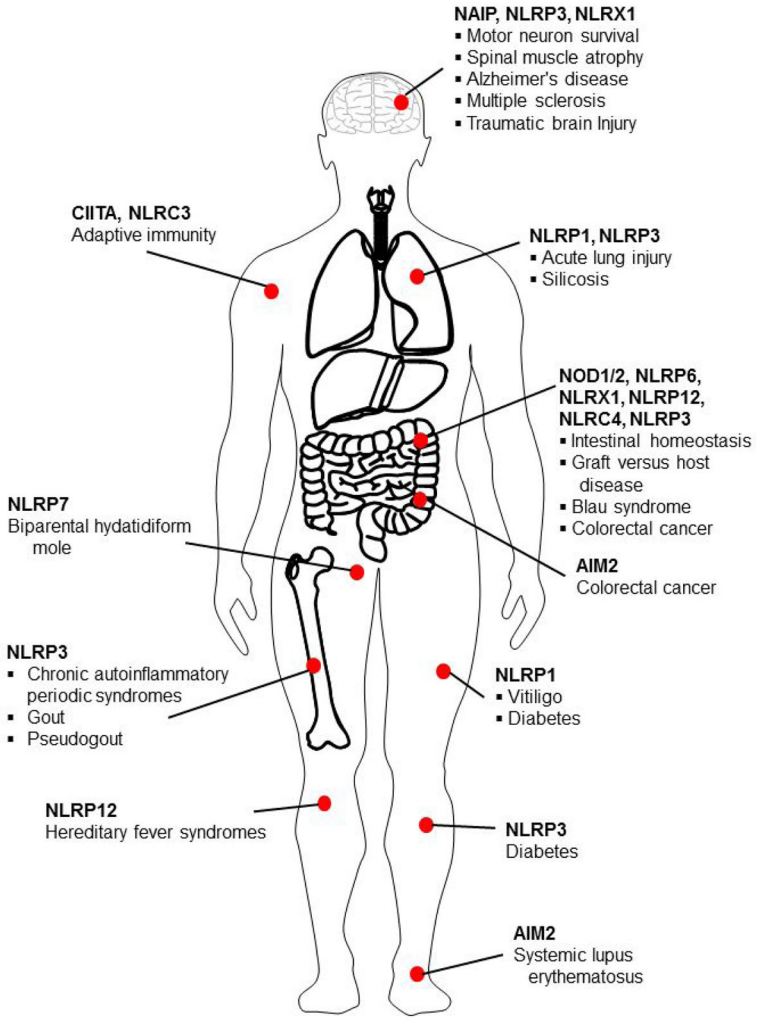

Figure 1. NLRs function in healthy and dysregulated disease states in the human body

NLRs recognized to be involved in various healthy or disease states are shown.

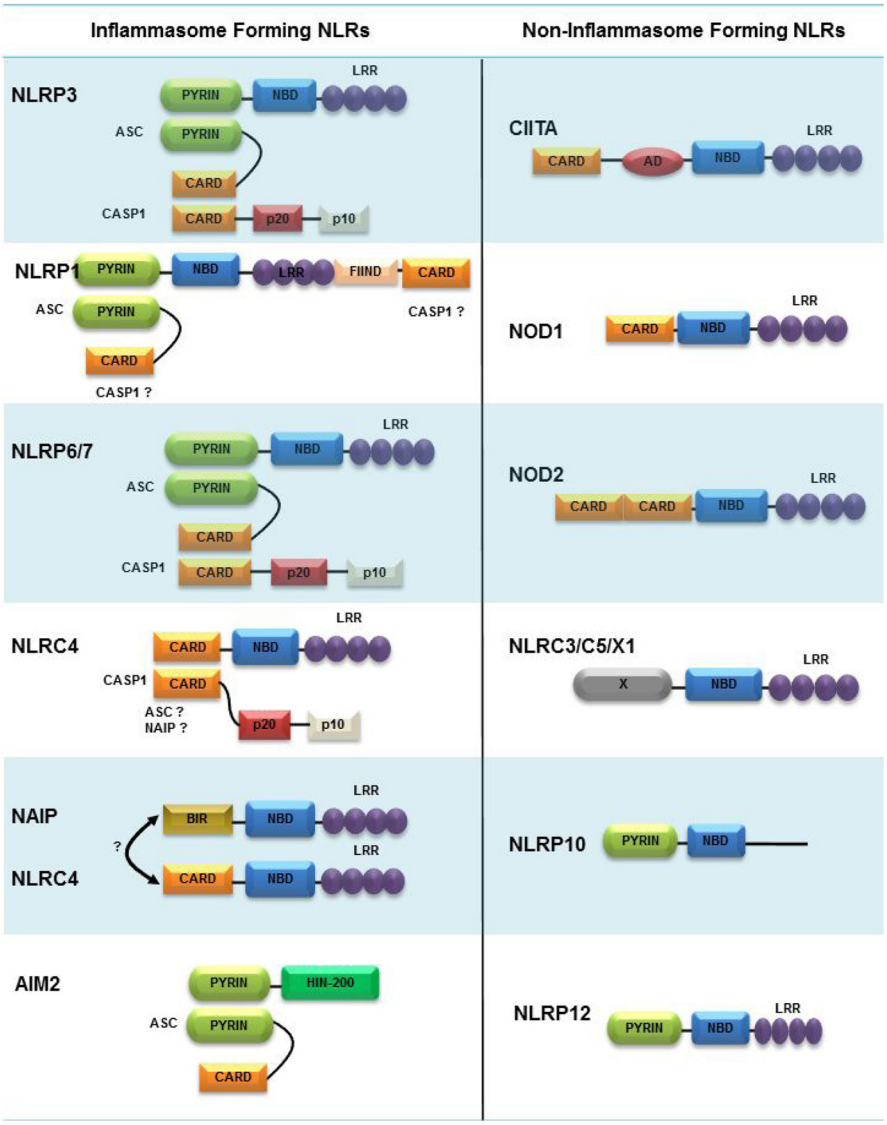

Figure 2. NLRs have a conserved tripartite structure and some form inflammasomes

NLRs have a conserved tripartite structure with an N-terminal effector domain, a central nucleotide binding domain (NBD) and C-terminal leucine rich repeats (LRR). The effector domains of NLRs may include: acidic transactivation domain (AD), baculoviral inhibitory repeat (BIR)-like domain, caspase recruitment domain (CARD), pyrin domain or domain of unknown function (X). In general, NLRP1, NLRP3, NLRP6, NLRP7, NLRC4, NAIP and AIM2 are known to form inflammasomes, while CIITA, NOD1, NOD2, NLRC3, NLRC5, NLRX1, NLRP10 and NLRP12 do not.

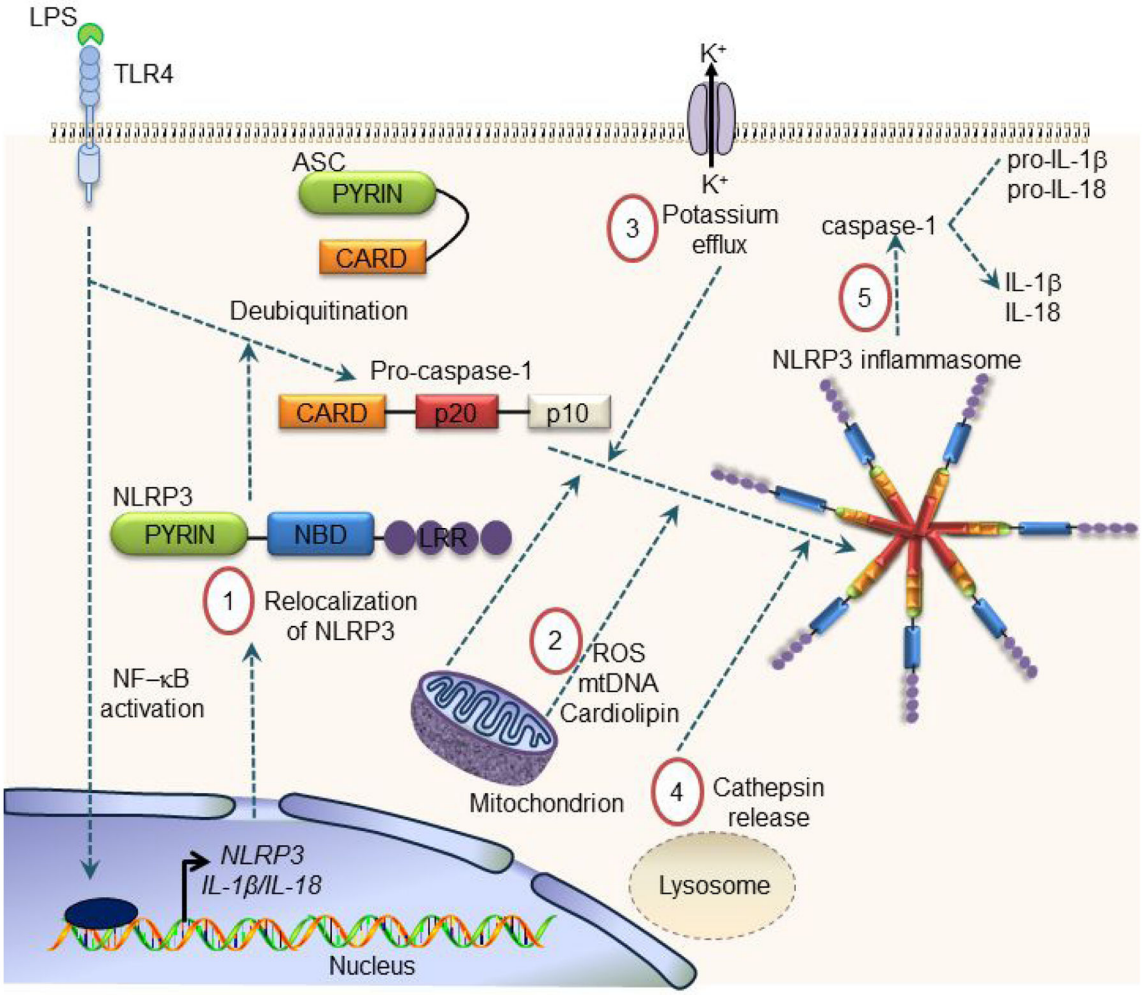

Figure 3. NLRP3 inflammasome is activated in response to multiple signals

The NLRP3 inflammasome is activated in response to several PAMPs and DAMPs including, but not limited to nucleic acids, lipopolysaccharide (LPS), lipooligosaccharide (LOS), muramyl dipeptide (MDP), ATP, uric acid crystals, hyaluronan sulfate, heparin sulfate, β-amyloid, asbestos and silica. NLRP3 inflammasome formation is a two signal process. The first signal involves priming: LPS engagement of TLR4 leads to NF-κB activation causing increased expression of NLRP3 and IL-1β (Step-1). NLRP3 forms a multi-protein inflammasome complex with the adaptor apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1. NLRP3 and ASC undergo deubiquitination prior to inflammasome assembly. After priming, canonical inflammasome activation requires a second signal. The second signal may be the release of mitochondrial factors into the cytoplasm such as ROS, mitochondrial DNA (mtDNA), or cardiolipin (Step-2), potassium efflux (Step-3) or lysosomal cathepsin release (Step-4). After receiving the second signal, NLRP3 recruits ASC via pyrin-pyrin interactions. ASC utilizes its CARD domain to recruit pro-caspase-1 by CARD-CARD interactions, thus leading to processing of pro-caspase-1 to active caspase-1 (Step-5). In turn, caspase-1 is critical for the processing

and release of IL-1β and IL-18. We gratefully acknowledge the support of National Institutes of Health funding (U19-AI109965 and U19-AI067798) to JPYT and WJB.