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NLRP12 in innate immunity and inflammation

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ABSTRACT

Nucleotide-binding leucine-rich repeat-containing proteins, or NOD-like receptors (NLRs), are intracellular innate immune sensors that can regulate several signaling pathways, including MyD88- and TRIF-dependent pathways. In addition to these regulatory roles, some NLRs can assemble into multimeric protein complexes known as inflammasomes. NLRP12 is a member of the NLR family that contains an N-terminal pyrin domain, a central nucleotide-binding domain, and a C-terminal leucine-rich repeat. It has been shown to play a role in forming an inflammasome in response to specific infections, and it can also function as a regulator of inflammatory signaling. During *Yersinia pestis* or *Plasmodium chabaudi* infection, NLRP12 induces the release of the inflammasome-dependent cytokines IL-1β and IL-18. These NLRP12-dependent cytokines confer protection against severe infections caused by these pathogens. Conversely, during infection with *Salmonella enterica* serovar Typhimurium, vesicular stomatitis virus, *Klebsiella pneumoniae*, or *Mycobacterium tuberculosis,* and in colonic tumorigenesis, NLRP12 acts as a negative regulator of the NFκB and MAPK signaling pathways. NLRP12 also negatively regulates canonical and non-canonical signaling in T cells and causes exacerbated autoimmune diseases. Furthermore, NLRP12 acts as a central component in maintaining intestinal inflammation and gut homeostasis. Therefore, the ability of NLRP12 to function as an inflammasome or as a negative regulator is context-dependent. In this review, we provide an overview of the NLR family members and summarize recent insights into the roles of NLRP12 as an inflammasome and as a negative regulator.

1. Introduction

Innate immunity acts as the first line of defense against pathogenic and sterile insults. Innate immune cells like monocytes, macrophages, dendritic cells, endothelial cells, and neutrophils, use fixed, germline-encoded pattern recognition receptors (PRRs) to recognize activating stimuli in the host system (Newton and Dixit, 2012; Takeuchi and Akira, 2010; Tuncer et al., 2014). PRRs can detect pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) (Kesavardhana and Kanneganti, 2017; Malik and Kanneganti, 2017). Based on their localization, PRRs are categorized as membrane-bound or cytoplasmic. Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), which are able to sense extracellular pathogens, are membrane-bound and are localized to the plasma membrane and endosomes. Retinoic acid inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding leucine-rich repeat-containing proteins (or NOD-like receptors, NLRs), absent in melanoma 2 (AIM2), and Pyrin are localized in the cytoplasm of the cell and act as surveillance molecules for intracellular microbes, PAMPs, and DAMPs (Fritz et al., 2006; Kanneganti et al., 2006; Meylan et al., 2006; Proell et al., 2008; Tuncer et al., 2014; Werts et al., 2006). These intracellular sensors can be activated when they recognize bacterial components (cell wall molecules, flagellin, inner rod or proteins from the bacterial secretion system), viral proteins, microbial nucleic acid, or microbial toxins. In addition to detecting microbial components, these sensors can also detect cellular components (e.g., ATP) released due to host cell damage or a disbalance in the potassium efflux or the presence of endosome danger signals, such as uric acid crystals (Bauernfeind et al., 2009; Broz and Dixit, 2016; Franchi et al., 2009a; Kesavardhana and Kanneganti, 2017; Man et al., 2017; Muñoz-Planillo et al., 2013). Following the recognition of these various ligands and cellular components, the PRRs are activated and induce a cascade of signaling pathways that can lead to the upregulation or suppression of inflammatory cytokines.

Upon activation, a subset of the PRRs can form a multiprotein complex known as the inflammasome to drive cytokine secretion and cell death. Though inflammasome activation is important in eliminating pathogens from the host, dysregulation leads to diseases such as atherosclerosis, type 2 diabetes, neurodegenerative diseases, cancer,

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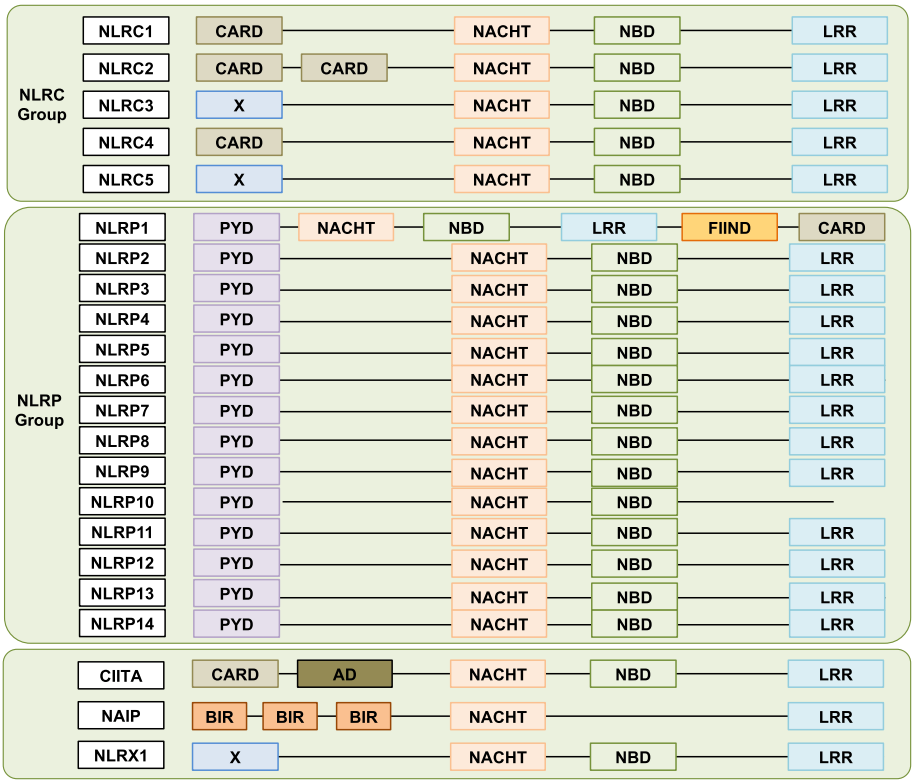

Fig. 1. Schematic representation of NLR family members, including members of the NLRC and NLRP groups. AD, activation domain; BIR, baculovirus inhibitor of apoptosis protein repeat; CARD, caspase recruitment domain; CIITA, class II major histocompatibility complex transactivator; FIIND, function to find domain; LRR, leucine-rich repeats; NACHT, NAIP, CIITA, HET-E, and TP1-containing domain; NBD, nucleotide-binding domain; PYD, pyrin domain.

and auto-inflammatory diseases. Thus, it is very important to fine tune the activation and inhibition of inflammasomes to avoid any accidental damage to the host tissue. Several NLR family members that form inflammasome complexes in response to the PAMPs and DAMPs have been well described, with the most well characterized being NLRP1, NLRP3, and NLRC4. In recent years, additional NLRs, such as NLRC1, NLRC2, NLRC3, NLRC5, NLRP6, NLRP12, and NLRX1, have been shown to play a role as positive or negative regulators of immune signaling. Studies have shown that NLRP6 and NLRP12 have dual functions, and each can function as an inflammasome or as a negative regulator of immune signaling. In this review, we will present an overview of the NLRs and focus on NLRP12 and its functions as an inflammasome and a negative regulator of signaling pathways.

2. The NLRs

The NLR family consists of more than 20 members, and these proteins play diverse roles in innate immunity and inflammation (Fig. 1) (Carneiro et al., 2008; Clay et al., 2014; Harton et al., 2002; Inohara and Nuñez, 2003; Martinon et al., 2009; Proell et al., 2008). NLRs are multi-domain proteins with tripartite architecture which share common structural motifs: they consist of a C-terminal LRR motif, a central NATCH domain that is responsible for ATP-dependent oligomerization, and an N-terminal effector domain that is either a pyrin domain (PYD), a caspase recruitment domain (CARD), or baculovirus inhibitor of apoptosis protein repeat (BIR) domain that links the NLR to downstream signaling molecules (Fig. 1) (Clay et al., 2014; Pinheiro et al., 2011; Proell et al., 2008). However, NLRs are distinct in their domain architecture and function (Cridland et al., 2012; Harton et al., 2002). Several NLRs can undergo a conformational change allowing them to oligomerize and recruit the adaptor protein apoptosis-associated speck-like protein (ASC), which contains a PYD and CARD, to form a large multi-protein complex known as the inflammasome (Karki and Kanneganti, 2019; Kesavardhana and Kanneganti, 2017; Lu et al., 2014; Man et al., 2017; Rathinam and Fitzgerald, 2016; Shaw et al., 2011). Recruitment of ASC and pro–caspase-1 to these sensors then allows autoproteolytic cleavage to form the catalytically active protease caspase-1, which mediates the processing of proinflammatory cytokines (IL-1β and IL-18) and gasdermin D (GSDMD) to their active forms, allowing GSDMD to execute a type of inflammatory cell death called pyroptosis (Broz et al., 2010; Broz and Dixit, 2016; Ding et al., 2016; He et al., 2015; Liu et al., 2016; Shi et al., 2015). Inflammasome sensors have also been implicated in PANoptosis, a unique inflammatory programmed cell death regulated by the PANoptosome, which provides a molecular scaffold that allows for interactions and activation of the machinery required for inflammasome/pyroptosis (such as NLRP3, ASC, caspase-1), apoptosis (caspase-8), and necroptosis (RIPK3/RIPK1) Christgen et al., 2020; Malireddi et al., 2020; Samir et al., 2020; Zheng et al., 2020. The ability of these molecules to interact allows for intricate coregulation between the cell death pathways that had previously been thought to be independent. PANoptosis has been implicated in infectious and autoinflammatory diseases, cancers, and beyond Christgen et al., 2020; Gurung et al., 2016; Karki et al., 2020; Kuriakose et al., 2016; Lukens et al., 2014; Malireddi et al., 2018, 2020, Zheng et al., 2020a, 2020b.

NAIP-NLRC4 inflammasomes assemble in response to bacterial flagellin or rod or needle subunits of the bacterial type III secretion system (T3SS) (Franchi et al., 2009b; Miao et al., 2010, 2006; Poyet et al., 2001; Reyes Ruiz et al., 2017; Zhao et al., 2011). The bacterial ligands do not directly interact with NLRC4; NLRC4 uses NAIPs as sensors upstream of its inflammasome assembly. Both the NAIPs and NLRC4 are transcriptionally regulated by IRF8 (Karki et al., 2018). NAIP1 and NAIP2 sense needle and rod from the T3SS, respectively, and NAIP5 and NAIP6 bind to flagellin (Kofoed and Vance, 2011; Lightfield

et al., 2008; Suzuki et al., 2014; Yang et al., 2013; Zhao et al., 2011).

NLRP1b recognizes anthrax lethal toxin, which is secreted by *Bacillus anthracis*. The lethal toxin cleaves at the N-terminal region of NLRP1b, causing autoproteolytic processing that leads to the activation and assembly of the NLRP1b inflammasome (Boyden and Dietrich, 2006; Chavarría-Smith et al., 2016; Chavarría-Smith and Vance, 2013; Chui et al., 2019; Eldeeb et al., 2019; Levinsohn et al., 2012; Nour et al., 2009; Sandstrom et al., 2019).

NLRP3 can be activated by a diverse array of DAMPs, such as uric acid, silica, alum, asbestos, and endogenous stimuli like ATP, newly synthesized mitochondrial DNA and PAMPs derived from viral, bacterial, fungal, and parasitic pathogens (Franchi et al., 2009a; Kanneganti et al., 2006, 2007; Lamkanfi and Kanneganti, 2010; Man and Kanneganti, 2015; Muñoz-Planillo et al., 2013; Zhong et al., 2018). However, no unified mechanism for NLRP3 inflammasome activation has been identified. It was recently discovered that the DEAD-box family member and helicase, DDX3X, is required for the formation of stress granules and the NLRP3 inflammasome, acting as a molecular switch between cell survival and cell death in response to certain stress signals (Samir et al., 2019). Furthermore, several other mediators like Z-DNA-binding protein 1/DNA-dependent activator of IFN-regulatory factors (ZBP1/DAI), TGF-β-activated kinase 1 (TAK1), Fas-associated death domain (FADD), and Toll or interleukin-1 receptor domain-containing adaptor inducing IFN-β (TRIF) have been shown to regulate NLRP3 inflammasome activation (Gurung et al., 2012, 2014; 2016; Kuriakose et al., 2016; Malireddi et al., 2018).

In addition to these canonical inflammasome-forming NLRs, studies have shown that other NLRs can function as either positive or negative regulators of crucial inflammatory signaling pathways such as NFκB, mitogen-activated protein kinase (MAPK), type I IFN, autophagy, and the generation of reactive oxygen species (ROS) (Anand et al., 2012; Chamaillard et al., 2003; Chen et al., 2019; Cui et al., 2010; Franchi et al., 2009b; Ghimire et al., 2018; Kanneganti et al., 2007; Kobayashi et al., 2005; Meissner et al., 2010; Park et al., 2007; Schneider et al., 2012; Xia et al., 2011; Zhang et al., 2014).

NLRC1 is expressed in various leukocytes and epithelial cells (Strober et al., 2006), whereas NLRC2 is expressed in macrophages, dendritic cells, Paneth cells, keratinocytes, epithelial cells in the lungs, and in the intestine and oral cavity (Franchi et al., 2009b; Ogura et al., 2003, 2001; Tada et al., 2005). These multi-domain proteins consist of one or two CARDs, a centrally located NOD, and several C-terminal LRRs. NLRC1 recognizes peptidoglycan (PGN) fragments containing meso-diaminopimelic acid (meso-DAP) produced by all Gram-negative bacteria such as *Shigella flexneri, Escherichia coli, Chlamydia, Pseudomonas aeruginosa* and *Helicobacter pylori* and some Gram-positive bacteria; alternatively, NLRC2 recognizes muramyl dipeptide (MDP) found in the PGN of both Gram-negative and Gram-positive microbes (Chamaillard et al., 2003; Girardin et al., 2001; Kim et al., 2004; Opitz et al., 2005; Travassos et al., 2005; Watanabe et al., 2011). Upon recognition of bacterial components, NLRC1 and NLRC2 are activated and can directly recruit serine-threonine kinase receptor-interacting protein (RIP)-like interacting CLARP kinase (RICK) via CARD-CARD interactions (Ogura et al., 2001). RICK binds to the NFκB essential modulator (NEMO) and promotes activation of IKKα and IKKβ, which leads to degradation of IκB and the release and translocation of NFκB to the nucleus (Abbott et al., 2004; Hasegawa et al., 2008; Kim et al., 2008; Kobayashi et al., 2005; Park et al., 2007).

NLRC3 is highly expressed in immune cells and consists of a central NOD and a C-terminal LRR domain (Schneider et al., 2012). NLRC3 acts as a negative regulator of signaling pathways that are activated by TLRs and the DNA sensor stimulator of IFN-inducible genes (STING) in response to PAMPs or viral infection (Karki et al., 2016; Li et al., 2019; Schneider et al., 2012; Zhang et al., 2014). During colorectal cancer, NLRC3 mediates protection by associating with PI3K and blocking the activation of AKT kinase, inhibiting mTOR pathways in the epithelial cells of the colon (Karki et al., 2016). Furthermore, NLRC3 regulates cellular proliferation and apoptosis by suppressing c-Myc expression and activating PI3K-AKT targets like FoxO3a and FoxO1 (Karki et al., 2017). NLRC3 has also been shown to be a negative regulator of $CD4^+$ T cell as it limits the activation, proliferation, and downstream IFN-γ and TNF expression in T cells by interfering with NFκB signaling (Hu et al., 2018; Uchimura et al., 2018).

NLRC5 is mostly expressed in bone marrow, lymph nodes, spleen, and in mucosal surfaces like lung, small intestine, colon, and uterus (Benko et al., 2010; Cui et al., 2010; Davis et al., 2011; Kuenzel et al., 2010; Lamkanfi and Kanneganti, 2012). NLRC5 contains a CARD-like domain, a central NOD domain, and a C-terminal LRR region (Cui et al., 2010; Dowds et al., 2003). The role of NLRC5 as a regulator of innate and adaptive immune responses during host defense is controversial. NLRC5 dampens production of proinflammatory cytokines and IFNs in response to viral infection (Benko et al., 2010; Cui et al., 2010). However, other studies have shown that NLRC5 promotes production of type I IFN and proinflammatory cytokines in fibroblasts and in primary human cells during cytomegalovirus or Sendai virus infection (Kuenzel et al., 2010; Neerincx et al., 2010).

NLRX1 is ubiquitously expressed in immune cells and is the only member of the NLR family that has a mitochondrial targeting sequence in its N-terminus (Shaw et al., 2010). NLRX1 inhibits type I IFN production by interacting with mitochondrial antiviral signaling protein (MAVS), RIG-I, and melanoma differentiation-associated protein (MDA5) (Allen et al., 2011; Qin et al., 2017; Xia et al., 2011). Studies have shown that NLRX1 dissociates from TRAF6 and interacts with the IKK complex to downregulate NFκB signaling (Allen et al., 2011; Xia et al., 2011). Furthermore, during Group A *Streptococcus* (GAS) infection, NLRX1 functions as a negative regulator by interacting with the Beclin 1-UVRAG complex, which regulates invasion and autophagy, via its NATCH domain. This interaction inactivates the complex (Aikawa et al., 2018). Although studies have shown NLRX1 to be a negative regulator of innate immunity, in human hepatocytes NLRX1 acts as a positive regulator and enhances antiviral responses by restricting the replication of Hepatitis A virus and Hepatitis C virus (Feng et al., 2017). Additionally, during Sendai virus infection, NLRX1 positively regulates interferon regulatory factor 1 (IRF1) signaling but suppresses IRF3 dimerization, showing that NLRX1 can act both as a positive and negative regulator; the functional consequences can be dependent on the cell type or pathogen involved (Feng et al., 2017).

NLRP6 is highly expressed in liver, lung, kidney, and small and large intestine (Chen et al., 2011; Elinav et al., 2011; Normand et al., 2011). Though the nature of the formation of an NLRP6 inflammasome and its agonist remain unclear, NLRP6 has been shown to recognize bacterial metabolites, bacterial lipoteichoic acid (LTA), and viral RNA (Hara et al., 2018; Levy et al., 2015). Recently it was found that LPS and ATP stimulation can activate NLRP6, causing it to form a homodimer and self-assemble into a linear platform (Leng et al., 2020). LTA binding activates NLRP6, leading to recruitment and processing of caspase-11 using ASC as an adaptor (Hara et al., 2018). Using filamentous and crystal structures, it was recently discovered that pyrin filaments from NLRP6 are critical for recruiting the PYD of ASC (Shen et al., 2019). It is thought that NLRP6 activation then leads to the polymerization and activation of ASC, which acts as a platform for the recruitment and activation of caspase-1 (Shen et al., 2019).

NLRP6 is also known to play a role in regulating TLR-induced canonical NFκB and MAPK signaling. The phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and IκB is significantly increased in *Nlrp6*$^{-/-}$ macrophages upon infection with *Listeria monocytogenes* (Anand et al., 2012). Furthermore, levels of NFκB and MAPK-dependent cytokines and chemokines such as TNF, IL-6, and KC are significantly increased, NFκB effector p105 is highly phosphorylated, and translocation of p65 to the nucleus is increased in *Nlrp6*$^{-/-}$ macrophages upon infection with *L. monocytogenes* (Anand et al., 2012). During *Staphylococcus aureus* infection, NLRP6 serves as a negative regulator of neutrophil-mediated host defense (Ghimire et al., 2018).

Table 1
Negative regulatory role of NLRP12.

Model	NLRP12 as a negative regulator of inflammation		
	In vitro	*In vivo*	Reference
Salmonella infection	• Increased expression of IL-6, KC, and TNF mRNA transcripts and proteins in murine *Nlrp12*$^{-/-}$ bone marrow-derived macrophages (BMDMs) infected with *Salmonella*. • Increased phosphorylation of IκBα and ERK in murine *Nlrp12*$^{-/-}$ BMDMs infected with *Salmonella*.	• Increased phosphorylation of IκBα and ERK in the liver of *Nlrp12*$^{-/-}$ mice infected with *Salmonella*.	Zaki et al., 2014
DSS	NA	• Increased IL-6 and TNF levels in CD11b^{+} colonic lamina propria myeloid cells obtained from AOM/DSS-treated *Nlrp12*$^{-/-}$ mice. • Increased production of proinflammatory cytokines such as IL-1β, IL-6, TNF, IL-17, and IL-15 and chemokines such as GCSF, eotaxin, KC, IP-10, MIP-1α, MIP-1β, and MIP2 in the colon of AOM/DSS-treated *Nlrp12*$^{-/-}$ mice. • Increased IκBα, ERK, and STAT3 activation in *Nlrp12*$^{-/-}$ mice treated with AOM/DSS. • Increased NIK activation in the colon of *Nlrp12*$^{-/-}$ mice treated with AOM/DSS. • *Nlrp12*$^{-/-}$ mice are more susceptible to DSS-induced colitis than WT mice. *Nlrp12*$^{-/-}$ mice raised under GF conditions are indistinguishable from GF WT mice during experimental colitis.	Allen et al., 2012; Zaki et al., 2011 Chen et al., 2017
HFD-induced obesity	NA	• *Nlrp12*$^{-/-}$ mice gained weight. • Impaired glucose tolerance and elevated levels of adipose tissue inflammation *Nlrp12*$^{-/-}$ mice.	Truax et al., 2018
DEN-induced HCC	NA	• Increased tumor burden and tumor size in livers of DEN-treated *Nlrp12*$^{-/-}$ mice. • Increased expression of proinflammatory cytokines such as IL-6 and TNF and chemokines such as KC, MIP2, MCP1, and COX2 in the liver of DEN-treated *Nlrp12*$^{-/-}$ mice. • Increased production of proinflammatory cytokines such as IL-6 and TNF and the chemokine KC in the liver of DEN-treated *Nlrp12*$^{-/-}$ mice. • Increased JNK activation in the liver of DEN-treated *Nlrp12*$^{-/-}$ mice. • Increased expression of pro-proliferative molecules such as Myc, Ccnd1, Ccnb1, Survivin, and MKi67 in the liver of DEN-treated *Nlrp12*$^{-/-}$ mice.	Udden et al., 2019
TNF	• Increased activation of NIK in murine *Nlrp12*$^{-/-}$ dendritic cells stimulated with TNF.	NA	Allen et al., 2012
TLR ligands	• Increased activation of IκBα and ERK in murine *Nlrp12*$^{-/-}$ dendritic cells stimulated with Pam3Cys4. • Increased activation of IκBα and ERK in murine *Nlrp12*$^{-/-}$ BMDMs stimulated with LPS, Pam3Cys4, and poly(I:C) in *Nlrp12*$^{-/-}$ BMDMs. • Increased mRNA expression of IL-6, KC, TNF, MIP2, COX2, and NOS2 transcripts in murine *Nlrp12*$^{-/-}$ BMDMs stimulated with LPS. • Increased activation of JNK in murine *Nlrp12*$^{-/-}$ hepatocytes stimulated with LPS. • Increased expression of Ccl2, Cxcl1, Cxcl2, Ccnd1, and Myc in murine *Nlrp12*$^{-/-}$ hepatocytes stimulated with LPS.	• Decreased neutrophil recruitment to the site of inflammation (lungs) in *Nlrp12*$^{-/-}$ mice challenged with LPS. • Decreased vascular leakage into the lungs of *Nlrp12*$^{-/-}$ mice challenged with LPS.	Lich et al., 2007 Allen et al., 2012 Udden et al., 2019 Ulland et al., 2016
Leishmania major infection	• No difference in NFκB, and ERK activation in murine WT and *Nlrp12*$^{-/-}$ bone marrow neutrophils. • Decreased neutrophil migration toward the neutrophil chemokine CXCL1/KC and *L. major* by murine *Nlrp12*$^{-/-}$ bone marrow neutrophils.	NA	Zamoshnikova et al., 2016
VSV infection	• Increased production of TNF and IFN-β in murine *Nlrp12*$^{-/-}$ dendritic cells infected with VSV. • Increased activation of TBK1 and IRF3 in murine *Nlrp12*$^{-/-}$ dendritic cells infected with VSV.	• Increased production of IFN-β in serum and cerebrospinal fluid of *Nlrp12*$^{-/-}$ mice infected with VSV.	Chen et al., 2019
Klebsiella pneumoniae infection	• Increased production of TNF and IL-6 in murine *Nlrp12*$^{-/-}$ dendritic cells infected with *K. pneumoniae*.	NA	Allen et al., 2013
Mycobacterium tuberculosis infection	• Increased production of TNF and IL-6 in murine *Nlrp12*$^{-/-}$ dendritic cells infected with *M. tuberculosis*.	NA	Allen et al., 2013
Brucella abortus infection	• Increased production of IL-12 in murine *Nlrp12*$^{-/-}$ BMDMs infected with *B. abortus*. • Increased activation of p65, JNK, and p38 in murine *Nlrp12*$^{-/-}$ BMDMs infected with *B. abortus*.	• Increased circulating IL-1β and IFN-γ in *Nlrp12*$^{-/-}$ mice infected with *B. abortus* S2308.	Silveira et al., 2017
Porphyromonas gingivalis LPS	• Increased expression of iNOS in *Nlrp12* silenced RAW264.7 murine macrophages stimulated with *P. gingivalis* LPS.	NA	Pudla et al., 2019

(*continued on next page*)

Table 1 (*continued*)

Model	NLRP12 as a negative regulator of inflammation		
	In vitro	*In vivo*	Reference
	• Increased production of TNF in *Nlrp12* silenced RAW264.7 murine macrophages stimulated with *P. gingivalis* LPS.		
Francisella tularensis LVS infection	NA	• Decreased neutrophil recruitment at the site of infection in *Nlrp12*$^{-/-}$ mice. • Increased *F. tularensis LVS* burden in *Nlrp12*$^{-/-}$ mice.	Ulland et al., 2016
Staphylococcus aureus infection	NA	• Decreased neutrophil recruitment at the site of infection in *Nlrp12*$^{-/-}$ mice. • Increased *S. aureus* burden in *Nlrp12*$^{-/-}$ mice.	Ulland et al., 2016
Pseudomonas aeruginosa infection	NA	• Decreased neutrophil recruitment at the site of infection in *Nlrp12*$^{-/-}$ mice. • Increased *P. aeruginosa* burden in *Nlrp12*$^{-/-}$ mice.	Ulland et al., 2016
Influenza A virus (IAV) infection	NA	• Decreased neutrophil chemoattractant CXCL1 in *Nlrp12*$^{-/-}$ mice infected with IAV. • Decreased pulmonary neutrophils in *Nlrp12*$^{-/-}$ mice infected with IAV. • Decreased neutrophil recruitment at the site of infection in *Nlrp12*$^{-/-}$ mice in response to IAV. • Decreased vascular permeability in *Nlrp12*$^{-/-}$ mice during IAV infection.	Hornick et al., 2018
Experimental autoimmune encephalomyelitis (EAE)	NA	• *Nlrp12*$^{-/-}$ mice have hyperinflammatory myelin-specific T-cell responses. • *Nlrp12*$^{-/-}$ T cells produce more IFN-γ and IL-17 per cell. • *Nlrp12*$^{-/-}$ T cells produce large amounts of Th2-associated cytokines like IL-4, IL-5, and IL-13, which ultimately contributes to the development of intestinal inflammation. • Enhanced phosphorylation of IκBα and processing of NFκB p100 to p52 in *Nlrp12*$^{-/-}$ T cells.	Lukens et al. (2015)

3. NLRP12 as a negative regulator

NLRP12 (also known as NALP12, MONARCH-1, and PYPAF-7) is an intracellular protein expressed in bone marrow neutrophils, granulocytes, macrophages and dendritic cells (Williams et al., 2003). The role of NLRP12 remains controversial, as it has been shown to function as both a negative regulator of inflammation (Table 1) and as an inflammasome (Table 2) (Pinheiro et al., 2011; Tuncer et al., 2014; Wang et al., 2002).

Studies have shown that NLRP12 functions as a negative regulator of both canonical and non-canonical NFκB signaling pathways (Fig. 2A). Attenuation of canonical NFκB signaling occurs when NLRP12 interacts with and inhibits the accumulation of hyperphosphorylated IRAK1, downstream of TLR signaling. Additionally, an association of NLRP12 with NFκB-inducing kinase (NIK) leads to rapid proteasomal degradation of NIK in non-canonical NFκB signaling (Lich et al., 2007; Williams et al., 2005). NLRP12 has also been shown to interact with TRAF3, which is involved in NIK degradation (Allen et al., 2012). Physiologically, the inhibition of NFκB signaling by NLRP12 suppresses colon inflammation (Allen et al., 2012; Zaki et al., 2011). During azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colitis, *Nlrp12*$^{-/-}$ mice are highly susceptible to inflammation in the colon and show significantly increased levels of proinflammatory cytokines and chemokines due to the activation of canonical NFκB and ERK signaling pathways (Zaki et al., 2011). In contrast, another study showed that the susceptibility of *Nlrp12*$^{-/-}$ mice to colitis and colitis-associated colon cancer is caused by the activation of non-canonical NFκB, ERK, and AKT signaling pathways. The discrepancy between studies could be attributed to differences in the NFκB complex components and cell types analyzed, the stimuli used, and the mouse colony and housing conditions. Despite the discrepancy, both studies suggest that NLRP12 serves as a pivotal checkpoint for NFκB signaling.

Additionally, NLRP12 plays a critical role in regulating the gut microbiota. While *Nlrp12*$^{-/-}$ mice are more susceptible to DSS-induced colitis than WT mice are, *Nlrp12*$^{-/-}$ mice raised under germ-free (GF) conditions are indistinguishable from GF WT mice during experimental colitis, indicating that the interaction between host cells and resident bacteria are important for the susceptibility of *Nlrp12*$^{-/-}$ mice to colitis (Chen et al., 2017). Overall this study found that NLRP12 functions during inflammatory bowel disease (IBD) to regulate the excessive production of inflammatory cytokines and maintain the commensal diversity of the gut microbiota to limit intestinal inflammation (Chen et al., 2017).

The colonic inflammation and microbiome dysbiosis that occur as a result of the loss of NLRP12 can cause obesity. Truax et al. evaluated the role of NLRP12 in high fat diet (HFD)-induced obesity and showed that *Nlrp12*$^{-/-}$ mice gained weight and had impaired glucose tolerance and elevated levels of adipose tissue inflammation compared with WT mice (Truax et al., 2018). By using antibiotics to treat *Nlrp12*$^{-/-}$ mice and cohousing WT and *Nlrp12*$^{-/-}$ mice, the authors also showed that HFD-induced weight gain in *Nlrp12*$^{-/-}$ mice was due to the gut microbiota (Truax et al., 2018). Together, these data strongly suggest that the microbiota contribute to inflammation and obesity in *Nlrp12*$^{-/-}$ mice and that NLRP12 restricts HFD-induced obesity and maintains the gut microbiota that dampens the inflammatory response.

The loss of NLRP12 has also been associated with increased susceptibility to hepatocellular carcinoma (HCC). In the mouse model of HCC induced by single administration of diethylnitrosamine (DEN), *Nlrp12*$^{-/-}$ mice had higher tumor burden and increased tumor size due to an increase in the expression of pro-proliferative molecules like Myc, Ccnd1, Ccnb1, MKi67, and Survivin (Udden et al., 2019). During DEN-induced HCC, *Nlrp12*$^{-/-}$ mice show significantly increased levels of proinflammatory cytokines and chemokines and activation of the JNK signaling pathways, suggesting that NLRP12 also regulates JNK signaling. Also, *Nlrp12*$^{-/-}$ hepatocytes stimulated with LPS show increased activation of JNK and expression of Ccl2, Cxcl1, Cxcl2, Ccnd1, and Myc (Udden et al., 2019).

Furthermore, NLRP12 has also been implicated in the immune response to various pathogens. During infection with *Mycobacterium tuberculosis* or *Klebsiella pneumonia*, bone marrow-derived dendritic cells (BMDCs) lacking NLRP12 induce production of TNF and IL-6 but do not confer inflammasome-mediated protection against these bacteria (Allen et al., 2013). During *Salmonella* infection, NLRP12 mediates NFκB and ERK inhibition by targeting the phosphorylation of IκBα and ERK, which

Table 2
NLRP12 as an inflammasome.

Triggers	Inflammasome activation		
	In vitro	*In vivo*	Reference
Yersinia pestis *Y. enterocolitica* *Y. pseudotuberculosis* infection	• Reduced IL-1β and IL-18 production in murine *Nlrp12*$^{-/-}$ peritoneal macrophages and BMDMs upon infection with virulent and attenuated *Y. pestis* strains. • Decreased caspase-1 and IL-1β cleavage in murine *Nlrp12*$^{-/-}$ BMDMs upon infection with attenuated *Y. pestis*. • Reduced IL-1β production in murine *Nlrp12*$^{-/-}$ BMDMs upon infection with *Y. enterocolitica* or *Y. pseudotuberculosis*.	• Decreased expression of active caspase-1 in bone marrow cells, and Ly6G- or F4/80-positive splenocytes obtained from *Nlrp12*$^{-/-}$ mice infected with virulent and attenuated *Y. pestis* strains. • Decreased levels of IL-1β and IL-18 in serum and spleen of *Nlrp12*$^{-/-}$ mice infected with virulent *Y. pestis*. • Decreased survival and increased bacterial load in the spleen of *Nlrp12*$^{-/-}$ mice upon infection with virulent and attenuated *Y. pestis* strains.	Vladimer et al., 2012
Plasmodium chabaudi infection	NA	• Decreased expression of active caspase-1 and cell death in splenic macrophages and neutrophils obtained from *Nlrp12*$^{-/-}$ mice infected with *P. chabaudi*. • Decreased caspase-1 cleavage in splenocytes of *Nlrp12*$^{-/-}$ mice infected with *P. chabaudi*. • Decreased serum IL-1β levels in *Nlrp12*$^{-/-}$ mice infected with *P. chabaudi* followed by LPS challenge. • Decreased expression of active caspase-1 in splenocytes and decreased IL-1β levels in serum of *Nlrp12*$^{-/-}$ mice infected with parasitized red blood cells followed by LPS challenge. • Reduced mortality in *Nlrp12*$^{-/-}$ mice infected with parasitized red blood cells followed by LPS challenge.	Ataide et al., 2014

results in reduced production of proinflammatory cytokines (Zaki et al., 2014). Though the activator of NLRP12 is currently not known, *Salmonella* LPS alone can induce NLRP12-mediated inhibition of NFκB activation (Zaki et al., 2014). This suggests that the activator of NLRP12 could be upregulated upon LPS stimulation. Also, NLRP12 regulates NFκB and MAPK signaling by inhibiting the phosphorylation of p65, JNK, and p38 in response to *Brucella abortus* infection (Silveira et al., 2017). When RAW264.7 macrophages that have NLRP12 silenced are stimulated with *Porphyromonas gingivalis* LPS, they have increased expression of iNOS and higher production of TNF, suggesting that NLRP12 negatively regulates iNOS and TNF during bacterial infection (Pudla et al., 2019). During viral infection, TRIM25 is required for Lys63-linked polyubiquitination and activation of RIG-I, which then activates MAVS. MAVS associates with the adaptor protein TRAF3 and TRAF family member-associated NFκB activator (TANK) to trigger the activation of TANK-binding kinase 1 (TBK1) and IκB kinase, leading to the activation of IRFs and IFN. During vesicular stomatitis virus (VSV) infection, NLRP12 interacts with the E3 ubiquitin ligase TRIM25 to disrupt its association with RIG-I, resulting in reduced type I IFN production (Fig. 2B) (Chen et al., 2019).

Along with regulating the canonical and non-canonical NFκB pathways, NLRP12 can also impact immune cell localization and recruitment. NLRP12 negatively regulates neutrophil migration and neutrophil recruitment to the site of infection during infection with viral, bacterial, and parasitic pathogens such as influenza A virus (IAV), *Francisella tularensis LVS, P. aeruginosa, S. aureus,* and *Leishmania major* (Hornick et al., 2018; Ulland et al., 2016; Zamoshnikova et al., 2016). Due to the lack of neutrophil recruitment to the site of infection, *Nlrp12*$^{-/-}$ mice are unable to the control replication of various bacterial and viral pathogens (Ulland et al., 2016; Zamoshnikova et al., 2016). CXCL1 and CXCL2 expression in perivascular macrophages in response to various stimuli triggers both the adhesion and transmigration of neutrophils out of the blood stream. In the absence of NLRP12, the macrophages are defective in producing the chemoattractant chemokine CXCL1 which results in impaired neutrophil recruitment in response to a variety of pathogens and TLR agonist (Ulland et al., 2016). During IAV infection, NLRP12 contributes to the severity of disease through its effect on CXCL1 production, which ultimately affects neutrophil recruitment and vascular permeability (Hornick et al., 2018.) Though it is not clear how NLRP12 regulates CXCL1 expression, failure to recruit neutrophils in response to a range of inflammatory stimuli is associated with a missense mutation in *Nlrp12* in C57BL/6J mice (Ulland et al., 2016).

NLRP12 has also been shown to negatively regulate T cells in response to experimental autoimmune encephalomyelitis (EAE) (Gurung and Kanneganti, 2015; Lukens et al., 2015). *Nlrp12*$^{-/-}$ mice have hyperinflammatory myelin-specific T-cell responses that result in exacerbated demyelinating disease. Using adoptive transfer studies, Lukens et al. showed that NLRP12 is an intrinsic negative regulator of T-cell responses; *Nlrp12*$^{-/-}$ T cells produce more IFN-γ and IL-17 per cell than do WT T-cells. Furthermore, *Nlrp12*$^{-/-}$ T cells were shown to produce large amounts of Th2-associated cytokines like IL-4, IL-5, and IL-13, which ultimately contributes to the development of intestinal inflammation and atopic dermatitis in *Nlrp12*$^{-/-}$ mice. Additionally, adoptive transfer of *Nlrp12*$^{-/-}$ T cells causes enhanced phosphorylation of IκBα and processing of NFκB p100 to p52, showing that NLRP12 negatively regulates canonical and non-canonical NFκB signaling in T cells (Lukens et al., 2015).

Overall, regulation of the immune response by NLRP12 can be multifaceted and pathogen-specific. Regulation of the NFκB signaling pathway by NLRP12 upon infection with various pathogens could contribute to pathogen survival and persistence in the host. Also, NLRP12 plays an important role in gut homeostasis, where it serves as a negative regulator that inhibits proinflammatory cytokines and chemokines (Chen et al., 2017; Lau and Dombrowski, 2018; Truax et al., 2018). These regulatory functions are important for the host, as NLRP12 influences key pathways to prevent overt damage to the tissues.

4. NLRP12 as an inflammasome

The role of NLRP12 as a negative regulator of immune signaling has been established during infection and colon cancer, IBD, and tumorigenesis. There are limited studies that have elucidated the role of NLRP12 as a component of the inflammasome (Table 2). During *Yersinia pestis* infection, NLRP12 has been shown to be an inflammasome component that becomes activated through an unknown mechanism and mediates *Y. pestis*-dependent release of IL-1β and IL-18 (Fig. 2C). Caspase-1 activation and IL-1β and IL-18 release are decreased in the spleen and bone marrow of *Nlrp12*$^{-/-}$ mice upon infection with *Yersinia*. Additionally, *Nlrp12*$^{-/-}$ mice succumb to *Yersinia* infection, while WT mice do not (Vladimer et al., 2012). Although the ligand that activates NLRP12 is not known, this study showed that the generation of ligands for NLRP12 activation during *Yersinia* infection requires the

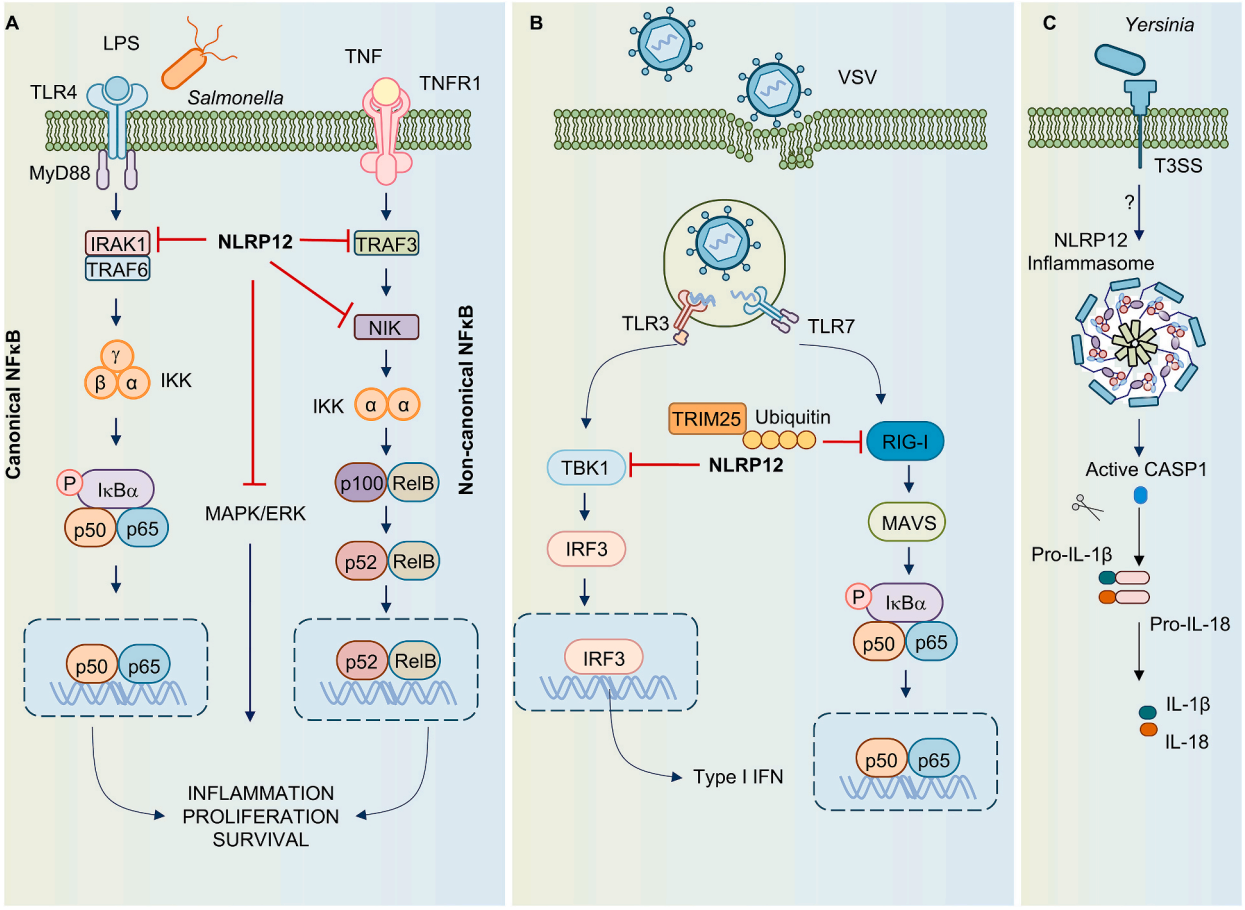

Fig. 2. NLRP12 acts in innate immune signaling in a pathogen-specific manner. (A) NLRP12 negatively regulates inflammatory signaling by suppressing canonical and non-canonical NFκB signaling and the MAPK/ERK signaling pathway in bone marrow-derived macrophages (BMDMs). (B) NLRP12 associates with TRIM25 to reduce polyubiquitination and inhibit the RIG-I-mediated IFN response during VSV infection. (C) The NLRP12 inflammasome can drive caspase-1 activation and IL-1β and IL-18 release in BMDMs during infection with *Yersinia pestis* and *Plasmodium chabaudi*.

virulence-associated T3SS. This further suggests that activation of NLRP12 may be associated with the sensing of damage that is associated with the T3SS, the effector proteins and other molecules that are secreted and channeled by the T3SS, or the host proteins that are modified. In the context of a parasitic infection, macrophages and dendritic cells in the spleen activate caspase-1 upon infection with *Plasmodium chabaudi.* This caspase-1 activation is ASC-dependent. During *P. chabaudi* infection, both NLRP3 and NLRP12 are required for caspase-1 activation, the systemic production of IL-1β, and pyroptosis, as *Nlrp12*$^{-/-}$ mice have decreased caspase-1 activation and IL-1β release upon *Plasmodium* infection (Ataide et al., 2014). While *Nlrp12*$^{-/-}$ mice infected with *Yersinia* or *Plasmodium* exhibit decreased caspase-1 activation and IL-1β release, infection with *B. abortus* results in increased IL-1β circulation in *Nlrp12*$^{-/-}$ mice (Silveira et al., 2017), complicating the potential role of NLRP12 as an inflammasome component.

Although NLRP12 can recognize *Yersinia* infection and contributes to *in vivo* resistance, *Nlrp12*$^{-/-}$ mice infected with *Yersinia* do not completely lose their ability to release IL-1β and IL-18. Additionally, both *Yersinia* and *Plasmodium* infections also require NLRP3 for host defense. Thus, this suggests that redundancy in the activation of various NLRs contributes to optimal protection in the host.

5. Summary and future directions

NLRP12 plays a multifaceted role in innate immunity, and its functions in inflammasome formation and as a negative regulator are context-dependent. During *Yersinia* and *Plasmodium* infection, NLRP12 activation leads to caspase-1 activation and the release of IL-1β and IL-18, suggesting it can contribute to inflammasome formation and proinflammatory signaling. Conversely, during experimental colitis, NLRP12 regulates canonical and non-canonical NFκB signaling pathways, suggesting that it has anti-inflammatory and anti-tumorigenic functions. NLRP12 has also been shown to play a role in gut homeostasis and maintaining the microbiota in the gut. Furthermore, NLRP12 regulates T cells and neutrophil migration. Lack of NLRP12 in T cells can cause them to become hyper-inflammatory, resulting in the development of autoimmune diseases.

Detailed studies of the structural components and assembly of inflammasomes and mechanisms of pyroptosis have provided tremendous advancement in our understanding of inflammasome formation, activation, and function. Though the role of NLRP12 in resisting microbial infections has been shown, it is still not clear how NLRP12 interacts with other components of the inflammasome or what molecules directly trigger NLRP12 inflammasome assembly. Further studies are required to fully understand what conditions cause NLRP12 to act as a negative regulator or as an inflammasome.

Overall, the conflicting roles of NLRP12 as a negative regulator or an inflammasome are dependent on the cell type analyzed and, most importantly, are pathogen-specific. Based on its critical function in disease, NLRP12 may serve as a therapeutic target to control infections and for diseases such as colitis and IBD.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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