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MINI-REVIEW

Negative regulation of NLRP3 inflammasome signaling

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ABSTRACT

Inflammasomes are multiprotein complexes that serve as a platform for caspase-1 activation and interleukin-1β (IL-1β) maturation as well as pyroptosis. Though a number of inflammasomes have been described, the NLRP3 inflammasome is the most extensively studied. NLRP3 inflammasome is triggered by a variety of stimuli, including infection, tissue damage and metabolic dysregulation, and then activated through an integrated cellular signal. Many regulatory mechanisms have been identified to attenuate NLRP3 inflammasome signaling at multiple steps. Here, we review the developments in the negative regulation of NLRP3 inflammasome that protect host from inflammatory damage.

KEYWORDS inflammasome, NLRP3, negative regulation, inflammation

INTRODUCTION OF INFLAMMSOMES

The innate immune system is a sophisticated system for sensing signals of "danger" such as pathogenic microbes or host-derived signals of cellular stress. Host innate immune system is activated by the engagement of germline-encoded pattern-recognition receptors (PRRs) to detect invariant motifs, which are the presence of unique microbial components called pathogen-associated molecular patterns (PAMPs) or endogenous danger-associated molecular patterns (DAMPs) generated in the setting of cellular injury or tissue damage (Takeuchi and Akira, 2010). PRRs are expressed by cells at the first line of defense against infection, including macrophages, dendritic cells (DCs), monocytes, neutrophils, epithelial cells, and also some cells of the adaptive immune system. There are four kinds of PRRs: Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-like helicases (RLHs) and C-type lectins (CTLs). TLRs and CTLs are membrane-bound, which detect the extracellular and endosomal compartments for PAMPs, whereas RLHs are intracellular PRRs that sense the cytosolic RNA. NLRs, the latest found, are also intracellular PRRs that detect a series of materials, including microbial components, endogenous stress and damage signals (Schroder and Tschopp, 2010).

To date, 23 human genes and 34 mouse genes are found for the NLR family, which is characterized by the presence of a central nucleotide-binding and oligomerization (NACHT) domain, C-terminal leucine-rich repeats (LRRs) and N-terminal caspase recruitment (CARD) or pyrin (PYD) domains. Phylogenetic analysis of NACHT domains reveals 3 distinct subfamilies within the NLR family: the NODs (NOD1-2, NOD3/NLRC3, NOD4/NLRC5, NOD5/NLRX1, CIITA), the NLRPs (NLRP1-14, also called NALPs) and the IPAF subfamily, consisting of IPAF (NLRC4) and NAIPs (Martinon et al., 2009; Schroder and Tschopp, 2010). The accepted theory posits that activation signals are sensed by the LRR domain of these NLRs, which can autoregulate the PYD/CARD and NACHT domains. The NACHT domain, the only domain common to all NLR family members, enables activation of the signaling complex via ATP-dependent oligomerization. The CARD and PYD domains mediate homotypic protein-protein interactions for downstream signaling (Tschopp and Schroder, 2010).

Recognition of a diverse range of microbial, stress and damage signals by NLRs results in inflammasomes formation. The inflammasome is a multiprotein complex composed of a sensor NLR protein, the PYD-and CARD-domain containing adapter protein ASC, and the inflammatory protease caspase-1 (Martinon et al., 2002). Once activated, NLR changes conformation to recruit ASC and assemble the inflammasome

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platform, which in turn promotes the activation of caspase-1. Caspase-1 subsequently cleaves pro-IL-1β and pro-IL-18 and renders maturation and secretion of these potent inflammatory cytokines, meanwhile, a form of cell death called pyroptosis is also resulted from the caspase-1 activation (De Nardo and Latz, 2011; Lamkanfi, 2011).

So far, four inflammasomes have been identified: NLRP1, NLRP3, NLRC4 and AIM2 (Schroder and Tschopp, 2010; Gross et al., 2011). Formation of the NLRP1, NLRC4, and AIM2 inflammasomes is promoted by specific stimuli. NLRP1, the first inflammasome to be described, is activated mainly by the lethal toxin from *Bacillus anthracis* (Martinon et al., 2002; Lamkanfi and Dixit, 2009). AIM2 senses dsDNA of viral or bacterial origin (Burckstummer et al., 2009; Fernandes-Alnemri et al., 2009; Hornung et al., 2009; Roberts et al., 2009) while NLRC4 responds to bacterial flagellin and PrgJ, a component of the type III secretion system (T3SS) (Franchi et al., 2006; Miao et al., 2006; Zhao et al., 2011; Gong and Shao, 2012). The NLRP3 inflammasome is currently the most fully characterized inflammasome, which responds to numerous physically and chemically diverse stimuli, and leads to a series of diseases when out of control. In this review, we focus on the negative regulation of NLRP3 inflammasome activation.

NLRP3 INFLAMMASOME AND ITS ACTIVATION

The activators of NLRP3 are quite varied and include environmental irritants, endogenous danger signals, pathogens, and distinct PAMPs. In detail, the NLRP3 inflammasome is activated by pathogens such as Sendai virus, adenovirus, influenza virus (Gram et al., 2012), *Candida albicans* (Gross et al., 2009), *Saccharomyces cerevisiae* (Kumar et al., 2009), *Listeria monocytogenes* (Meixenberger et al., 2010) and *Staphylococcus aureus* (Munoz-Planillo et al., 2009), and also by endogenous stimuli and particulate matter, including extracellular ATP (Mariathasan et al., 2006; Sutterwala et al., 2006), extracellular glucose (Masters et al., 2010; Zhou et al., 2010), monosodium urate (MSU) crystals (Martinon et al., 2006), cholesterol (Duewell et al., 2010), silica (Dostert et al., 2008), aluminum salts (Eisenbarth et al., 2008), asbestos (Dostert et al., 2008), malarial hemozoin (Shio et al., 2009), amyloid deposits (Halle et al., 2008) and fatty acids (Wen et al., 2011).

NLRP3 inflammasome is triggered by a variety of stimuli, thus it has close relations with many diseases as proposed. Firstly, gain-of-function mutations within the NACHT domain of NLRP3 were found associated with three autoinflammatory disorders characterized by skin rashes and prolonged episodes of fever in the absence of any apparent infection. Then these three hereditary periodic fever syndromes, Muckle–Wells syndrome (MWS), familial cold autoinflammatory syndrome (FACS), and neonatal-onset multisystem inflammatory disease (NOMID), are collectively referred to as the cryopyrin NLRP3-associated periodic syndromes (CAPS) (Martinon and Tschopp, 2004; Lamkanfi and Dixit, 2009). Furthermore, mononuclear cells from these CAPS patients spontaneously secrete IL-1β and IL-18, and IL-1 receptor antagonists have been proved to be an effective treatment for these autoinflammatory syndromes (Hoffman et al., 2004; Rosengren et al., 2007). Recently, increasing evidence indicates that dysregulated production of IL-1β are implicated in the pathophysiology of several common diseases, including atherosclerosis (Duewell et al., 2010), osteoarthritis (Denoble et al., 2011), metabolic syndrome (Strowig et al., 2012), and type 2 diabetes (Zhou et al., 2010).

Activation of the NLRP3 inflammasome requires two signals in mouse macrophages. The first priming signal is provided by microbial or endogenous molecules that activate NF-κB to induce the expression of not only pro-IL-1β, but also NLRP3, thus controls the threshold of inflammasome activation. The second signal directly activates NLRP3 and is provided by ATP, bacterial toxins or particulate matter (De Nardo and Latz, 2011). But in human monocytes and microglia cells, the situation may be different, as TLR ligands alone can induce the release of IL-1β (Ferrari et al., 1997; Kahlenberg and Dubyak, 2004; Netea et al., 2009).

Given the chemical and structural diversity of the NLRP3 activators, it has been hypothesized that NLRP3 does not interact directly with its activators. Instead, the actual triggering of NLRP3 is an integrated and intermediate cellular signal elicited by all these activators. A number of theories have been proposed for the identity of the cellular signal responsible for NLRP3 activation, including potassium (K^+) efflux, pore formation in cell membranes, lysosomes damage, the elevation of reactive oxygen species (ROS) and damage in the mitochondria. The NLRP3 agonists, including ATP, the antibiotic nigericin and pore-forming toxins, lead to lower intracellular concentration of K^+, and a high extracellular concentration of K^+ inhibits activation of the NLRP3 inflammasome as supposed (Mariathasan et al., 2006; Gross et al., 2011). The activation of NLRP3 by crystals requires endocytosis, which leads to lysosomal rupture. The NLRP3 inflammasome senses lysosomal content in the cytoplasm such as cathepsin B as a direct NLRP3 ligand. This hypothesis is supported by the efficacy of endocytosis inhibitors in blocking inflammasome activation by particulates. Furthermore, inhibitors of cathepsin B can prevent the activation of caspase-1 induced by certain microbes (Martinon et al., 2006; Hornung et al., 2008; Duewell et al., 2010). The production of ROS has also been suggested to act as a common cellular signal upstream of NLRP3 activation. When treated with ROS scavengers and NAPDH-oxidase inhibitors, the NLRP3 activation is blocked (Allen et al., 2009; Zhou et al., 2011). However, a recent study showed that the ROS inhibitors interfered with LPS mediated priming instead caspase-1 activation from ATP pulse (Bauernfeind et al., 2011). Additional study found that, thioredoxin-interaction protein (TXNIP) binds an activated NLRP3 after the production of ROS by NLRP3 activators (Zhou et al., 2010). Moreover, by using inhibitors of the respiratory chain, the source of ROS that mediates activation of the NLRP3 inflammasome is suggested to be mitochondria (Zhou et al., 2011). Furthermore, the release of mitochon-

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drial DNA by damaged mitochondria is proved to activate the NLRP3 inflammasome (Nakahira et al., 2011; Shimada et al., 2012). Although none of the aforementioned studies provides a satisfactory explanation for the mechanism of NLRP3 activation, we propose that NLRP3 activation requires integrate and complicated signals that indicate cellular damage or stress.

NEGATIVE REGULATION OF NLRP3 INFLAMMASOME

The maturation and release of IL-1β and IL-18, as well as the pyroptosis that followed with inflammasome activation, have the potential to cause tissue damage in the host. Misregulation of inflammasome might lead to autoinflammatory such as in the cases of familial Mediterranean fever (FMF) or CAPS. Thus to control injury effectively, the inflammasome has to be quickly and efficiently engaged and then must be tightly controlled and switched off once the stimuli are no longer present, or the adaptive immune response has been initiated to avoid unnecessary collateral damage. To this end, both priming and activation of inflammasome are regulated tightly. During this process, several proteins, both of endogenous as well as of microbial origin, have been studied.

Autophagy

Autophagy, a lysosome-mediated cytoprotective process, is a cellular response to starvation, can deliver damaged organelles and long-lived proteins engulfed by autophagosomes from the cytoplasm to lysosomes for degradation. Recent studies have disclosed multiple roles of autophagy in the regulation of cell death, differentiation, antigen presentation and anti-microbial response (Levine et al., 2011). By studies of autophagocytosis-deficient Atg16L1$^{-/-}$ (autophagy-related gene 16-like 1) mice, autophagy is demonstrated as an inhibitor of NLRP3 inflammasome. Blocking autophagy by genetic deletion of Atg16L1 potentiates inflammasome activity induced by TLR4 signaling. Mice lacking Atg16L1 suffer severe dextran sulfate sodium–induced colitis, which can be alleviated by neutralization of IL-18 and IL-1β (Saitoh et al., 2008). The autophagy inhibits IL-1β activation indirectly by lowering the endogenous sources of inflammasome activation and directly via autophagic degradation of inflammasome components. For indirect inhibition, autophagy can suppress inflammasome activity by diminishing the generation of ROS. The ROS, generated from damaged mitochondria by blocking autophagy, activate NLRP3 inflammasomes as mentioned above. Conversely, suppressing mitochondrial activity inhibits activation of the NLRP3 inflammasome due to less generation of ROS (Zhou et al., 2011). Two other autophagic proteins, LC3B and beclin1, are thought involved in NLRP3 inflammasome activation by regulating the release of mitochondrial DNA (mtDNA) besides of ROS. Depletion of LC3B and beclin1 enhances the activation of caspase-1 and secretion of IL-1β and IL-18 as a result of promoting the accumulation of dysfunctional mitochondria and cytosolic translocation of mtDNA in response to LPS and ATP in macrophages. Moreover, LC3B-deficient mice produced more caspase-1-dependent cytokines in sepsis models and were susceptible to LPS-induced mortality (Nakahira et al., 2011). mtDNA, precisely oxidized mtDNA, later is proved binding to NLRP3 directly to induce the NLRP3 inflammasome activation (Shimada et al., 2012). For direct inhibition, additional evidence indicates that the induction of inflammasomes is accompanied by autophagosome formation, which limits inflammasome activity by degrading inflammasome via ASC ubiquitination and the recruitment of p62 and LC3 in turn (Shi et al., 2012). There is also an inflammasome-independent manner in which autophagy acts to regulate IL-1β responses; autophagy sequesters pro-IL-1β and targets it for lysosomal degradation to limit the substrate necessary for caspase-1 activation (Harris et al., 2011).

Type I interferons

Type I interferons (IFNs) inhibit IL-1β production through two distinct mechanisms. Type I IFNs suppress the activity of the NLRP1 and NLRP3 inflammasomes to reduce caspase-1-dependent IL-1β maturation dependent on the transcription factor STAT1 (Guarda et al., 2011). But how STAT1 blocks the activation of caspase-1 exactly is unclear. In addition, Type I IFNs diminish the abundance of intracellular pro-IL-1β by inducing production of the anti-inflammatory cytokine IL-10 in a STAT1-dependent manner. IL-10 then inhibits the synthesis of pro-IL-1β and pro-IL-1α via the STAT3 signaling pathway. In line with the inhibitory role for type I IFNs on the inflammasome *in vitro*, poly(I:C)-induced type I IFNs suppress NLRP3 activation by alum and *C. albicans*, thus increasing susceptibility to this fungal pathogen. Importantly, the NLRP3 inflammasome activation in monocytes from patients with multiple sclerosis that are being treated with IFN-β is repressed as decreased IL-1β production than that from healthy donors (Guarda et al., 2011). Another paper has indicated the importance of type I IFNs in suppressing IL-1 in both inflammatory monocyte-macrophage and DC populations and *in vivo* during infection with *M. tuberculosis*, in which IL-1α and IL-1β are critically required for host resistance (Mayer-Barber et al., 2011).

T cell

The adaptive immune system can exert a profound inhibitory effect on the innate immune system. Effector and memory CD4$^+$T cells abolish inflammasome-mediated caspase-1 activation and IL-1β release in macrophages and DCs. This inhibitory effect requires cell-to-cell contact and mediates by CD40L, OX40L and RANKL, which are ligands of the TNF superfamily. But it is still unclear how interactions between ligands of the TNF family and their receptors mediate the inhibition of caspase-1-dependent production of IL-1β (Guarda et al., 2009). Additionally, the other study found the anti-inflammatory role for CD4$^+$T cell-derived IFN-γ in dampening IL-1 expression by monocyte-macrophages. But the effect of IFN-γ is controversial: IFN-γ potentiates IL-1β release from human cells, but

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transiently inhibits the production of IL-1β from mouse cells. In mice, the inhibition of IFN-γ on IL-1β production is regulated strictly by suppressor of cytokine signaling 1 (SOCS1) (Mayer-Barber et al., 2011). In conclusion, as a feedback loop, effector and memory T cells suppress potentially damaging inflammation, yet leave the primary inflammatory response intact, which is crucial for the onset of immunity. IFN-γ is the signature cytokine of T helper type 1 and $CD8^+$T cell responses, which may also act as a feedback regulator of inflammasome responses once the adaptive immune response has been elicited. Such an inhibitory pathway is likely to aid in "switching off" innate immune responses once the adaptive arm of the immune system is engaged.

The TRIM family of proteins

Emerging evidence indicates that the TRIM family proteins also modulate the activation of inflammasome. The initial evidence was provided by studies that missense mutations in the C-terminal B30.2 domain of TRIM20 (pyrin or MEFV) cause FMF, the most common Mendelian autoinflammatory disease. Targeted disruption of Pyrin in mice causes increased endotoxin sensitivity and enhanced caspase-1 activation (Chae et al., 2003). The PYD of Pyrin interacts with the PYD of ASC, suggesting that it may be involved in blocking the recruitment of ASC and inflammasome formation. Later study has demonstrated that a gain-of-function mutant of TRIM20 constitutively forms inflammasome complexes containing ASC and caspase-1 in mice (Chae et al., 2011).

Previous work in our laboratory has demonstrated that TRIM30, a RING domain-containing TRIM protein which has been known as a negative regulator of TLR signaling, specifically suppresses the activation of the NLRP3 inflammasome. Expression of TRIM30 is induced by TLR stimulation and in turn restrict NLRP3 inflammasome activation by inhibiting ROS production, in response to a variety of ligands, including ATP, nigericin, silica and monosodium urate *in vitro* and *in vivo* (Hu et al., 2010).

Regulation of inflammasome activation by microRNA

microRNA (miRNA)-mediated posttranscriptional regulation plays an important role in controlling gene expression. miRNAs are endogenous noncoding RNAs that are 20–23 nt in length and exert regulatory functions through complementary base pairing to the 3′ untranslated regions (3′ UTRs) of protein-coding mRNAs (Bartel, 2009). Although miRNA has been found involved in many cell signalings, and its role in regulating innate immune responses has primarily been addressed for TLR signal-transduction pathways, there has not been observed in inflammasome. Recently, miR-223 is identified as the regulator of NLRP3 inflammasome, by targeting the NLRP3 3′-UTR and preventing accumulation of NLRP3 protein. In addition, the study also showed that EBV miR-BART15 targeted the same site in the NLRP3 3′-UTR to dampen inflammasome activation (Bauernfeind et al., 2012; Haneklaus et al., 2012).

POPs and COPs

Pyrin-only proteins (POPs) and CARD-only proteins (COPs) are regulators of the inflammasomes mainly in humans, because except caspase-12, neither POPs nor COPs is encoded in the mouse genome. The POP regulators include POP1, POP2, and viral PYDs (vPYDs), which are believed to interfere with PYD-PYD interaction between NLRPs and the adaptor ASC. Poxviruses deficient in vPYD produce enhanced activation of caspase-1 and secretion of IL-1β (Johnston et al., 2005). POP1 interacts with ASC and sequesters it from other PYD-containing proteins, such as the NLRs, because of its higher degree of homology with the PYD of ASC (64%), which ultimately results in the inhibition of inflammasome activation. Otherwise, POP2 binds NLRs and suppresses inflammasome activation by resembling the PYD of NLRP2 and NLRP7 (Dorfleutner et al., 2007; Stehlik and Dorfleutner, 2007; Martinon et al., 2009).

In contrast to the POPs, the COPs have similarity to the CARD of caspase-1 and function as decoy inhibitors of caspase-1 via CARD interaction, thereby sequestering it from the association with activating adaptors. To date, five proteins qualify to belong to the COP protein family: Iceberg, COP1/Pseudo-ICE, INCA, caspase-12s, and Nod2-S. Iceberg, the first demonstrated as COP, is highly similar to the CARD of caspase-1 and might function as a negative feedback regulator to prevent systemic inflammation because of elevating expression during inflammation (Humke et al., 2000). COP1/Pseudo-ICE and INCA, additional COPs found later, interact with the CARD of caspase-1 to prevent its activation similar to Iceberg (Druilhe et al., 2001; Lamkanfi et al., 2004). Nod2-S, a short variant of Nod2, encodes only the first CARD. Nod2-S does not interact with caspase-1 but competes with Nod2 for Rip2 binding, resulting in impaired caspase-1 activation (Rosenstiel et al., 2006). The best studied COP, caspase-12, has been explored in detail in mice. The pro-domain (a CARD) is sufficient for causing reduced cytokine secretion. In mice, caspase-12 deficiency confers resistance to sepsis, and the presence of caspase-12 exerts a dominant-negative suppressive effect on caspase-1 (Saleh et al., 2004; Saleh et al., 2006).

Nitric oxide

Nitric oxide (NO) is a small molecule synthesized by many cell types in various tissues and is involved in multiple physiological and pathological responses, including circulation, blood pressure, platelet function, host defense and neurotransmission in the central nervous system and peripheral nerves (Bogdan et al., 2000). In immune responses, NO also plays many roles (Bogdan, 2001), including the control of infection and the regulation of signaling cascades, transcription factors, vascular responses, leukocyte rolling, migration, cytokine production and T-cell differentiation (Clancy et al., 1998; Rawlingson, 2003; Niedbala et al., 2011). Our recent work shows that NO inhibits the activation of the NLRP3 inflammasome, thus preventing ASC pyroptosome formation, caspase-1 activation and IL-1β

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secretion in myeloid cells from both mice and humans. In contrast, in iNOS-deficient macrophages, NLRP3 inflammasome activation was enhanced by the accumulation of dysfunctional mitochondria. *In vivo*, iNOS deficiency or pharmacological inhibition of NO production enhanced NLRP3-dependent cytokine production, increasing mortality from LPS-induced sepsis in mice, which was prevented by NLRP3 deficiency. NO is known as an immunomodulatory molecule, although the mechanisms underlying this immunomodulation are poorly understood. In the study, NO is found as a critical negative regulator of the NLRP3 inflammasome via the stabilization of mitochondria (Mao et al., 2013). At the same time, two other studies also found that NO induced by IFN-γ specifically inhibited assembly of the NLRP3 inflammasome via S-nitrosylation of NLRP3 (Hernandez-Cuellar et al., 2012; Mishra et al., 2012).

Strategy of virus

Viruses inhibit activation of the NLRP3 inflammasome by several means to the benefit of their own infection. Mice lacking components of the NLRP3 inflammasome, such as NLRP3, ASC, or caspase-1, exhibited dramatically increased mortality and a viral clearance defect after exposure to the influenza virus (Allen et al., 2009; Ichinohe et al., 2009). In addition to POPs and miRNA mentioned above, some other viruses encode specific proteins to suppress host innate immune responses. Orf63 is a viral homolog of human NLRP1 encoded by KSHV. Orf63 blocks NLRP1-dependent innate immune responses, including caspase-1 activation and processing of IL-1β and IL-18. Inhibition of Orf63 expression resulted in increased expression of IL-1β during the KSHV life cycle. Although Orf63 does not demonstrate significant similarity to NLRP3, it interacts with NLRP3 and blocks NLRP3 activity (Gregory et al., 2011). Another virus, measles virus (MV), also encodes the nonstructural V protein to antagonize host innate immune responses. The recombinant MV lacking the V protein induces more IL-1β than the parental virus. On the contrary, THP-1 cells stably expressing the V protein suppress NLRP3 inflammasome-mediated IL-1β secretion. Furthermore, the study indicates that the V protein of MV interacts with NLRP3 through its C-terminal domain, thereby inhibiting NLRP3 inflammasome-mediated IL-1β secretion (Komune et al., 2011).

CONCLUSION

In the past decades, great advances have been made in our understanding of molecular mechanisms in innate immune system activation, particularly about inflammasomes. The activation and regulation mechanisms of NLRP1, NLRP3, NLRC4, and AIM2 inflammasomes are beginning to be characterized in detail, among which NLRP3 inflammasome is the best indentified, several activation models are proposed and parts of the negative regulatory mechanisms are proved. Pathogens inhibit activation of the NLRP3 inflammasome by evading recognition or disrupting the formation and signaling of it. On the other hand, the host keeps inflammasome under control through autophagy, T cell modulation, endogenous host molecules such as Trims and NO, microRNA and cytokines of innate or adaptive origin. Such multiple and nonredundant negative regulators of the NLRP3 inflammasome provide multiple checkpoints to ensure appropriate immune responses by concerted effort. But other regulators not found yet as well as the relative importance of these regulators need to be investigated in future.

ABBREVIATIONS

3′UTRs, 3′ untranslated regions; Atg16L1, autophagy-related gene 16-like 1; CAPS, cryopyrin/NLRP3-associated periodic syndromes; CARD, caspase recruitment domain; COPs, CARD-only proteins; CTLs, C-type lectins; DAMPs, endogenous damage-associated molecular patterns; DC, dendritic cell; FACS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; IFNs, interferons; IL, interleukin; LRRs, leucine-rich repeats; miRNA, microRNA; MSU, monosodium urate; mtDNA, mitochondrial DNA; MV, measles virus; MWS, Muckle–Wells syndrome; NLRs, NOD-like receptors; NO, nitric oxide; NOMID, neonatal-onset multisystem inflammatory disease; PAMPs, pathogen-associated molecular patterns; POPs, Pyrin-only proteins; PRRs, pattern-recognition receptors; PYD, pyrin domain; RLHs, RIG-like helicases; ROS, reactive oxygen species; T3SS, type III secretion system; TLRs, Toll-like receptors; TXNIP, thioredoxin-interaction protein

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