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Microbes and Infection xx (2013) 1−10

www.elsevier.com/locate/micinf

Review

NLRP7 and related inflammasome activating pattern recognition receptors and their function in host defense and disease

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Received 7 January 2013; accepted 9 April 2013

Abstract

Host defense requires the maturation and release of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 and the induction of pyroptotic cell death, which depends on the activation of inflammatory Caspases within inflammasomes by innate immune cells. Several cytosolic pattern recognition receptors (PRRs) have been implicated in this process in response to infectious and sterile agonists. Here we summarize the current knowledge on inflammasome-organizing PRRs, emphasizing the recently described NLRP7, and their implications in human disease.

Keywords: Inflammasome; Pattern recognition receptor; Nod-like receptor; AIM2-like receptor; Inflammation; Hydatidiform mole

1. Introduction

To maintain tissue homeostasis, a strong defense against pathogenic microorganisms as well as the restriction of commensal bacteria is crucial. Pattern recognition receptors (PRRs) are germline-encoded "sensors" of the innate immune system that detect infections and tissue damage as a first line of defense. PRRs sense so-called conserved non-self pathogen-associated molecular patterns (PAMPs) and host-derived danger signals (damage-associated molecular patterns or DAMPs) to initiate a host defense program through activation of various signal transduction pathways, which culminates in pathogen clearance and initiation of wound healing. Most of these pathways activate a transcriptional response leading to the up-regulation of nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK) and interferon (IFN)-dependent genes, which encode cytokines, chemokines, adhesion receptors and others. However, for the maturation of the pro-inflammatory cytokines IL-1β and IL-18 into their biologically active and secreted forms, as well as for the induction of pyroptotic cell death of infected and damaged cells, additional processing in inflammasomes is required. Although inflammasome activation is beneficial for host defense, its dysregulation and in particular, excessive and uncontrolled release of IL-1β and IL-18, is linked to an increasing number of inflammatory and metabolic diseases. Therefore, the mechanism and regulation of inflammasome activation are under active investigation and relevant for multiple disciplines. Here, we discuss PRRs that are currently known to assemble inflammasomes, including the recently characterized PRR, the nucleotide-binding domain and leucine-rich repeat containing gene family member with a pyrin domain 7 (NLRP7, also know as *PYPAF3*, *NALP7*, *PAN7*, *NOD12*, *CLR19.4* and *HYDM*) and its role in inflammasome signaling and human disease.

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http://dx.doi.org/10.1016/j.micinf.2013.04.001

2. Inflammasomes

Inflammasomes are cytosolic multi-protein complexes that link pathogen recognition by specific cytosolic PRRs, including the NOD-like receptors (NLRs) and the Absent in melanoma 2 (AIM2)-like receptors (ALRs) to the activation of pro-inflammatory Caspases, including Caspase-1, -4 and -5 in humans and Caspase-1 and -11 (the Caspase-4 ortholog) in mice (Fig. 1) [1]. Caspase-1 mediates the proteolytic cleavage of pro-IL-1β and pro-IL-18, resulting in the bioactive, secreted form of these cytokines that act to initiate and perpetuate inflammatory host responses. Caspase-1 also promotes the release of other mediators, including IL-1α, IL-1Ra, HMGB1, FGF-2 and others through an unconventional secretion mechanism [2]. Infections by Gram-negative bacteria further require IFN-induced up-regulation of Caspase-11 upstream of Caspase-1 [3]. In addition, recent evidence shows that Caspase-8 can substitute for Caspase-1 under certain conditions [4,5]. Besides cytokine maturation, Caspase-1 also mediates inflammatory cell death (pyroptosis) of infected host cells [6]. Caspase-1 is recruited to activated PRRs by the central inflammasome adaptor apoptosis-associated speck-like protein containing a Caspase recruitment domain (CARD) (ASC, PyCard, TMS-1) [7,8]. Subsequently, Caspase-1 clustering causes its auto-activation through induced proximity. ASC is crucial for all inflammasomes activated by NLR family members containing a PYRIN domain (NLRPs) and ALRs (Fig. 1). However, NLRC4 (IPAF, CLAN), an NLR family member containing a CARD (NLRC), can directly recruit Caspase-1 [9–11], but ASC is nevertheless required for inflammasome activation in response to certain bacterial infections *in vivo*. In contrast to Caspase-1-dependent cytokine processing, which requires ASC and occurs in a singular distinct perinuclear inflammasome complex [12], Caspase-1-dependent pyroptosis proceeds independently of ASC and Caspase-1 autoproteolysis [13]. While the induced proximity mechanism of Caspase-1 activation is fairly well understood, the signaling events upstream of inflammasome-initiating PRRs of the NLRP, NLRC and ALR families are largely unknown.

2.1. NLR inflammasomes

22 *NLRs* are encoded in humans, while 34 *Nlrs* exist in mice. They are divided into five subfamilies based on their N-terminal effector domain: 1) *NLRA* (NLR containing an acidic domain), 2) *NLRB* (NLR containing a BIR domain), 3) *NLRC*, 4) *NLRP* and 5) *NLRX* (NLR with no homology to the N-terminal domain of any other NLR member). However, only a few members have so far been linked to inflammasome activation, including NLRP1, NLRP3 and NLRC4. NLRs sense and respond to a diverse array of infectious and sterile inflammatory signals with activation that promotes a conformational change, followed by receptor oligomerization, which is driven by nucleotide triphosphate binding and hydrolysis and the formation of the inflammasome platform upon recruitment of ASC-Caspase-1 and likely other proteins.

2.1.1. NLRP1

NLRP1 recognizes muramyl-dipeptide (MDP) and the lethal toxin (LT) from *Bacillus anthracis* [14,15]. While the recently generated *Nlrp1b* deficient mice confirmed the response to LT, they failed to show defects in the MDP response, which required Nlrp3 [16]. NLRP1 is unique among NLRs, due to the presence of an N-terminal PYRIN domain (PYD) and a C-terminal CARD, which not only allows it to recruit ASC and Caspase-1 through its PYD but also simultaneously to bind Caspase-5 directly through its CARD [1]. Of note is that the *NLRP1* gene has three paralog mouse genes, *Nlrp1a*, *Nlrp1b* and *Nlrp1c*, which all lack the PYD present in NLRP1. This might contribute to the conflicting observations

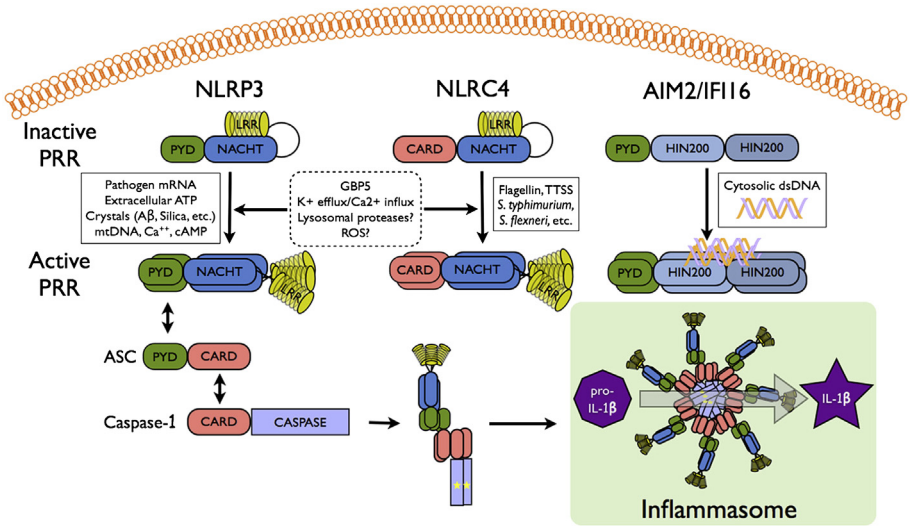

Fig. 1. Model for inflammasome activation. Stimuli that activate known inflammasomes are indicated, which cause oligomerization of the respective PRR. In the case of NLRs, oligomerization is induced by NACHT domain-mediated NTP binding. Subsequently, ASC and Caspase-1 are recruited by PYD–PYD and CARD–CARD interaction, respectively, which results in assembly of the inflammasome platform and activation of Caspase-1, as depicted by an asterisk. Proteolytically active Caspase-1 then converts pro-IL-1β and pro-IL-18 into their bioactive, mature forms.

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found in the MDP-induced inflammasome response. ATPase activity within the NACHT is required for NLRP1 oligomerization and Caspase-1 activation [15].

2.1.2. NLRP3

NLRP3 (Cryopyrin) is clearly the best studied of the NLRs, which senses a wide variety of structurally different infectious and non-infectious agonists. Generally, NLRP3 activators affect potassium efflux, destabilization of the acidic lysosomal compartment and subsequent cathepsin B release, generation of reactive oxygen species (ROS), although the precise contribution of ROS is still controversial, and ultimately converge on the release of mitochondrial oxidized DNA and calcium mobilization from ER stores upon calcium-sensing receptor (CASR) activation [17−19]. For non-particulate activators, association of the PYD of NLRP3 with the guanylate-binding protein 5 (GBP5) is necessary for potent inflammasome activation [20]. Furthermore, depletion of intracellular levels of cAMP upon CASR activation prevents cAMP-mediated inhibition of the NACHT domain, which is also necessary for NLRP3 activation [17]. Thus, mice deficient in *Nlrp3* are impaired in clearing numerous viral, microbial, fungal and protozoan pathogens due to defects in mounting an IL-1β and IL-18-based host response. The leucine-rich region (LRR) of NLRP3 is necessary for NLRP3 activation, since deletion of this domain impairs NLRP3 activation in response to monosodium urate monohydrate (MSU) crystals *in vivo* [21].

2.1.3. NLRP6

NLRP6 interacts with ASC and forms an inflammasome by overexpression [22]. More recently, *Nlrp6* deficient mice revealed that it is essential for restricting commensal bacteria to maintain homeostasis through promoting IL-18 release [23]. *Nlrp6* deficient mice are also resistant to infection with *Listeria monocytogenes*, *Salmonella typhimurium* and *Escherichia coli* due to an enhanced production of MAPK- and NF-κB-dependent cytokines [24]. However, the ligands specifically sensed by NLRP6 are currently not known.

2.1.4. NLRC4

NLRC4 (IPAF) is essential for inflammasome activation in response to flagellated bacteria through sensing flagellin, but is also activated through a flagellin-independent mechanism (Fig. 1) [9,11]. The latter occurs through the bacterial type III and IV secretion system (T3SS and T4SS, respectively) [25]. Activation of NLRC4 requires the recognition and binding of flagellin or the T3SS rod proteins by upstream NLRB (NAIP) proteins, which causes phosphorylation of NLRC4 [26]. Although, only one *NLRB* exists in humans, mice encode seven *Naip* genes. While Naip2 interacts with T3SS rod proteins, such as PrgJ from *S. typhimurium* and BsaK from *Burkholderia*, Naip5 and Naip6 bind to flagellin from *Legionella pneumophila* and similarly, human NAIP is necessary for sensing the T3SS needle protein CprI from *Chromobacterium violaceum* [27].

2.1.5. NLRC5

The precise function of NLRC5 is still controversial [28], but it is strongly implicated in the regulation of MHC class I gene expression [29]. Nevertheless, it has also been linked to inflammasome activation in response to bacterial infection through a mechanism involving heterodimerization with NLRP3 [30]. However, while HEK293 cell-reconstituted NLRC5 inflammasomes were active, deficiency of *Nlrc5* in mouse BMDM and DC did not affect Caspase-1 activation and IL-1β release with any stimuli that are known activators of other inflammasomes, suggesting that NLRC5 likely responds to unknown pathogenic or endogenous inflammasome activators, or alternatively, functions in other, non-macrophage cells [31].

2.2. ALR inflammasomes

In humans, 4 ALRs (IFI16, IFIX, MNDA, and AIM2) have been annotated, while 13 genes are predicted to exist in mice, which are referred to as γ-IFN-inducible (*Ifi*) genes or the hematopoietic interferon-inducible nuclear antigens with a 200 amino acid repeat (HIN200) members 202 to 214 and the encoded p200 proteins (p202 to 214) [32]. Strikingly, these genes are highly diverse and only AIM2 (p210) is conserved between mouse, rat and humans, although *Ifi204* is predicted to be the mouse IFI16 ortholog [32]. All ALRs, except for p202, contain an N-terminal PYD and contain one or two C-terminal partially conserved HIN200 DNA-binding domains [33]. However, so far only AIM2 and IFI16 have been shown to assemble an inflammasome.

2.2.1. AIM2

Although the ALR AIM2 is structurally different from NLRs, it functions as a cytosolic PRR involved in inflammasome activation. It contains an N-terminal PYD and one copy of the conserved HIN-200 DNA-binding domain. AIM2 directly binds to cytosolic double stranded (ds) DNA through the HIN-200 domain and forms an inflammasome in response to bacterial and viral infections, including *Francisella tularensis*, *L. monocytogenes*, Vaccinia virus and murine cytomegalovirus (MCMV) (Fig. 1) [34,35]. Despite its lack of a PYD, p202 has been shown to sense cytosolic DNA and to form a heterodimer with AIM2 *in vitro*, which is predicted to inhibit AIM2-induced clustering of the adaptor protein ASC and Caspase-1 activation [36].

2.2.2. IFI16

The ALR IFI16 is a predominantly nuclear protein also involved in DNA binding and recognition, but contains two copies of the HIN-200 domain (Fig. 1). *IFI16* is not encoded in mice, but has a putative orthologous gene, *ifi204*. In contrast to infection by MCMV, infection with another herpes virus, the Kaposi sarcoma-associated herpes virus (KSHV), which replicates and establishes a latent infection in the nucleus, does not trigger a cytosolic DNA response but initially activates a nuclear IFI16 inflammasome [37].

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2.3. Other inflammasomes

2.3.1. Pyrin

Pyrin interacts with various inflammasome components and is able to negatively regulate inflammasome responses [38,39]. However, Pyrin has also been implicated in inflammasome activation upon binding to PSTPIP1 and in particular to PAPA syndrome-linked PSTPIP1 mutants [40,41]. An inflammasome activating function of Pyrin is further supported by the recently generated knock-in mice expressing the constitutive active, FMF-linked mutation of Pyrin ($Mefv^{M680I}$, $Mefv^{M694V}$ and $Mefv^{V726A}$), which show constitutive and ASC-dependent Caspase-1 activation and elevated IL-1β [42].

3. NLRP7 and its link to inflammasomes

There is emerging evidence that NLRP7 is able to regulate inflammasomes. However, conflicting reports describe NLRP7 as either an inflammasome activator or as an inhibitor of Caspase-1-dependent production of mature IL-1β and IL-18 (Fig. 2) [43–45]. The *NLRP7* gene, also referred to as *PYPAF3*, *NALP7*, *PAN7*, *NOD12*, *CLR19.4* and *HYDM* is located on the long arm of human chromosome 19 at position q13.42, but no true mouse orthologous gene exists. *Nlrp2* is the closest relative and NLRP2 is located adjacent to NLRP7 on human chromosome 19. Similar to NLRP3, NLRP7 transcription is induced in response to pro-inflammatory stimuli, including LPS and IL-1β in peripheral blood mononuclear cells (PBMC) and is abundantly expressed in thymus, spleen and bone marrow, suggesting a role in inflammation and host defense. However, its expression is not restricted to the immune system and is also high in the nervous system and testis [44]. The domain architecture of NLRP7 is reminiscent of other NLR family members and contains an N-terminal PYD followed by a NACHT domain and 11 LRRs at the C-terminus. As observed for other NLR family members, NLRP7 is subjected to differential splicing (Fig. 3), which primarily affects the number of LRRs, but one alternative transcript also lacks the NACHT domain, likely yielding a dominant negative protein due to defective oligomerization.

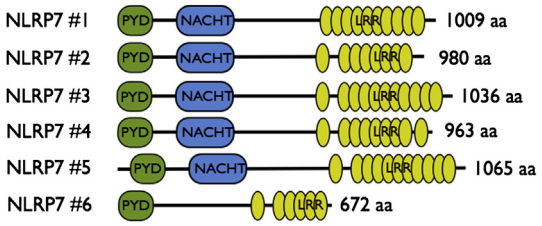

Fig. 3. Differential splicing of NLRP7. Several alternative transcripts exist for NLRP7, which encode a varying number of LRRs or delete the NACHT, further supporting the importance of these domains for the function of NLRP7.

Although the function of NLRP7 is poorly understood, several proteins have been identified that interact with NLRP7, including pro-Caspase-1, pro-IL-1β, ASC and Fas associated factor 1 (FAF1), which likely influence the functional aspects attributed to NLRP7 as discussed below.

3.1. Negative regulation of inflammasome responses by NLRP7

Several NLR family members trigger inflammasome formation and regulate NF-κB activation, but the initial *in vitro*

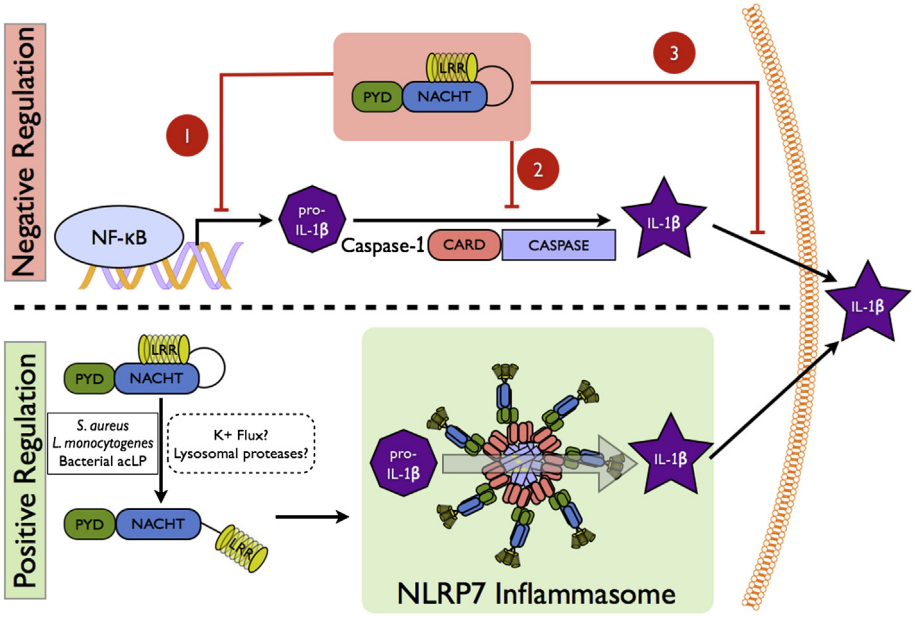

Fig. 2. Mechanisms of NLRP7 function in inflammation and host defense. The top panel depicts the proposed mechanisms by which NLRP7 inhibits IL-1β release. 1) NLRP7 inhibits NF-κB activation by an unknown mechanism, which may involve FAF1, which prevents transcription of pro-IL-1β. 2) NLRP7 directly interacts with pro-Caspase-1 and pro-IL-1β, which might prevent their activation or recruitment into inflammasomes. 3) NLRP7 localizes to the Golgi and was predicted to affect trafficking of mature IL-1β containing vesicles necessary for release. The bottom panel depicts NLRP7 inflammasome formation in response to sensing bacterial acylated lipoproteins (acLP).

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characterization of the NLR family member NLRP7 revealed an inhibitory function of NLRP7 on IL-1β secretion. Utilizing an inflammasome reconstitution assay in HEK293 cells, Kinoshita and colleagues demonstrate that NLRP7 (PYPAF3) inhibits NLRP3 and Caspase-1 mediated IL-1β release, as well as pro-Caspase-1 and pro-IL1β processing without affecting ASC-mediated NF-κB activation [44]. The proposed mechanism for inflammasome inhibition of NLRP7 is through its direct interaction with pro-Caspase-1 and pro-IL-1β, which was shown by co-immunoprecipitation, but not through inhibition of IL-1β transcription, since NF-κB was not impaired. In addition, stable expression of an N-terminal fragment of NLRP7 prevents LPS-induced IL-1β release in THP-1 cells. However, it should be noted that this NLRP7 fragment lacked some of the functional domains of NLRP7 and could therefore represent a dominant negative form of this protein functioning as an inflammasome inhibitor.

Another study of NLRP7 by Messaed and colleagues focuses on the functional consequences of NLRP7 mutations found in patients with recurrent hydatidiform moles (HM) [43]. Interestingly, IL-1β and TNFα secretion is diminished in response to LPS in PBMCs containing HM-associated NLRP7 mutations compared to PBMCs from healthy controls. However, processing of intracellular pro-IL-1β into mature IL-1β is not affected and all but one HM patients have normal to higher protein levels of intracellular pro- and mature IL-1β, which implies an inflammasome independent function of NLRP7, but suggests a function of NLRP7 in cytokine secretion. In PBMCs, NLRP7 co-localizes to the Golgi apparatus and the microtubule-organizing center, where mutated NLRP7 may affect cytokine trafficking and secretion by interfering with the classical and non-classical secretory pathways. While expression levels of NLRP7 and mutated NLRP7 in HM patients are similar, overexpression of NLRP7 or HM-associated missense mutants of NLRP7 in HEK293 cells causes reduced protein levels of overexpressed intracellular pro- and mature IL-1β. However, HM associated nonsense mutants of NLRP7, which harbor a stop codon shortly after the PYD, are unable to decrease intracellular pro- and mature IL-1β. Similarly, overexpression of several NLRP7 domain or domain-deletion constructs all cause reduced intracellular pro- and mature IL-1β, except for the PYD [43]. Overall, NLRP7 is expected to down-regulate intracellular pro- and mature IL-1β, while HM-associated mutations in NLRP7 prevent this function and lead to increased intracellular pro- and mature IL-1β. The precise mechanism for regulating intracellular IL-1β as well as the mechanism describing NLRP7 involvement in IL-1β and TNFα secretion remain unclear.

Several NLRs have an anti-inflammatory function including NLRP6, NLRP10 (PYNOD) and NLRP12 (Monarch-1), which are able to prevent NF-κB activation and subsequent cytokine production, although an anti-inflammatory role for Nlrp10 is not observed *in vivo*. NLRP7 could also be linked to the inhibition of inflammation by interacting with NF-κB regulatory proteins, such as FAF1, which interacts with several NLRs, including NLRP2, NLRP3, NLRP7, NLRP10 and NLRP12 and promotes apoptosis and inhibits NF-κB activation [46]. However, a study investigating the effects of several NLRs, including NLRP7, on NF-κB activation failed to detect an inhibitory role of NLRP7 on NF-κB activation in a COS-7L cell system and silencing of NLRP7 in human macrophages also does not modulate cytokine and LPS-induced NF-κB activation [22,45].

Collectively, *in vitro* evidence supports a role of NLRP7 in inhibiting inflammation by several possible mechanisms, including direct binding and inhibition of inflammasome components, impairing transcription of pro-IL-1β and modulating the trafficking and release of IL-1β (Fig. 2). However, as most of these studies were performed in a reconstitution system in the absence of the essential inflammasome adaptor ASC, their findings will require further confirmation.

3.2. Positive regulation of inflammasome responses by NLRP7

Overexpression of NLRP7 inhibits inflammation through several mechanisms, as discussed above. However, there is also evidence for a pro-inflammatory role of NLRP7 in human macrophages. Using an siRNA-based screen, NLRP7 was specifically identified as an intracellular sensor for bacterial acylated lipoproteins, which is required for IL-1β release (Fig. 2) [45]. While Toll-like receptor (TLR) 2 heterodimers are responsible for mediating NF-κB activation and subsequent transcription of pro-IL-1β in response to bacterial acylated lipoproteins, NLRP7 is essential for bacterial acylated lipoprotein-mediated Caspase-1 activation and maturation of IL-1β and IL-18. Similar to other inflammasome-activating NLRs, also NLRP7 shifts into a large, high molecular weight complex, where it interacts with ASC and Caspase-1 and promotes Caspase-1 activation [45]. Even though the PYD of NLRP7 lacks a positively charged electrostatic interaction patch, which promotes interaction with ASC, endogenous NLRP7 and ASC are able to interact [45,47]. More importantly, NLRP7 is also crucial for restricting growth of intracellular bacteria, including *Staphylococcus aureus* and *L. monocytogenes* in macrophages [45]. *L. monocytogenes* is also sensed by NLRC4, NLRP3 and AIM2, suggesting that several distinct NLRs form inflammasomes to control bacterial infections. Although NLRP3 does not sense bacterial acylated lipoproteins, a similar mechanism involving lysosomal damage upstream of NLRP7 is required for inflammasome activation. Thus, there is compelling evidence that NLRP7 acts as a direct or indirect cytosolic sensor of microbial acylated lipopeptides during infection.

While these findings appear to be contradictive, it is conceivable that NLRP7 prevents inflammasome formation and IL-1β release in quiescent cells, while in the response to a proper stimulus, such as bacterial infection, NLRP7 is activated, recruits ASC and assembles an inflammasome to promote Caspase-1 activation, IL-1β and IL-18 release for bacterial clearance. This mechanism could ensure that cytokine release occurs only when required. NLRP7 may also exhibit these opposing functions in a cell-type-specific manner. However, the molecular details and the specificity

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of NLRP7 sensing bacterial acylated proteins are still elusive. While NLRP3 and its role in inflammasome activation is well established, we are just now beginning to unravel the mechanism of its activation. Similar to NLRP3 disease-causing mutations, NLRP7 mutations are also linked to human disease. Therefore elucidating the function of NLRP7 is important for a better understanding of innate immune responses as well as NLRP7-linked disease.

4. Inflammasomes and disease

4.1. Mutations in inflammasome proteins

Due to their critical role in host defense, mutations in NLRs and the resulting dysregulated inflammasome activation is also linked to several human autoinflammatory diseases, which are characterized by unprovoked episodes of inflammation in the absence of high-titer autoantibodies and antigen-specific T cells, and are commonly referred to as inflammasomopathies [48]. After positional cloning identified Pyrin (marenostrin, *MEFV*) as the underlying cause for one of the most common autoinflammatory disease, Familial Mediterranean fever (FMF), more than 80 mutations of Pyrin have been identified in FMF patients. Recently generated mouse models implicate excessive inflammasome activation in the pathogenesis of FMF [42]. Similarly, positional cloning for several related autoinflammatory diseases, including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID or CINCA), identified NLRP3 (Cryopyrin, *CIAS1*), and subsequently mutations in NLRP3, as the underlying cause for these diseases, which are now referred to as Cryopyrinopathies (CAPS) [49]. Similar to Pyrin, knock-in of mutant NLRP3 in mice caused excessive inflammasome activation and release of IL-1β, and confirmed that CAPS originate from NLRP3 mutations causing dysregulated inflammasome activation [50,51]. However, these mice also displayed a skewed Th17 response and further support a role of the NLRP3 inflammasome in regulating adaptive immunity.

4.2. Inflammasomes and crystalline arthropathies

A number of crystalline and particulate substances have been identified as agonists for the NLRP3 inflammasome. Hence, the presence of these substances causes inflammasome activation, excessive IL-1β release and the development of crystalline arthropathies. In gout and pseudogout the NLRP3 inflammasome is activated in response to monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPPD) crystals and responds to asbestos and silica fibers in asbestosis and silicosis, respectively [52–55]. Similarly, amyloid-β fibrils and islet amyloid polypeptide (IAPP) activate the NLRP3 inflammasome, which may contribute to Alzheimer's disease and the progression of type 2 diabetes, respectively [56,57]. Interestingly, cholesterol crystals are also sensed by NLRP3, which may contribute to the chronic vascular inflammation caused by cholesterol crystal deposition at the artery wall and the development of atherosclerotic lesions. Hence, inflammasome deficient mice develop reduced atherosclerotic lesions compared to wild type mice [58]. In addition the vaccine adjuvant aluminum hydroxide (alum) and hemozoin crystals, produced by malaria-causing parasites, are able to induce an NLRP3 dependent inflammasome response [59–62].

4.3. Inflammasomes and metabolic disease

Recent evidence revealed that inflammasomes are also central in maintaining metabolic homeostasis, and that defects in this inflammasome-mediated surveillance of the gastrointestinal tract contribute to obesity, insulin resistance, type 2 diabetes, atherosclerosis, non alcoholic fatty liver disease (NAFLD) and eventually development of non-alcoholic steatohepatitis (NASH). This is not surprising, given that chronic inflammation is a key factor driving metabolic disease. In particular, NLRP6 was discovered to play a central role within the gastrointestinal tract to restrict colitogenic microbiota species, specifically members of the *Prevotellaceae* and TM7 environmental bacteria families, which have also been linked to increased body mass index in humans [23]. Restricting these colitogenic species is dependent on IL-18, rather than IL-1β and dysbiosis causes increased PAMP-perpetuated inflammation, eventually leading to systemic metabolic dysfunction [23,63]. Similar results were also obtained for mice deficient in *Nlrp3* and *Nlrc4*, indicating that several PRRs collaborate also in this context [63–65].

Increasing evidence also supports a contribution of NLRP3 to obesity-initiated insulin resistance and type 2 diabetes, since increased lipid storage in hypertrophic adipocytes supplies NLRP3-activating DAMPs, including the saturated fatty acid palmitate and saturated fatty acid metabolism-derived ceramide [66–68]. Subsequently, excessive production of IL-1β impairs glucose tolerance and insulin sensitivity in peripheral insulin target tissues, and also directly promotes cell death of pancreatic β-cells. Further, the NLRP3 activator IAPP is deposited in the pancreas of type 2 diabetes patients which, in combination with high glucose levels, promotes inflammasome priming [57].

4.4. Inflammasomes and adaptive immunity

Inflammasomes are most significant for host defense in innate immune cells, such as macrophages and DC as a first line of defense. IL-1β, the IL-1RI, and IL-18 are also required for the induction of Th17 cells and IL-17 production by unconventional γδT cells in the presence of commensal bacteria and in several auto-immune disease models, including experimental autoimmune encephalomyelitis (EAE) [69,70]. Inflammasome-derived IL-1β also promotes GM-CSF production from $CD4^+$ and γδT cells, which has an essential role in EAE [71]. IL-22, which has protective, but pro-inflammatory properties, is produced by innate lymphoid cells, Th17 cells and Th22 cells and is regulated through its soluble receptor, IL-22BP. In turn, IL-22BP is inhibited through IL-18 produced at mucosal surfaces by NLRP3 and

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NLRP6 inflammasomes [72]. Synergistically with IL-12, IL-18 stimulates Th1-mediated and IFN-γ-dependent immune responses, but also promotes auto-immunity [73]. Thus, increasing evidence supports the notion that inflammasome activation in antigen presenting cells provides the necessary cues for regulating adaptive immunity in models of contact skin hypersensitivity, EAE and aluminum hydroxide adjuvant-mediated T-cell priming, extending the role of inflammasomes from innate to adaptive immunity. The contribution of IL-1β and IL-18 in the context of alum-induced inflammasome-mediated regulation of adaptive immunity remains controversial [60].

5. NLRP7 and disease

Until now, the only clinical evidence for the involvement of NLRP7 in human disease originated from genetic studies mapping the locus responsible for hydatidiform mole (HM), an abnormal human pregnancy referred to as molar pregnancy to human chromosome 19q13, and subsequently linked to several mutations within the *NLRP7* (*NALP7*) gene [74]. In addition, the lack of *NLRP7* mutations in a large control cohort and co-segregation of mutated alleles with disease phenotypes, supports a contribution of NLRP7 in the development of HM [74]. While recurrent molar pregnancies occur in 1 in 150 to 1 in 1000 pregnancies, depending on the ethnic group, familial recurrent HM (FRHM) is exceptionally rare. However, women who had a previous mole have a higher risk of recurrence (1.2–1.4%), which increases to 20% after the second mole. HM is a form of trophoblastic neoplasia characterized by cystic degeneration of the chorionic villi and abnormal or lack of embryonic growth. It is a heterogeneous condition, which is classified into two major groups according to karyotypic and histopathological features: complete HM and partial HM. Both HM subtypes result in reproductive wastage and/or spontaneous abortion. However, while 5–25% of complete HMs eventually develop into gestational choriocarcinoma, only 2–3% of partial HMs develop this highly aggressive cancer, which may spread to the lungs, lower genital tract, brain, liver, kidney and gastrointestinal tract via the bloodstream or lymphatic vessels [75]. So far 214 unique sequence variants of *NLRP7* have been associated with this group of diseases [76]. While HM patients harbor homozygous, compound heterozygous and heterozygous *NLRP7* genotypes, FRHM can also occur in the absence of *NLRP7* mutations, which underlines the multifactorial nature of the disease [77]. Although mutations are found throughout most exonic and intronic regions of *NLRP7*, the region encoding the LRR represents a particularly common location of missense mutations and many identified nonsense mutations yield NLRP7 proteins lacking the LRR domain, emphasizing the importance of this domain for the function of NLRP7 (Fig. 4) [78]. Recently, the importance of the NLRP7 LRR was also recognized for sensing bacterial acylated lipoproteins *in vitro*, since NLRP7$^{\Delta LRR}$ failed to respond to bacterial acylated lipoproteins, compared to wild type NLRP7 [45]. Similarly, deletion of the Nlrp3 LRR rendered the protein unresponsive to MSU crystals *in vivo*, resulting in ameliorated airpouch synovitis [21]. Overall the LRR seems to play an important functional role for NLRs.

The functional consequence of *NLRP7* mutation and its effect on reproductive fidelity is not understood. The distinctive and arguably opposing models for NLRP7 function in inflammatory signaling allows for different interpretation of its possible role in molar pregnancy. Whether IL-1β, IL-18 or any inflammation, infection or commensal bacteria contribute to HM at all is currently not known. However, histopathological analysis of placentas from HM patients revealed an increased

Selected NLRP7 Mutations by Domain

Domain	Genetic Variant	Protein Variant	Associated Phenotype
PYD	C219T	N73N	Unknown
	G251A	C84Y	RHM
NACHT	G544A	V182M	CHM, NRHM
	C628T	L210F	None
	T701C	L234S	RHM, Normal Pregnancy
	A829C	K277Q	RHM
	G1137C	V319I	RHM, Normal Pregnancy
	G1441A	A481T	RHM, Normal Pregnancy
	G1460A	G487E	RHM
LRR	G2078C	R693P	RHM
	G2282A	C761Y	RHM, PTD
	C2383T	R795C	NRHM
	G2497A	A833T	Unknown
	A2738G	N913S	RHM, Invasive Mole

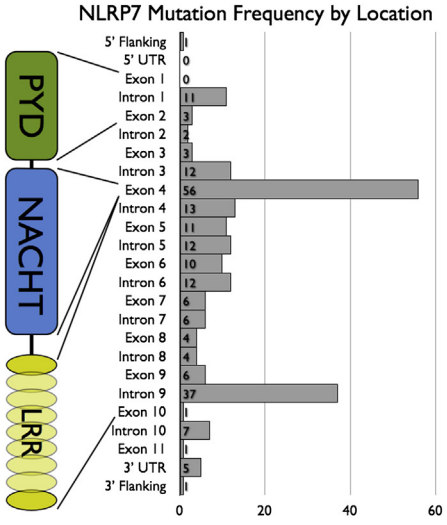

Fig. 4. NLRP7 mutations and linkage to reproductive disease. (left) Selected characterized genetic variations in exonic regions of the *NLRP7* locus and the resulting amino acid changes in NLRP7 are listed by domain. Associated phenotypes for each individual mutation and mutations with higher frequency are indicated that occur in more than five unrelated families. (right) Histogram of mutations in the *NLRP7* locus, which are organized by frequency within both coding- and non-coding regions and location to the individual NLRP7 domains. RHM: recurrent hydatidiform mole; CHM: complete hydatidiform mole; NRHM: non-recurrent hydatidiform mole; PTD: persistent trophoblastic disease.

Please cite this article in press as: A.D. Radian, et al., NLRP7 and related inflammasome activating pattern recognition receptors and their function in host defense and disease, Microbes and Infection (2013), http://dx.doi.org/10.1016/j.micinf.2013.04.001

incidence of chorioamnionitis, necrosis and chorangiosis, potentially implicating excessive tissue inflammation [79]. Analysis of PBMCs from several HM patients revealed a spectrum of IL-1β levels ranging from lower to higher than controls, with a similar broad range that has also been observed in earlier studies in the general population [43]. While wild-type NLRP7 inhibits pro-IL-1β transcription/translation *in vitro*, all tested missense mutations of NLRP7 do not affect this function, suggesting that this function of NLRP7 is not affected by HM mutations [43]. A potential loss-of-function could prevent NLRP7 to regulate physiological inflammation and may allow for increased insult from commensal and other pathogens in the lower reproductive tract, or potentially renders HM patients to tolerate growth of moles due to impaired immune surveillance [43]. Conversely, a pro-inflammatory role of NLRP7 in response to *S. aureus* infection could also imply a gain-of-function, in which NLRP7 mutants are hyperactive and contribute to excessive inflammation. Indeed, gain-of-function mutations have been classified in other NLR family members, such as NLRP3, where mutations cause Cryopyrinopathies [49]. In fact, several common HM-linked NLRP7 mutations show hyperactivity *in vitro*, which, however, has not yet been confirmed in a more physiological context [45]. Thus, a contribution of inflammatory signaling in the development of molar pregnancy has still to be firmly established. In addition, inflammation-independent functions for NLRP7 may potentially contribute to the development of HM. Interestingly, expression levels of NLRP7 are highly elevated in embryonal carcinomas and testicular seminomas, when compared to normal testis, implying a potential role in germ-cell proliferation. Further, RNAi-mediated silencing of NLRP7 causes growth suppression of testicular germ-cell tumors, suggesting a role in cell proliferation, which could contribute to HM [80].

6. Concluding remarks

Despite an emerging role of NLRP7 in inflammation, the precise role by which it impacts inflammasome activity is still poorly understood and thus, additional studies are necessary to unravel the mechanism of action of NLRP7. In particular, the mechanism of ligand recognition by NLRP7 and its potential conversion from an inhibitor to an activator of inflammasomes and the consequences on inflammatory signaling requires further studies. Moreover, since a significant percentage of HM patients lack mutations in *NLRP7*, additional studies with wild type and HM-linked NLRP7 mutants are necessary to elucidate the detailed mechanism, by which potential gain- or loss-of-function defects in NLRP7 contribute to the multifactorial HM disease.

Acknowledgments

This work was supported by grants from the NIH to C.S (R01GM071723, R21AI092490, R21HL097183, R01AR064349, R01AI083506 and P30AR057216) and A.D (R03AR057532). L.d.A. is supported by a postdoctoral fellowship from the American Heart Association (11POST585000). The authors have no conflicting financial interests.

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Please cite this article in press as: A.D. Radian, et al., NLRP7 and related inflammasome activating pattern recognition receptors and their function in host defense and disease, Microbes and Infection (2013), http://dx.doi.org/10.1016/j.micinf.2013.04.001