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REVIEW

NALP Inflammasomes: a central role in innate immunity

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Abstract Inflammasomes are cytoplasmic multiprotein complexes that mediate the maturation of the proinflammatory cytokines interleukin-1β (IL-1β), IL-18, and possibly IL-33 by controlling the activation of the inflammatory caspases-1 and -5. Assembly of inflammasomes depends on NOD-like receptor (NLR) family members such as NALPs, NAIP, and IPAF. Various microbial and endogenous stimuli activate different types of inflammasomes. This article focuses on the Pyrin domain containing NLRs, known as NALP proteins. Recent findings provide exciting insights into how these proteins might be activated and also provide evidence of the critical role of the NALP inflammasomes in innate immunity and inflammatory diseases.

Keywords Inflammasome · NLRs · Interleukin-1β · Innate immunity · Autoinflammation

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Abbreviations

ASC	Apoptosis-associated speck-like protein containing a CARD
CARD	Caspase recruitment domain
DNFB	2,4-dinitrofluorobenzene
ICE	interleukin-1β -converting enzyme
IL-1	interleukin-1
IPAF	ICE protease-activating factor
LRR	leucine rich repeat
MDP	Muramyl dipeptide
MSU	Monosodium urate crystals
MyD88	Myeloid differentiation protein 88
NALP	NACHT, LRR and PYD containing proteins
NACHT	Domain present NAIP, the major histocompatibility complex (MHC) class II transactivator (CIITA), HET-E and TP1
NAIP	Neuronal apoptosis inhibitory protein
NB-ARC	nucleotide-binding adaptor shared by APAF-1, *R* gene products and CED-4
NBS-LRR	nucleotide binding site-leucine-rich repeat
NLR	NOD-like receptors
PAMP	Pathogen-associated molecular patterns
PYD	Pyrin domain
TNP-CL	Trinitrophenylchloride
TNCB	Trinitrochlorobenzene

Introduction

Five years have passed since the first biochemical description of a molecular complex named the inflammasome.

This complex, containing the protein NALP1 as a scaffolding protein, was shown to activate caspase-1 and promote interleukin-1β (IL-1β) maturation [94]. IL-1β, also known as the endogenous pyrogen, is a well-known player in the process of inflammation and fever [32]. Concomitantly, various studies in humans revealed that mutations in the NALP1-related gene NALP3 (also known as cryopyrin, Table 1) were the cause of periodic fever syndromes such as the Muckle-Wells (MWS), familial cold autoinflammatory syndrome (FCAS), and chronic infantile neurological cutaneous and articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease [22, 52]. These hereditary autoinflammatory syndromes are characterized by an increased IL-1β production that directly triggers the inflammatory cascade in these patients [2, 101]. The central role of IL-1β in this pathology was highlighted

Table 1 The human and mouse NALP family

	Common nomenclature	Chromosome localization	Other names and aliases	Structure
Human	NALP1	17p13	DEFCAP; NAC; CARD7; CLR17.1; NLRP1	PYD-NACHT-NAD-LRR-FIIND-CARD
Mouse	NALP1a	11B4	Nlrp1a	NACHT-NAD-LRR-FIIND-CARD
	NALP1b	11B4	Nlrp1b	NACHT-NAD-LRR-FIIND-CARD
	NALP1c	11B4	Nlrp1c	NACHT-NAD-LRR-FIIND-CARD
Human	NALP2	19q13.42	Pypaf2; NBS1;PAN1; CLR19.9;NLRP2	PYD-NACHT-NAD-LRR
Mouse	NALP2	7A1	Nlrp2	PYD-NACHT-NAD-LRR
Human	NALP3	1q44	Pypaf1;CIAS1;Cryopyrin; CLR1.1; NLRP3	PYD-NACHT-NAD-LRR
Mouse	NALP3	11B1.3	Cias1, Pypaf1, Mmig1, Nlrp3	PYD-NACHT-NAD-LRR
Human	NALP4	19q13.43	Pypaf4;PAN2; RNH2; CLR19.5; NLRP4	PYD-NACHT-NAD-LRR
Mouse	NALP4a	7A1	Nalp-eta, NALP9D, Nlrp4a	PYD-NACHT-NAD-LRR
	NALP4b	7A1	Nalp-gamma, NALP9E; Nlrp4b	PYD-NACHT-NAD-LRR
	NALP4c	7A1	Nalp-alpha, Rnh2; Nlrp4c	PYD-NACHT-NAD-LRR
	NALP4d	7A1	Nalp-beta; Nlrp4d	PYD-NACHT-NAD-LRR
	NALP4e	7A2	Nalp-epsilon; Nlrp4e	PYD-NACHT-NAD-LRR
	NALP4f	13B3	Nalp-kappa, NALP9F; Nlrp4f	PYD-NACHT-NAD-LRR
	NALP4g	9	Nlrp4g	PYD-NACHT-NAD-LRR
Human	NALP5	19q13.42	Pypaf8; Mater, PAN11; CLR19.8; NLRP5	PYD-NACHT-NAD-LRR
Mouse	NALP5	7A2	mater; Op1; Nlrp5	NACHT-NAD-LRR
Human	NALP6	11p15.5	Pypaf5; PAN3; CLR11.4; NLRP6	PYD-NACHT-NAD-LRR
Mouse	NALP6	7F4	Nlrp6	PYD-NACHT-NAD-LRR
Human	NALP7	19q13.42	Pypaf3; NOD12; CLR19.4; NLRP7	PYD-NACHT-NAD-LRR
	NALP8	19q13.42	PAN4; NOD16; CLR19.2; NLRP8	PYD-NACHT-NAD-LRR
	NALP9	19q13.42	NOD6; CLR19.1; NLRP9	PYD-NACHT-NAD-LRR
Mouse	NALP9a	7A3	Nalp-theta; Nlrp9a	PYD-NACHT-NAD-LRR
	NALP9b	7A2	Nalp-delta; Nlrp9b	PYD-NACHT-NAD-LRR
	NALP9c	7A3	Nalp-zeta; Nlrp9c	PYD-NACHT-NAD-LRR
Human	NALP10	11p15.4	PAN5; NOD8; Pynod; CLR11.1; NLRP10	PYD-NACHT-NAD
Mouse	NALP10	7E3	Pynod; Nlrp10	PYD-NACHT-NAD
Human	NALP11	19q13.42	Pypaf6; NOD17; CLR19.6; CLR19.3; NLRP11	PYD-NACHT-NAD-LRR
	NALP12	19q13.42	Pypaf7; Monarch1; RNO2; PAN6; NLRP12	PYD-NACHT-NAD-LRR
Mouse	NALP12	7A1	Nlrp12	PYD-NACHT-NAD-LRR
Human	NALP13	19q13.42	NOD14; CLR19.7; NLRP13	PYD-NACHT-NAD-LRR
	NALP14	11p15.4	NOD5; CLR11.2; NLRP14	PYD-NACHT-NAD-LRR
Mouse	NALP14	7 E3	Nalp-iota, GC-LRR, Nlrp14	PYD-NACHT-NAD-LRR

LRR Leucine-rich repeat; *NACHT* domain present in NAIP, CIITA, HET-E, TP-1; *BIR* baculovirus; *PYD* pyrin domain; *FIIND* function to find; *CARD* caspase recruitment domain

by clinical trials and case studies demonstrating the efficacy of therapeutic strategies targeting the IL-1β cytokine [50]. These studies were complemented in mice, where a decisive role for NALP1 and NALP3 in various pathologies related to inflammation could be demonstrated [92, 100]. The human genome contains 14 members of the NALP family, and it is likely that other NALPs can form inflammasomes and play a role in immunity [155]. NALPs are members of a large superfamily of proteins involved in innate immunity known as NOD-like receptors (NLRs; previously also called caterpillers) [97]. Besides the NALPs, three other NLRs, IPAF, NAIP and NOD2 can form inflammasomes (see accompanying review by Ed Miao and Alan Aderem). In this review, however, we will focus on NALP inflammasomes. The structural characteristic of NALPs that distinguishes them from other NLRs is the presence at the protein N terminus of the Pyrin domain (PYD; Table 1).

Pyrin domain-containing proteins

The Pyrin domain is a member of the death fold domain superfamily, which was initially identified in proapoptotic mediators and includes the death domain (DD), the caspase recruitment domain (CARD) and the death effector domain (DED) [54, 119]. The death fold is characterized by six α-helices that are tightly packed in a Greek key fold [38]. The interactions that characterize death fold domains are highly specific, with in general two or three partners capable of interacting with each other. In every known case, the interaction is homotypic: a DD interacts with a DD; a CARD with a CARD; and a DED with a DED; there is no cross interaction across families. In proapoptotic signaling pathways, such as the one triggered by the death receptor Fas, the interactions between different initiator units, various adaptor proteins, and caspases are primarily mediated by DD, DED, and CARD [119]. The rule that every death fold-containing family member is able to bind another partner with the same domain was of great help in the identification of molecular signaling pathways involved in apoptosis and more recently in immunity.

A few years ago, while searching additional CARD domain-containing proteins, a new protein called ASC (also known as PYCARD or TMS1) was identified [11, 93, 120]. In addition to the CARD domain, a sequence similarity was recognized in the N terminus of ASC and other proteins that delineated a new domain named PYD (also known as PAAD or DAPIN). Moreover, the PYD turned out to be a new member of the death fold family. The name PYD stems from the PYD-containing protein Pyrin that was found 10 years ago to be mutated in patients with the hereditary periodic fever syndrome known as familial Mediterranean fever [39, 61]. This was the first clue linking this new family of PYD-containing proteins with inflammation and autoinflammatory syndromes (see also accompanying review by Dan Kastner). The largest family of PYD-containing proteins are the NALPs. Others include members of the IFI200 family and a protein synthesized by Poxviruses [35, 120, 147]. Interestingly, this viral PYD-containing protein was shown to block NALP inflammasomes [65] (reviewed in an accompanying article by Grant McFadden). The IFI200 (HIN-200) are hematopoietic interferon-inducible proteins with a typical 200-amino acid domain [66]. All members of the family have a N-terminal PYD followed by one or two IFI200 domains, except for the mouse p202 that is lacking the PYD. Comparative analysis of the mouse and human cluster shows no significant sequence conservation in noncoding regions, suggesting that this family emerged before human and mouse speciation and subsequently diverged by gene duplication [27]. The function of the IFI200 genes is poorly characterized, but their pattern of expression is reminiscent of the NALPs suggests a function in immunity [77].

NALP repertoire

Genomic analysis of NALPs suggests that these genes have a strong tendency to evolve through gene-duplication events. Some NALPs, such as NALP2 and NALP7 in humans, are apparently paralogues, whereas others, such as NALP4 and NALP9, have expanded in mice (Table 1). A similar evolutionary trend has been followed by NAIPs (an NLR member) in mice where the locus expanded to seven NAIP paralogues. Interestingly, recent genetic studies of the NAIP locus in human, rat, and mouse suggested that multiple domesticated long terminal repeats (LTRs) of endogenous retroviral elements control NAIP promoter functions [129]. The tissue-specific activities of these promoters differ from species to species further suggesting a host–pathogen evolution of the NAIP locus [129]. Retroviruses that infect gametes (egg or sperm) have the capacity to transmit their viral DNA, including the LTRs, from parents to offspring [8, 9]. Some genes such as APOBEC3G or the Pyrin-like protein TRIM5α are involved in cellular antiretroviral defenses [10, 116]; however, little is known about specific innate immune mechanisms that protect gametes from being infected by such viruses. Many NALPs and NAIPs are specifically expressed in gametes [100] (see below). The function of these innate immune sensors in gametes is unknown. The genetic interaction between viral LTRs and NAIP genes may hint that some NAIPs and NALPs could be involved in immunity against retroviruses in gametes [129]. This speculative hypothesis could also explain the

high degree of evolution among the NALPs expressed in gametes.

The overall structure of NALPs consists of an N-terminal PYD domain followed by a NACHT domain and a variable number of leucine rich repeats (LRRs). LRRs are short motifs (22–28 residues in length) found in a variety of cytoplasmic, membrane and extracellular proteins [70], including the Toll-like receptors (TLRs) and the plant resistance proteins, two important families of innate immune receptors that sense pathogens via the LRRs. Although these modules are associated with a wide range of functions, they are generally involved in protein–protein interactions. NALP genes have a striking relationship between their intron–exon structure and their modular organization, particularly in the LRR region [100]. In all NALPs, the LRR region is encoded by repeats of exons that have exactly 171 nucleotides in length. Remarkably, for all NALP-LRRs, the size, the reading frame phase, and the intron–exon junction sites are conserved. The phasing and position of the introns are consistent with rapid and efficient exon amplification during evolution. Moreover, we can anticipate that this modular organization contributes to extensive alternative splicing of the LRR region that can occur without disturbing the three-dimensional fold of the region, providing maximal plasticity to the ligand-sensing area [100]. All these observations indicate that the NALP repertoire within a species and across vertebrates is large and made up of different genes and splice variants that mainly differ in their LRR region, which is defined completely by its intron–exon structure.

Assembly of the inflammasome leads to activation of inflammatory caspases

Caspases are produced in cells as catalytically inactive zymogens and generally undergo proteolytic processing upon activation [166]. The subset of caspases that directly initiates signaling cascades are known as “initiator caspases”. These initiator caspases (for example caspase-8, -10, -2, or caspase-9) are characterized by the presence of an N-terminal death fold domain (CARD or DED). The mechanism of their activation depends on the assembly of recruitment platforms, such as the death-inducing signaling complex for caspase-8 and 10, the PIDDosome for caspase-2, and the apoptosome for caspase-9 [63, 124, 151]. These platforms integrate cellular signals, promote dimerization of initiator caspases, and lead to the generation of an active enzyme that initiates specific signaling cascades [13, 126]. They consist of various molecules assembled around a central scaffold protein that prototypically possesses three main domains: a region involved in ligand sensing, a domain promoting oligomerization, and a domain involved in caspase recruitment. The best described example is the apoptosome scaffold protein Apaf-1, which possesses a CARD for caspase-9 recruitment, an NB-ARC domain for oligomerization, and a WD repeat that senses the release of cytochrome c from the mitochondria, a pivotal signal that triggers apoptosis by activating the apoptosome (Fig. 1a).

NLRs, which are structurally related to Apaf-1, are intracellular sensors of pathogens and endogenous stresses [36, 97, 163]. In humans, there are 22 NLRs including a subfamily of proteins (NOD1 and NOD2) that senses bacterial peptidoglycan (PGN) and activates the kinase RIP2 and NF-κB [59] and three subfamilies involved in the formation of caspase-1-activating inflammasome complexes: NALPs, IPAF, and NAIPs [100].

For several of the 14 NALPs, there is ample evidence for their role as scaffolding proteins of inflammasomes [2, 94, 96]. The PYD of the NALPs binds the adaptor ASC via PYD–PYD interaction. The CARD domain within ASC then recruits caspase-1 to the inflammasome [94, 144] (Fig. 1b). The inflammasome may also recruit caspase-5 via the C-terminal CARD of NALP1, or, alternatively, a second caspase-1 can be recruited via the C-terminal CARD of CARDINAL, another potential component of the inflammasome that shares similarity with the C-terminal extension found in NALP1 [2, 94].

IPAF (also known as CARD12 or CLAN) is a well-conserved protein that contains an N-terminal CARD, a central NACHT domain, and a C-terminal LRR region. The CARD domain associates directly with the CARD domain of caspase-1 [127]. The NACHT domain promotes oligomerizations, whereas the C-terminal LRR is involved in ligand sensing [127] (Fig. 1c). The bacterial ligand activating the IPAF-inflammasome was recently identified as flagellin, and the activity of the IPAF-inflammasome is implicated in phagosome–lysosome fusion [3]. The neuronal apoptosis inhibitor protein (NAIP) shares with IPAF the highest sequence similarity of the NACHT and LRR domains, suggesting that these molecules are evolutionary and functionally related [155]. Instead of a CARD, the NAIP molecule harbors three N-terminal baculovirus inhibitor-of-apoptosis repeats (BIR) [28, 131]. Mouse NAIPs are encoded by seven paralogous genes, naip1 to naip7, mainly expressed in macrophages [34]. NAIP was proposed to interact with IPAF indicating that it may be part of the same caspase-1-activating complex [40, 167].

NALP recognition of “danger signals”: similarity with plant R genes

Plants do not have an adaptive immune system, but like animals, plants also have the potential to recognize pathogens and mount efficient innate immunity to pathogens

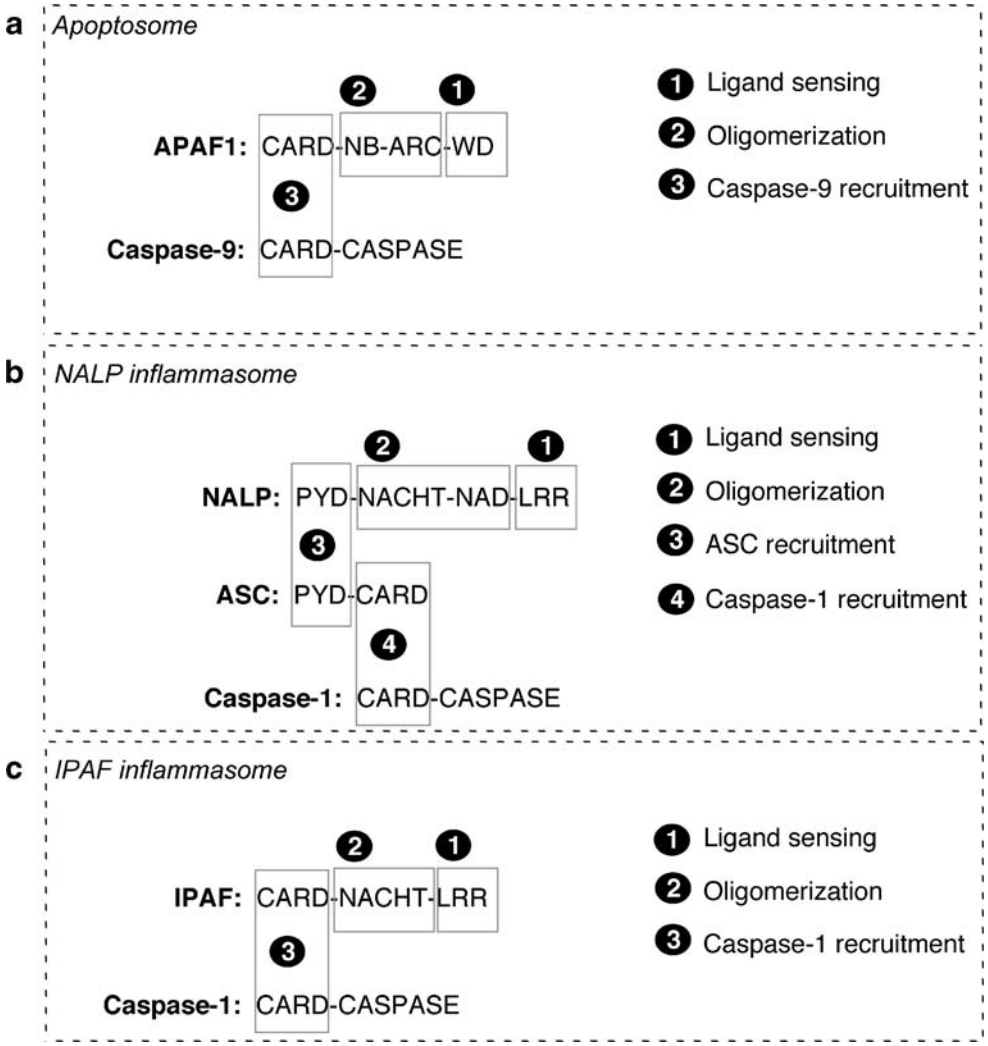

Fig. 1 Structural organization of the apoptosome and typical NALP and IPAF inflammasomes. **a** The apoptosome scaffold protein APAF1 recognizes cytosolic cytochrome c via its WD repeat, oligomerizes via its NB-ARC domain, and recruits caspase-9 via its CARD domain. **b** The core structure of the NALP-inflammasome is formed by a NALP, the adaptor ASC, and caspase-1. The LRR repeats of the NALP sense the activating signals. The NACHT-NAD region initiates the formation of NALP-oligomers. PYD-PYD and CARD–CARD homotypic interactions are crucial for the recruitment and activation of either the adaptor ASC or the inflammatory caspases. **c** IPAF recruits caspase-1 directly via CARD–CARD interactions

[67]. Two types of immunity are present. The first, known as pathogen-associated molecular pattern (PAMP)-triggered immunity or nonhost resistance, recognizes common PAMPs. These PAMPs are conserved structures present in microbes that trigger a "nonspecific" type of immunity and are similar to the mammalian TLR agonists predicted by Janeway [107]. The second branch of the innate immune system in plants responds to virulence factors specific to certain pathogens. This branch, also called effector-triggered immunity, is more specific and is the result of an exclusive evolutionary adaptation between a precise pathogen and its host. This effector-triggered immunity may detect some pathogen genes directly, or may indirectly detect pathogen-driven modifications, stress or "danger signals" in the host. This model, also known as the "guard hypothesis" [135, 156], resembles some of the models of mammalian immunity proposed by Matzinger [103], who predicted that "danger signals" help the immune system to discriminate pathogens from nonpathogenic microbes. Similarly to animals, it is likely that plant PAMP-induced immunity and "danger signal"-triggered immunity form a continuum in innate immune recognition that synergizes and collaborates to sense dangerous microbes efficiently. Both systems may use similar receptors to detect or sense microbes and pathogens. Nevertheless, the majority of PAMP sensors in plants use transmembrane pathogen recognition receptors that resemble mammalian TLRs [168]. Whereas "danger signal" sensors in plants are mainly formed by a large family of hundreds of NALP-like or more generally NLR-like proteins [29], it is interesting to note that NALPs are also proposed to be "danger signal" sensors. The first inflammasome described is activated upon loss of integrity of plasma membrane without any additional PAMP or ligand [94]. Other "danger signals", such as extracellular adenosine triphosphate (ATP) or uric acid crystals, have been identified more recently as NALP activators [91, 99], further suggesting that convergent evolution has resulted

in analogous mechanisms in both plant and mammalian innate immunity.

SGT1 a conserved regulator of plant R genes and NALPs activation

The resemblance between human and plant innate immune activation is also obvious at the structural level. Both plant genes involved in the effector-tiggered immunity (also known as NBS-LRRs) and mammalian NLRs have the same modular organization [5, 6, 155] (that consists, as described above, of a recognition domain made of LRRs, an oligomerization domain and an effector domain). Furthermore, the LRRs of various mammalian NLRs bind SGT1 and HSP90 [24, 104], two proteins whose plant orthologues were previously shown to interact with the LRR of plant NBS-LRRs [111]. Plant SGT1 controls the accumulation and stability of some NBS-LRRs [7, 56, 108]. In other NBS-LRRs, SGT1 appears to be directly involved in the activation of the scaffold protein by promoting intramolecular interactions and by contributing to the formation of a precomplex that is competent for activation without playing a major role in the stability of the NBS-LRRs [12, 14, 80]. The combined action of HSP90 and SGT1 is required to modulate plant NBS-LRRs accumulation and signaling competence [12, 58, 85]. In mammals, the activity of SGT1 is essential for NALP3 and NOD1 activation [24, 104]. SGT1 depletion affects HSP90 binding to the LRR of NALP3. Low doses and short incubations with HSP90 inhibitors reduce SGT1 interactions with the LRR of NALP3, thus blocking its activation. This suggests that an HSP90-SGT1 complex keeps the inflammasome inactive but competent for activation. HSP90 binds to the NACHT domain of NLRs, and the stability of NALP3 and NOD1 is consequently affected by sustained inhibitions with HSP90 [24, 104]. In contrast, SGT1 is not crucial for the activation of another NLR, NOD2 [24], whereas low doses of HSP90 inhibitors blocked NOD2 activation [104], suggesting that similar to plant NBS-LRRs the role and the dependence on SGT1 for activation varies between NLRs.

NALP-inflammasome assembly results in IL-1β and IL-18 maturation

Inflammasomes are machines involved in caspase-1 activation that results in the activation of IL-1β, IL-18, and possibly IL-33. The biological relevance of the inflammasome is therefore intimately linked to the biology of inflammatory caspases and their substrates. Ample support for the requirement of caspase-1 for IL-1β and IL-18 activities comes from studies of mice deficient in caspase-1 [45, 48, 75, 82]. They have a defect in the maturation of proIL-1β and proIL-18 and are more resistant to the lethal effect of endotoxins than wild type mice. IL-18 was first described as an endotoxin-induced factor that stimulates the production of interferon-γ by splenocytes. However, IL-18 has many other functions including induction of proinflammatory cytokines, up-regulation of adhesion molecules, and activation of natural killer cell activity [31]. IL-1β affects virtually every tissue including the central nervous system where it can promote induction of slow-wave sleep, anorexia, and inflammatory pain hypersensitivity [73, 132]. Importantly, IL-1β controls tumor angiogenesis and invasiveness of different tumor cells in mice [113, 159]. IL-1β also plays a role in destructive joint and bone diseases and displays toxicity for insulin-producing β-cells in islets of Langerhans [88, 140] and neurons, where it is involved in acute neurodegeneration and stroke [86]. Recombinant IL-1β induces fever in experimental animals, an activity shared with other cytokines, including TNF [30]. In general, IL-1β initiates and/or amplifies an astonishingly wide variety of effects associated with innate immunity and host responses to microbial invasion and tissue injury [32]. A better understanding of the biology of the inflammasomes is therefore crucial to fully understand the mechanisms of IL-1β regulation.

NALP1 inflammasome

Mechanisms controlling proIL-1β maturation were discovered with the help of an in vitro assay that monitors maturation of proIL-1β after it has been incubated with partially fractionated extracts from human monocytes or the monocytic cell line THP-1 [71]. This assay was successfully used to purify and sequence the IL-1β-converting enzyme (ICE), or Caspase-1 [20, 109, 150]. A similar assay allowed the biochemical identification and characterization of the first described inflammasome, the NALP1 inflammasome [94]. The NALP1 inflammasome undergoes spontaneous activation upon hypotonic lysis of THP-1 cells and incubation of cytosolic extracts at 30°C [94]. In a recent study using purified recombinant proteins, Faustin et al. [36] were able to reconstitute in vitro the NALP1 inflammasome by combining recombinant NALP1 and caspase-1. This directly demonstrated that recombinant NALP1 can activate caspase-1 via its C-terminal CARD. Activation of caspase-1 is enhanced by the recruitment of ASC via the N-terminal PYD. NALP1 is an exception among the NALPs in that it contains a C-terminal extension adjacent to the LRR that encompasses a CARD; the CARD of NALP1 was originally shown to recruit caspase-5 in the complex [94]. Whether the activation of caspase-1 by the C terminus of recombinant NALP1 is relevant in vivo

requires further investigation. Using the same in vitro system, this study suggested that the bacterial product muramyl dipeptide (MDP) binds and activates NALP1 directly. This finding is quite remarkable as it shows for the first time that a PAMP can act as a direct ligand for NLRs [36]. These data are in agreement with results in THP1 cells where NALP1 was shown to be essential for MDP-mediated activation of IL-1β [16]. On the other hand, this finding is at odds with observations demonstrating that IL-1β activation by MDP is NALP3 dependent and that, at least in mice, deficiency of NALP3, ASC or NOD2 blocks the activation of IL-1β by MDP [95, 118] (see below). Whether NALP1 is part of a mega complex involved in the activation of IL-1β upon MDP stimulation needs to be addressed in future studies. Interestingly, the NALP1 inflammasome, which shares similarities in the structure with Apaf-1-like *Caenorhabditis elegans* CED-4 protein and mammalian Apaf-1 apoptosomes, is directly inhibited by the anti-apoptotic proteins Bcl-2 and Bcl-xl [16]. CED-4 also interacts directly with the Bcl-2 member CED-9 in *C. elegans*, thereby interfering with its activity, while in mammals, Bcl-2 members indirectly block Apaf-1 activation by inhibiting cytochrome c release from mitochondria. The direct inhibition of NALP1 by Bcl-2 members shows that an evolutionary conserved branch of the apoptosis machinery regulates innate immune responses and further suggests an evolutionary link between apoptosomes and inflammasomes [16].

NALP1 and susceptibility to anthrax lethal toxin

The NALP1 locus in mice contains three paralogues; NALP1a, NALP1b, and NALP1c (Table 1). Recent studies in mice showed that macrophages from inbred mice are either susceptible or resistant to cell death by a toxin from *Bacillus anthracis* called lethal toxin (LeTx). This trait difference has been mapped to a locus on chromosome 11 and was recently associated with the *nalp1b* gene [15]. *B. anthracis* is the causative agent of anthrax and depends for virulence on secretion of factors that form functional toxins. LeTx is one of the major toxins produced by *B. anthracis* and is believed to be responsible for causing death in systemic anthrax infections. The mechanisms of how LeTx activates NALP1 and the role of the inflammasome in anthrax pathology are still ill-defined. Murine NALP1b does not contain a PYD; hence it is not clear whether it requires ASC or dimerization with another NALP for caspase-1 recruitment. On the other hand, NALP1b possesses a CARD and a region related to CARDINAL. It is therefore possible that this region per se is able to activate caspase-1 in an ASC-independent manner, as it was shown for human NALP1 in vitro [36].

NALP1, vitiligo and autoimmunity

Vitiligo is characterized by an acquired depigmentation of the skin due to the absence of melanocytes, which are cells responsible for the production of melanin, the pigment giving the skin its brown to black color. Although the etiology of the disease is not fully understood, several lines of evidence suggest an autoimmune involvement. Antibodies directed against melanocyte-derived proteins can be readily detected in vitiligo patients [114], as well as in skin infiltrating T cells [79], suggesting that both the humoral and the cellular response may be involved. It remains unclear, however, whether this is the cause or consequence of melanocyte cell death. Good evidence for an autoimmune origin of this disease comes from the fact that familial vitiligo, which accounts for one third of cases, is associated with other autoimmune diseases, including autoimmune thyroid disease, latent autoimmune diabetes, rheumatoid arthritis (RA), Addison's disease, and systemic lupus erythematosous [136]. The locus for familial vitiligo on chromosome 17 was recently demonstrated to harbor the gene coding for NALP1 [64]. Specific mutants of NALP1 are possibly associated with vitiligo alone, with an autoimmune disease phenotype or both. Although the functional effects of NALP1 variants were not determined, this study strongly suggests that mutations in NALP1 may result in a deregulated secretion of IL-1β. This may favor the priming of T cells that subsequently attack melanocytes, in a manner reminiscent of the role of NALP3 in contact hypersensitivity, where T cell priming due to IL-1β release results in cytotoxicity directed against keratinocytes (see below). Interestingly, microtraumatisms are known to play a role in the etiology of vitiligo, although the exact mechanism is still unclear [42]. Whether these microtrauma trigger NALP1 activation in individuals with predisposing mutations in this gene is a seductive hypothesis that remains to be investigated.

NALP3 inflammasome: a danger signal sensor?

The best characterized danger signal that activates IL-1β is extracellular ATP, which is most likely released by dying or injured cells. Exposure of cells to extracellular ATP has been known to activate caspase-1 for years [37, 55], and numerous studies have shown the requirement of $P2X_7$ receptors for ATP-induced caspase-1 activation and subsequent IL-1β release [17, 76, 123, 134, 143]. More recently, another type of channel, the pannexin-1 channel, activated by $P2X_7$ activation was shown to be required for ATP-induced caspase-1 activation [121, 122]. Yet the physiological relevance of extracellular ATP-mediated inflammasome activation, especially in the course of pathogen-induced

IL-1β maturation and release, remains unclear as the concentration of ATP (5 mM) required seems unreasonably high. $P2X_7$ receptor activation mimics a hypotonic stress situation and requires potassium efflux for caspase-1 activation [68]. Thus, it is possible that the mechanisms leading to the activation of caspase-1 in the cell-free system and after ATP stimulation are similar. Likewise, other models of hypotonic stress and potassium efflux produce comparable levels of caspase-1 activation [68]. Intriguingly, the inhibition of pannexin-1 completely blocked nigericin (an antibiotic and potassium ionophore from *Streptomyces hygoscopus*), maitotoxin (another potassium ionophore and potent marine toxin produced by the dinoflagellate *Gambierdiscus toxicus*), and ATP-mediated caspase-1 and IL-1β maturation without affecting potassium depletion in the cells [121, 122]. This suggests that potassium depletion in the cell is not sufficient for inflammasome activation (Fig. 3).

The generation of ASC-deficient mice demonstrated that ATP-mediated caspase-1 activation requires ASC and was therefore probably dependent on the activation of a NALP protein [89] (Fig. 3). This hypothesis was confirmed in studies using NALP3-deficient mice [91, 99, 148]. Another study suggested that NALP3 is required for caspase-1 activation by bacterial RNA or the small antiviral compounds R848 and R837 [69]. Nigericin and maitotoxin depend on the NALP3-based inflammasome for caspase-1 activation [91]. NALP3 and ASC are also required for caspase-1 activation by the Gram-positive bacteria *Staphylococcus aureus* and *Listeria monocytogenes* [91, 117]. *L. monocytogenes*-mediated caspase-1 activation requires the bacterial toxin listeriolysin O (LLO). Whether this toxin and the unidentified caspase-1 activating factor from *S. aureus* are dependent on potassium efflux requires further investigation [91]. Finally, other "danger signals" such as uric acid crystals and some skin irritant allergens also activate NALP3 (see below).

NALP3 and NOD2 sense MDP

PGN is a molecular complex that is common to all bacteria. Degradation of PGNs in the phagolysosomes of macrophages leads to the release of inflammatory mediators in the cytosol including; D-Glu-meso-diaminopimelic acid (DAP) dipeptide and GlcNAc-MurNAc-L-alanine-D-glutamate (MDP) [51]. DAP and MDP are sensed in the cytosol by two NLRs, NOD1 and NOD2, respectively. Activation of NOD1 or NOD2 leads to the recruitment and activation of the RIP2 kinase that turns on various signaling pathways ultimately leading to the activation of the transcription factor NF-κB [74]. MDP also activates caspase-1 and IL-1β via NALP3 in human monocytes suggesting that NALP3 is an additional MDP sensor [95, 97]. However, initial studies using mouse macrophages failed to demonstrate inflammasome activation by MDP [91, 92, 148]. Meanwhile, it became apparent that the strength of the immune response to MDP and DAP derivatives varies greatly and depends on the animal species and genetic background of the animal strain. It has been known for decades that mice are much less sensitive than humans, guinea pigs, or rats to these PGN-derived peptides, and that C57BL/6 mice are less sensitive than BALB/c mouse strains [112, 146]. This technical issue was overcome by a recent study that used cyclohexamide (CHX) to render mouse macrophages competent for MDP stimulation. Interestingly, both NF-κB activation and IL-1β were greatly enhanced by MDP in presence of CHX, signifying that CHX may affect MDP internalization or its presentation to the NLRs [118]. However, it is unknown whether CHX is acting directly or indirectly by affecting the expression of an inhibitor. Using CHX, Pan et al. [118] showed that IL-1β activation in mice requires both NOD2 and NALP3 activation, suggesting that they may cooperate either directly or indirectly for IL-1β activation and secretion (Fig. 2). This finding is consistent with observations in monocytes from Crohn's disease patients that have lack of function mutations in the *NOD2* gene and fail to activate IL-1β upon MDP stimulation [72, 115, 158] and findings in Muckle-Wells patients that harbor a gain of function mutation in the *NALP3* gene and overproduce IL-1β upon stimulation with MDP [95]. Similarly, a probable gain of function mutation in *NOD2* in the mouse leads to increased IL-1β production upon stimulation of macrophages with MDP [87].

NALP3 and autoinflammatory hereditary diseases

MWS, FCAS, and CINCA are characterized by periodic fever, increase in the serum levels of acute phase proteins, joint inflammation, skin rashes and eventually amyloidosis. CINCA is the most severe of these diseases with the eventual development of blindness and mental retardation. In FCAS patients, attacks are usually triggered by exposure to cold [101].

In 2001, NALP3 was identified as the gene responsible for all these syndromes [1, 33, 52, 101]. The identified mutations are mainly gain of function mutations found in the NACHT domain of NALP3 [1, 33, 52], which lead to increased activation of the inflammasome, resulting in aberrantly high production of IL-1β [2]. Monocytes from MWS patients secrete more mature IL-1β than healthy donors even in the absence of NALP3 agonists [2]. Interestingly, the same, or similar, mutations can lead to the various disorders, suggesting that other genes or

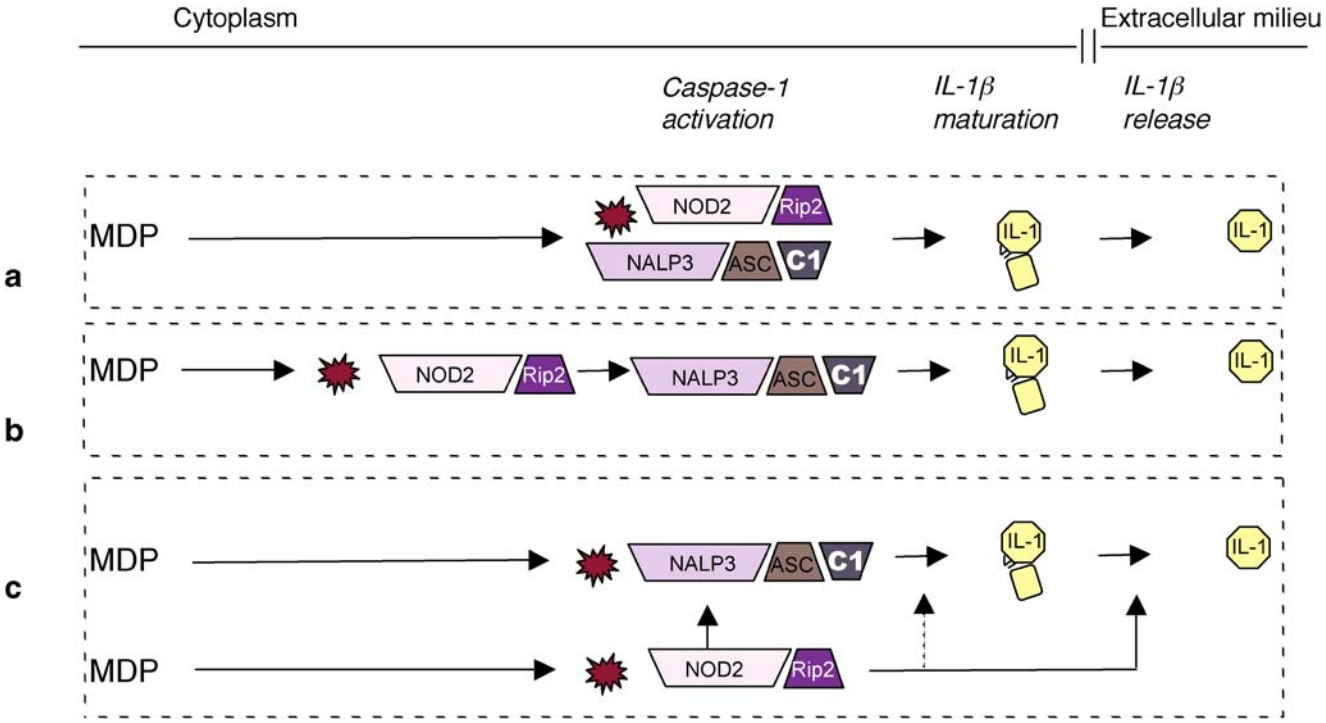

Fig. 2 Models for the activation of the inflammasome by MDP. **a** Mega-inflammasome model: NOD2 and NALP3 form a mega-inflammasome that contains NOD2, NALP3, ASC, RIP2, and caspase-1. The complex is activated directly or indirectly by MDP. **b** Sequential activation model: NOD2 is activated by MDP and signaling through RIP2 activates the NALP3 inflammasome. **c** Regulatory model: MDP activates both NOD2 and NALP3 complexes. NOD2 activation contributes in the production of IL-1β by influencing NALP3 activation and/or IL-1β secretion

environmental factors also contribute to the severity of the phenotype. Treatment of those patients with IL-1 receptor antagonist (IL-1ra), a natural decoy IL-1 molecule, rapidly and dramatically decreases disease manifestations [46, 50, 53], further demonstrating that IL-1β is directly responsible for the disease.

NALP3, a role in gout and pseudogout

Gout and pseudogout are two autoinflammatory diseases that are characterized by arthropathies generated by the inflammatory reaction to microcrystals in the joints [98, 106]. Pseudogout is caused by deposition of calcium pyrophosphate dihydrate (CPPD) crystals, whereas gout is caused by deposition of monosodium urate (MSU) crystals in joints and periarticular tissues. MSU crystals were identified as "danger signals" released by damaged cells [128, 137]. MSU and CPPD stimulate the caspase-1-activating NALP3 inflammasome to produce active IL-1β [99]. Macrophages from mice deficient in various components of the inflammasome, including caspase-1, ASC and NALP3, show a reduced crystal-induced IL-1β activation. Moreover, in a model of crystal-induced peritonitis in rodents, impaired inflammation is found in inflammasome-deficient mice or mice deficient in the IL-1β receptor (IL-1R) suggesting that in the above-mentioned autoinflammatory diseases, inflammation is caused by overproduction of IL-1β [21, 99]. Interestingly, IL-18 production is also activated by MSU [60, 99]; but despite this, IL-18 does not seem to play a crucial role in vivo [60]. The importance of IL-1β in the pathology of gout is also highlighted by promising preliminary studies in humans. Indeed, a pilot open-labeled study using inhibitors of IL-1β to treat 10 patients with documented acute gouty attacks that could not tolerate or had failed standard anti-inflammatory therapies revealed a very rapid and efficient response in those patients to IL-1 blockade [142]. These preliminary data suggest that targeting IL-1 or the inflammasome could be an effective therapeutic alternative in gout.

NALP3, eczema, and adjuvanticity

Repeated exposure of the skin to irritant allergens induces a T cell-mediated immune response called contact hypersensitivity (CHS) [47]. The response can be divided into a sensitization phase and an elicitation phase. The former is known to depend on antigen uptake by skin-resident

antigen-presenting cells and their migration to draining lymph nodes where T cell priming occurs. An irritant effect of the antigen is essential at this stage, as is the presence of functional caspase-1, IL-1β and IL-18 [4, 138]. The elicitation phase occurs upon challenge with a relevant hapten for the primed T cells and is independent of caspase-1 or an irritant effect of the chemical. Likewise, ASC- and NALP3-deficient mice demonstrate an impaired contact hypersensitivity response to trinitrophenylchloride (TNP-Cl) [148], 2,4,6-trinitrochlorobenzene (TNCB) and 2,4-dinitrofluorobenzene (DNFB) [161]. In these mice, transfer of primed T cells results in a normal CHS, suggesting that only the sensitization phase requires NALP3 and ASC. Interestingly, DNFB promotes the release of IL-1β in a caspase-1-dependent manner in primary keratinocytes as well as in a skin dendritic cell line, suggesting that the inflammasome may directly detect such compounds, [102, 161]. This suggests that NALPs can bridge the irritant effect of sensitizing chemicals with the activation of IL-1β and IL-18, thus allowing an efficient activation of the adaptive immune system.

Uric acid crystals and bacterial MDP are not only known as activators of the NALP3 inflammasome [95, 99] but are also used as adjuvants that are competent in promoting the adaptive immune response. Similarly, aluminum hydroxide adjuvant, which is the only approved adjuvant for routine use in humans, activates caspase-1, IL-1β and IL-18 [81]. Whether IL-1β, which is also an adjuvant per se, or the NALP3 inflammasome are responsible for the adjuvantic properties of these factors remains to be determined in vivo.

NALPs, a role in hydatidiform mole and in the biology of reproduction

The expression profiles of some NALPs, together with genetic studies, suggest a possible function for these proteins in the biology of reproduction [100]. Human and mouse NALP5 (also known as MATER) is expressed only in the oocyte [153, 154]. NALP5-deficient female mice are sterile due to an arrest at the two-cell stage in the development of the embryos [153]. Other NALPs such as some mouse NALP4 and NALP9 paralogues and bovine NALP5 appear to be expressed exclusively in the ovary, whereas other mouse NALP9 paralogues, NALP14, and bovine NALP9 and NALP8 seem to be essentially expressed both in the ovary and the testis [25, 26, 49, 57, 125]. Moreover, NALP expression levels in the oocyte diminish during maternal aging [49]. In addition, knock-down experiments with RNAi in mouse fertilized mouse eggs revealed that a decrease in NALP14 expression results in an arrest in development between the one-cell and eight-cell stages of the embryo [49]. Allelic variants of NALP5 are also possible candidates involved in susceptibility to a mouse model of Autoimmune Ovarian Dysgenesis, an autoimmune disease also characterized by ovary inflammation and the production of autoantibodies against NALP5 [130]. Furthermore, mutations in NALP7 cause recurrent hydatidiform mole and reproductive failure in humans [110]. Hydatidiform mole is an abnormal human pregnancy with no embryo and cystic degeneration of placental villi. While it is known that inflammation and bacterial infection cause infertility, ectopic pregnancy, and abortion, the role of NALP7 in this disease is unknown [141]. It is also unknown whether the developmental failures associated with NALP5- or NALP14-deficiency in the mouse are caused by a deregulated inflammasome activation and consequent over-production of IL-1β in the ovary. On the other hand IL-1β is well-known to play a role in both ovulation and oocyte maturation [44]. In the mare, intrafollicular injection of IL-1β leads to increased ovulation but also to a very low rate of embryo development most likely due to an defect in oocyte maturation [19]. Similarly, IL-1β perfusion in the rabbit ovary blocks embryo development at the four-cell stage [149]. It is therefore possible that NALPs may link some aspects of innate immunity and reproductive biology.

Unidentified NALPs that may play a role in innate immunity against *Salmonella*, *Shigella* or *Francisella*

Caspase-1 plays an important role in defense against several intracellular bacteria. Many studies have shown that absence of caspase-1 in macrophages and dendritic cells protects from *Salmonella*-, *Shigella*- or *Francisella*-induced cell death, whereas absence of caspase-1 in vivo renders the mice highly sensitive to infections due to defective clearance [62, 78, 91, 133, 157]. Although IPAF has been identified as the major NLR responsible for caspase-1 activation in response to *Salmonella* or *Shigella*, ASC, the crucial adaptor that links NALPs to caspase-1 activation, also plays a role. ASC-deficient macrophages fail to activate caspase-1 and to produce mature IL-1β; albeit they are still sensitive to cell death [91, 148, 169]. Despite the requirement for ASC in IL-1β maturation, NALP3 is not involved in *Salmonella* sensing, suggesting a role for other NALPs.

In a similar way, cytoplasmic *Francisella* induces a host response which is dependant on caspase-1 [90]. Interestingly, activation of caspase-1 by *Francisella* is dependent on phagosome escape and cytosolic replication [43, 90, 162]. The requirement for cytosolic *Francisella* replication in caspase-1 activation could suggest that the inflammasome is sensing a product resulting from this replication. Intriguingly, the inflammasome seems to cooperate with

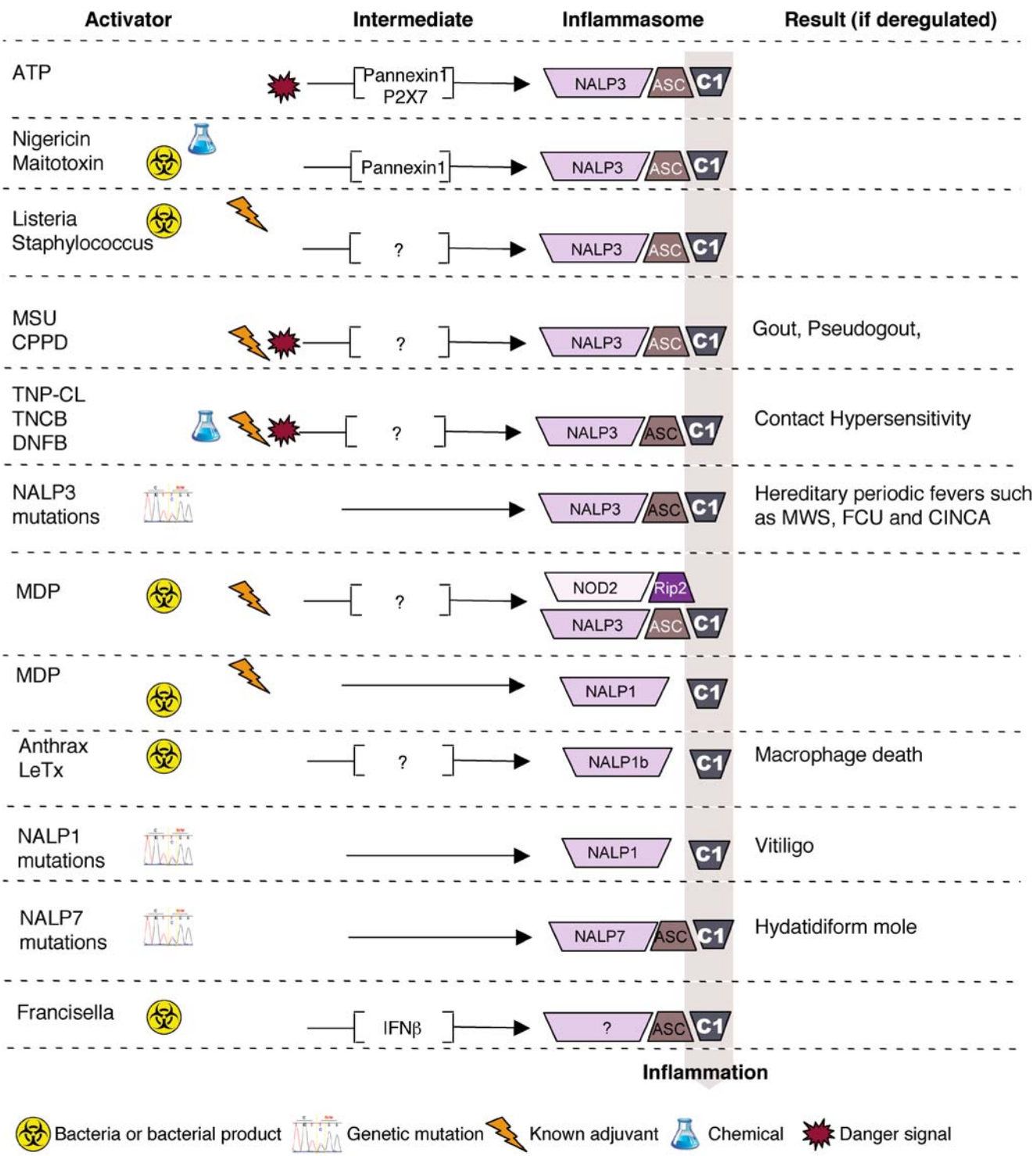

Fig. 3 NALP inflammasomes. Various NALPs and their respective activators which are discussed in this review are schematized. Note that biochemical evidence for the formation of some inflammasomes, such as the NALP7 inflammasome, is missing. Activation is believed to generally result either from direct binding of the activators or indirect activation requiring other pathways or molecules. When such connecting pathways are known, they are indicated within *brackets* as intermediate. Mutations in NALPs are directly affecting activation. Diseases, or unphysiological responses, associated with increased activation or defects in various NALPs are summarized. See text for references and discussion. *C1* Caspase-1

another pathway yet to be defined that promotes IFN-β secretion upon *Francisella* infection. This step is necessary for caspase-1 and inflammasome activation by *Francisella* [162]. Although ASC is fully required to mediate caspase-1-dependant cell death and IL-1β maturation, neither IPAF nor NALP3 are involved, again suggesting that another NALP, or another ASC activator, is involved in forming the *Francisella* responsive inflammasome [91, 148]. Whether type I interferon directly activates this inflammasome or promotes the expression of an essential component such as an hypothetical yet to be found NALP remains to be studied [162].

Therapeutics to control NALPs and caspase-1 activation

IL-1β was shown to be involved in the pathogenesis of several inflammatory disorders such as RA, MWS, FCAS, and CINCA and systemic-onset juvenile idiopathic arthritis [18, 22]. Different strategies have been designed to block IL-1β signaling. Targeting the IL-1 receptor with recombinant IL-1ra is the only clinical treatment approved so far, but new approaches using caspase-1 inhibitors or molecules trapping IL-1β are under investigation [105].

The finding that periodic fever-associated mutations in NALP3 cause over-production of IL-1β [2] highlighted the mechanisms underlining the spectacular response of MWS, FCAS, and CINCA patients to clinical trials with recombinant IL-ra called Anakinra or Kineret (an inhibitor of the IL-1 receptor complex). By targeting the first step of the inflammatory cascade (IL-1β signaling) in those patients, subcutaneous injections of Anakinra led, within hours, to symptoms cessation and normal serum levels of the acute phase proteins C-reactive proteins and serum amyloid A. Moreover, long-term treatment also stopped neurological complication progression, demonstrating the central role of IL-1β in these disorders [46, 50, 53]. Based on the efficiency of Anakinra, IL-1β inhibition is now tested with encouraging results in other inflammatory diseases that are caused by an overactivation of the inflammasome such as gout [99, 142].

New IL-1β signaling antagonists are being developed to acquire new molecules with different routes of administration and increased potency. In fact, Anakinra has a very short half-life and thus requires daily subcutaneous injection [105]. The oral caspase-1 inhibitor VX-765 has been shown to be effective in blocking IL-1β production in monocytes from FCAS patients [145]. It has also been successfully tested in mouse RA models [23]. Similarly, caspase-1 inhibitors also block the maturation of IL-18. IL-18 is highly expressed by keratinocytes and Langerhans cells. Using the caspase-1 inhibitor in a delayed-type hypersensitivity mouse system, Wannamaker et al. [160] showed a decrease in skin inflammation. Thus, blocking IL-18 production could be a successful approach to treat skin inflammatory disorders such as psoriasis.

Other strategies aimed at targeting the activation of the inflammasome may also provide new therapeutics, as demonstrated by the very significant efficiency of the HSP90 inhibitor 17-DMAG in blocking inflammation in a mouse model of gout [104].

Constitutive blocking of cytokine production or activation might decrease the efficiency of our immune system to prevent pathogens infections [84]. We could then wonder whether the inhibition of cytokines is really without consequences. Anti-TNF-α treatments result for example, in an increase in *Mycobycterium tuberculosis* infection in treated patients. However, only a few opportunistic infections have been recorded with long-term Anakinra treatment, highlighting the safety of the treatment [84]. Using specific caspase-1 inhibitors, inflammasome inhibitors, or IL-1 and IL-18 inhibitors is therefore a very specific and promising therapy to treat autoinflammatory diseases associated with overactivation of inflammasomes, but nevertheless these treatments might increase opportunistic infections. Large-scale clinical trials are required to address these questions.

Conclusion

As summarized in Fig. 3, various types of NALP-inflammasomes have been identified, and several of them are associated with diseases and pathologies. The reason why disease-associated mutations in the NALP-inflammasomes in man appear to be much more common than other PAMP receptors collectively remains a mystery.

The mechanism and the role of NALPs in these pathways are still poorly defined. Overall, studies performed during the last 5 years have revealed that this danger-sensing system is complex and involves many members of the NLR family of proteins. Identification of ligands and the mechanisms involved in NALPs activation are crucial puzzles that need to be solved. Beyond the function of NALPs in the activation of inflammatory cytokines, a few studies also suggest that some NALPs may have other functions and regulate transcriptional events or other signaling pathways [83, 164, 165]. Some studies have also identified NALPs as possible candidate genes involved in cancer [139], or in some forms of cell death [41, 152].

Future studies and new mouse models will undoubtedly shed more light on the respective roles of various NALPs in human infections and inflammatory diseases and possibly identify or validate new roles of NALPs in other pathways and diseases.

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