

# Primer: inflammasomes and interleukin 1 $\beta$ in inflammatory disorders

Leigh D Church, Graham P Cook and Michael F McDermott\*

## SUMMARY

Inflammasomes are large, multimeric protein complexes that link the sensing of microbial products and metabolic stress to the proteolytic processing of prointerleukin (pro-IL)-1 $\beta$  to its active form. NALP1 and NALP2 are founding members of the Nod-like receptor family. Other Nod-like receptors, including NALP3 and NOD2, which are associated with inflammatory disorders, have also been described. The NALP1 and NALP3 inflammasomes are located in the cytoplasm and can, therefore, detect intracellular infection through recognition of microbial pathogen-associated molecular patterns. The inflammasome pathways cooperate with Toll-like receptor pathways to mediate a rapid and appropriate response to pathogens and genotoxic stress. Mutations in both pyrin and NALP3 components of inflammasomes are associated with innate-immune-mediated diseases (familial Mediterranean fever and the ‘cryopyrinopathies’), and aberrant IL-1 $\beta$  processing has been reported in several autoinflammatory conditions, including Muckle–Wells syndrome, chronic infantile neurologic, cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease, and gout. The effectiveness of IL-1 $\beta$  blockade in treating many of these conditions has transformed the understanding and management of these disorders and also highlighted the role of aberrant IL-1 $\beta$  signaling in other conditions, such as adult-onset Still’s disease and systemic juvenile idiopathic arthritis.

**KEYWORDS** gout, inflammasome, interleukin 1 $\beta$ , NALP, systemic-onset juvenile idiopathic arthritis

## REVIEW CRITERIA

Papers discussed in this Review were identified from the authors’ databases and supplemented by searches on PubMed and online journals from 1997 to 2007. Only full-text papers from peer-reviewed, English-language journals were included. The keywords “interleukin 1 $\beta$ ”, “inflammasome”, “NALP”, “NALP3”, “cryopyrin”, “CIAS1”, “inflammatory disorders”, “juvenile arthritis”, and “gout” were used in various combinations.

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## INTRODUCTION

The concept of innate immunity as the primitive cousin of the adaptive system, being nonspecific in most aspects of both recognition and response, has been transformed by the identification of the membrane-associated Toll-like receptors (TLRs) and the cytosol-expressed Nod-like receptors (NLRs).<sup>1,2</sup> Various levels of crosstalk between these two pathways have been described—most notably involving ‘inflammasomes’, intracellular multiprotein scaffold complexes that require input from both pathways. A series of discoveries involving a group of inherited chronic autoinflammatory disorders, the hereditary periodic fever syndromes, has helped to define the central roles of pyrin and NALP3 (NACHT domain, leucine-rich-repeat [LRR] domain, and pyrin domain [PYD]-containing protein 3; also known as cryopyrin, PYPAF1 [pyrin-containing Apaf1-like protein 1] and CIAS1 [cold-induced autoinflammatory syndrome 1]) in the genesis of inflammation. Characterization of both the NALP1 and NALP3 inflammasomes has provided remarkable insights into different mechanisms of innate immune responses and the regulation of one of the most important soluble mediators of inflammation, interleukin (IL)-1 $\beta$ .

IL-1 $\beta$  is considered the prototypic ‘multi-functional’ cytokine, affecting nearly all cell types, either alone or in combination with other cytokines. Since its cloning in the early 1980s,<sup>3</sup> investigation of the diverse biological activities of IL-1 $\beta$  has significantly increased our understanding of the pathogenesis of several diseases, including type 1 diabetes,<sup>4</sup> gout,<sup>5</sup> and many autoinflammatory disorders, including the NALP3-associated disorders (familial cold autoinflammatory syndrome [FCAS], Muckle–Wells syndrome [MWS], chronic infantile neurologic, cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease [CINCA/NOMID]), in addition to pyogenic sterile arthritis with pyoderma gangrenosum and acne (PAPA).<sup>6</sup> This Review will focus on

inflammasomes—in particular, on the role of NALP3 in the regulation of IL-1 $\beta$  production and the potential implications of IL-1 $\beta$  dysregulation in the pathogenesis of several of these disorders.

### TOLL-LIKE RECEPTORS AND NOD-LIKE RECEPTORS

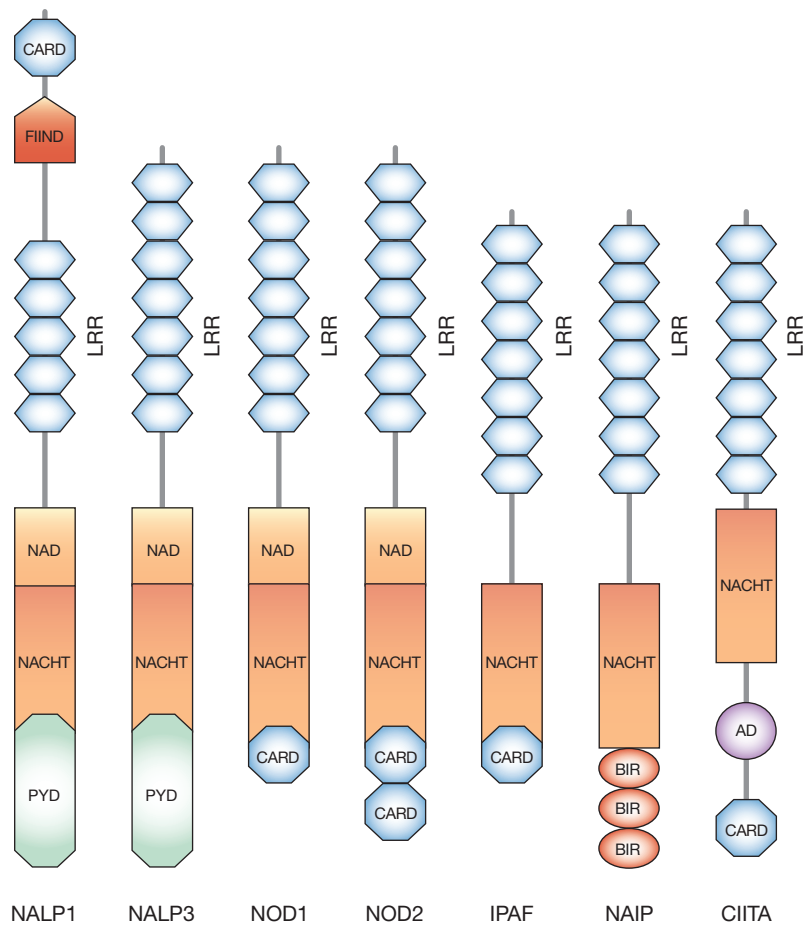
Innate immunity provides a rapid means of host defense by responding to microbial 'pattern' molecules, such as cell-wall products (e.g. peptidoglycan). Recognition occurs through a variety of germline-encoded pattern receptor molecules (PRMs), such as TLR family members, which sense extracellular ligands. Recognition triggers a series of events that leads to the expression of many immune and inflammatory genes. To date, a total of 10 TLRs (TLR1–10) in humans and 12 TLRs (TLR1–9 and TLR11–13) in mice have been described.<sup>7</sup> These are homologs of the prototype Toll molecule, which was originally identified in *Drosophila melanogaster*, and are arguably the most studied of the PRMs.<sup>8,9</sup> Endogenous cellular products associated with tissue injury or self 'danger' signals, such as toxic compounds, defective nucleic acids, or the presence of normal cell components in atypical extracellular or intracellular locations, can also stimulate innate immune mechanisms through NLRs.<sup>10,11</sup> The NLR family of PRMs includes 22 members in humans. The NLRs are the cytoplasmic counterparts of TLRs and sense microbial patterns that gain access to the cell, in addition to various metabolic stresses. Nucleotide-binding oligomerization domain (NOD) 1 and NOD2 were the first NLRs reported to function as intracellular sensors, recognizing distinct substructures of bacterial peptidoglycan. The NLR family broadly encompasses 5 members of the NOD subfamily, 14 NALPs, IPAF (IL-1 $\beta$ -converting enzyme [ICE]-protease-activating factor), NAIPs (neuronal apoptosis inhibitor factors), and CIITA (major histocompatibility complex [MHC] class II transactivator).<sup>12</sup> The basic structural features and immunology of the NLR system have been reviewed in detail.<sup>13,14</sup> Briefly, NLRs are characterized by three domains: an N-terminal effector domain, which can be a PYD, a caspase-recruitment domain (CARD), or a baculovirus inhibitor of apoptosis protein repeat (BIR);<sup>1</sup> an intermediary nucleotide-binding domain (NBD; NACHT or NAD); and a C-terminal LRR domain (Figure 1).

The ligands and functions of many of these NLRs are still being identified (Supplementary Table 1 online); NOD2 recognizes muramyl dipeptide, a molecular motif released from peptidoglycan that is common to Gram-negative and Gram-positive bacteria.<sup>15</sup> NOD2 mutations have been identified as determinants of genetic susceptibility to Crohn's disease, but the pathogenic role of these mutations remains unclear.<sup>16,17</sup> Mutations in the NACHT domain of NOD2 also underlie susceptibility to Blau syndrome, an autosomal-dominant condition comprising granulomatous arthritis, iritis, and skin rash.<sup>18,19</sup> These mutations are thought to lead to excessive downstream basal activity of the transcription factor nuclear factor  $\kappa$ B.<sup>20</sup> Interestingly, the three residues in the NACHT domain of NOD2 affected by mutations in Blau syndrome correspond to the same positions of pathogenic mutations in the NACHT domain of the closely related NALP3 protein that cause susceptibility to CINCA/NOMID, FCAS, and MWS.<sup>20</sup> More recently, NOD2 mutations have also been implicated in early-onset sarcoidosis, a disease with similar clinical features to Blau syndrome.<sup>21</sup>

Much intracellular crosstalk occurs between TLRs and NLRs, which might lead to the generation of pro-IL-1 $\beta$  and other inflammatory cytokines, including IL-18 and IL-33.<sup>22–24</sup> For instance, TLR ligands, such as lipopolysaccharide, induce activation of nuclear factor  $\kappa$ B, thereby triggering gene expression and synthesis of pro-IL-1 $\beta$ . Conversion of pro-IL-1 $\beta$  to its active form requires not only activation of caspase 1 (also known as IL-1 $\beta$ -converting enzyme),<sup>25</sup> but also a second stimulus to induce the formation of the inflammasome, to enhance the proteolytic maturation and secretion of IL-1 $\beta$ .<sup>14</sup>

### NALPS

NALPs form the largest family of PYD-containing proteins; the human genome contains 14 NALP genes (NLRP [NLR family, pyrin-domain-containing] is the Human Genome Organization [HUGO] Gene Nomenclature Committee approved nomenclature for NALP genes but, because this topic is currently one of active discussion, the NALP nomenclature in current use is used here). Genomic analysis implies that these genes have evolved through duplication events. Several NALP genes, such as NALP2, NALP4, and NALP7 in humans, are apparent paralogs of mouse loci.



**Figure 1** Domain structure of several Nod-like receptors (NLRs). For comparison, the structure and domains of seven of the more prominent NLR family members are shown. The CARD domain depicted in CIITA is only present in some splice forms; the majority of transcripts encoding CIITA do not have a CARD. Abbreviations: AD, activation domain; BIR, baculovirus IAP (inhibitor of apoptosis protein) repeat; CARD, caspase-recruitment domain; CIITA, major histocompatibility complex (MHC) class II transactivator; FIIND, domain with function to find; IPAF, interleukin 1 $\beta$ -converting enzyme protease-activating factor; LRR, leucine-rich repeat; NACHT, domain present in NAIP, CIITA, HET-E (incompatibility locus protein from *Podospora anserine*) and telomerase-associated protein; NAD, NACHT-associated domain; NAIP, neuronal apoptosis inhibitor protein; NALP, NACHT domain, LRR domain, and pyrin domain-containing protein; PYD, pyrin domain.

As outlined above, NALPs comprise an N-terminal PYD domain, a NACHT domain, and a variable number of LRRs (Figure 1). LRRs are short repeat motifs (22–28 residues) that are found in a variety of cytoplasmic, membrane, and extracellular proteins, including TLRs and plant resistance proteins, both of which sense pathogens via this domain. Although NALPs have a wide range of functions, most seem to be involved in protein–protein interactions.

**THE INFLAMMASOMES**

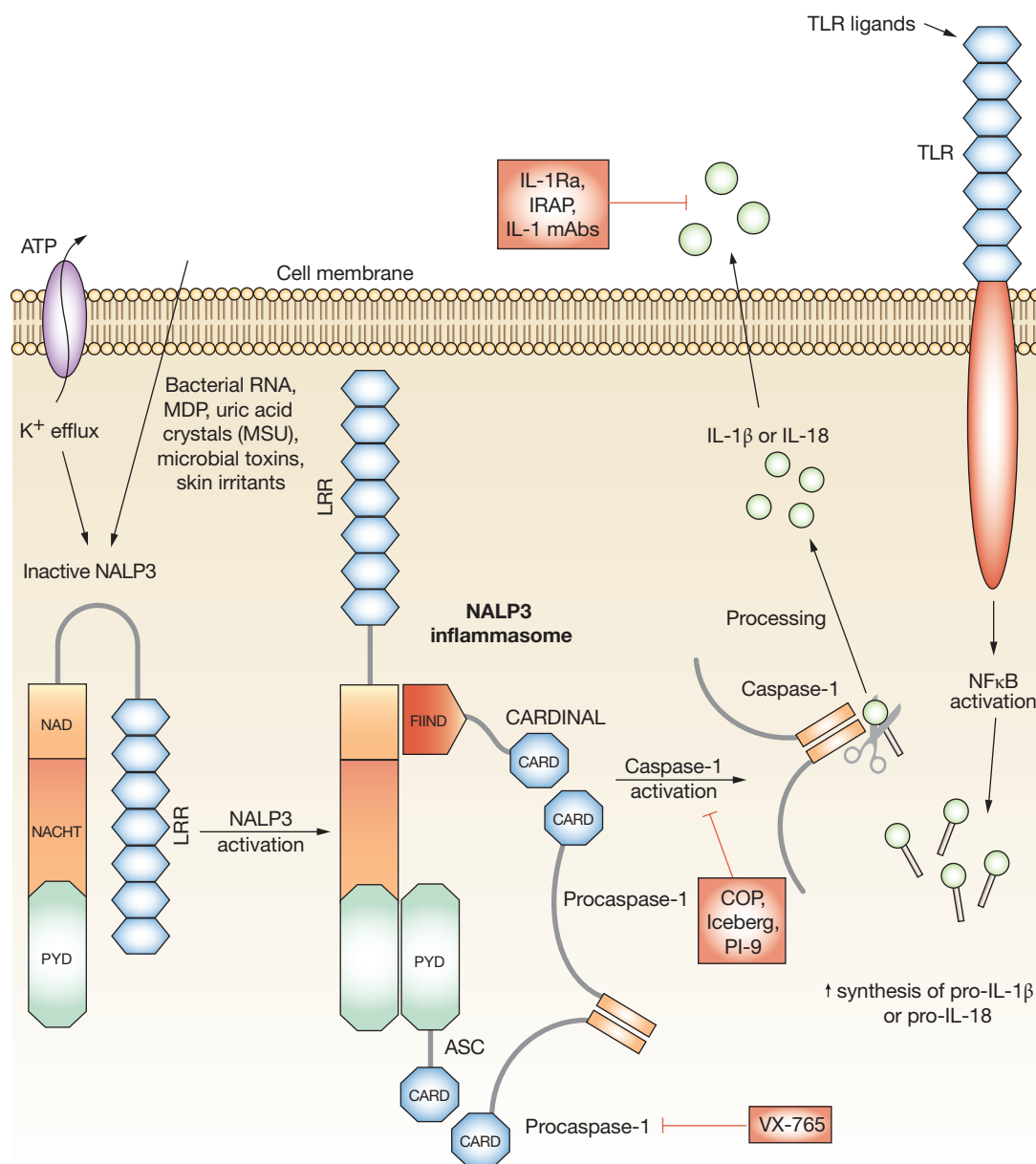
Inflammasomes are multiprotein cytoplasmic complexes that mediate the activation of inflammatory caspases: caspase 1 can be activated by both the NALP1 and NALP3 inflammasomes, whereas only the NALP1 inflammasome activates caspase 5. Caspase 1 cleaves pro-IL-1 $\beta$  to IL-1 $\beta$  and also activates IL-18 and IL-33; in this manner, the enzyme controls the maturation of some of the proinflammatory cytokines. The NALP1 inflammasome, which was the first molecular platform to be described, is a large intracellular complex composed of caspase 1, caspase 5, NALP1, and an adaptor known as apoptosis-associated speck-like protein containing a CARD (ASC).<sup>26</sup> However, several other inflammasomes have subsequently been identified.

**The NALP3 inflammasome**

NALP3, which is probably the best understood of the different NALPs, is involved in the recognition of numerous exogenous and host ligands.<sup>27</sup> The different components of the NALP3 inflammasome include NALP3 itself, CARDINAL (which is thought to be a functional homolog of the C-terminus of NALP1), ASC, and caspase 1.<sup>28</sup> After being processed by caspase 1, IL-1 $\beta$  is secreted together with the active caspase 1 molecule (Figure 2).<sup>29,30</sup>

The mechanisms of activation of the NALP3 inflammasome are gradually being deciphered; it recognizes a range of compounds, including bacterial RNA, ATP, and uric acid crystals (hence the acute inflammation observed in gout), and the antiviral imidazoquinoline compounds R837 and R848.<sup>31,32</sup> NALP3 activation is also triggered by low concentrations of intracellular potassium<sup>33</sup> and by UVB ultraviolet light;<sup>34</sup> sensing of these stimuli causes NALP3 to oligomerize, recruit ASC and caspase 1, and form an active inflammasome complex (Figure 2).<sup>35,36</sup>

Inflammasome activity can be dampened down by a variety of cytoplasmic proteins, including pyrin,<sup>37</sup> a protein associated with susceptibility to familial Mediterranean fever (FMF).<sup>38</sup> Recently, NALP3 has been proposed to be involved in the sensitization phase of contact-hypersensitivity allergic responses. Mice that lack either ASC or NALP3 have impaired contact-hypersensitivity responses to skin irritants, such as trinitrophenylchloride, 2,4,6,-trinitrochlorobenzene, and 2,4-dinitrofluorobenzene.<sup>39,40</sup> Dinitrofluorobenzene can trigger the release of IL-1 $\beta$  in keratinocytes and dendritic cells, which



**Figure 2** Activation of the NALP3 inflammasome. Engagement of specific TLRs leads to activation of NFκB signaling pathways, inducing the expression of pro-IL-1β or pro-IL-18. NALP3 is the central component of the NALP3 inflammasome; in its inactive state the LRR domain of NALP3 is thought to self-associate, preventing interaction with CARDINAL or ASC. NALP3 activation by agonists, such as ATP, MDP, uric acid crystals, bacterial messenger RNA, or skin irritants, unfolds the NALP3 molecule, enabling the assembly of the inflammasome components CARDINAL, ASC, and procaspase 1 through homotypic interactions between their respective pyrin (PYD) and CARD domains; CARDINAL interacts with the NAD domain of NALP3 through its FIIND domain. The oligomerization of inflammasome complexes induces cleavage of procaspase 1 to its active form, resulting in the generation of active IL-1β from its inactive precursor pro-IL-1β. VX-765 is a potent, selective, competitive inhibitor of caspase 1; COP, Iceberg, and PI9 can interfere with caspase activation. Several molecules (IL-1Ra, IRAP, and IL-1 mAbs) inhibit IL-1 activity. Abbreviations: ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase-recruitment domain; COP, CARD-only protein; FIIND, domain with function to find; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; IRAP, IL-1 receptor accessory protein; LRR, leucine-rich repeat; mAb, monoclonal antibody; MDP, muramyl dipeptide; MSU, monosodium urate; NACHT, domain present in neuronal apoptosis inhibitor protein (NAIP), major histocompatibility complex class II transactivator, HET-E (incompatibility locus protein from *Podospora anserina*) and telomerase-associated protein; NAD, NACHT-associated domain; NALP, NACHT domain, LRR domain, and pyrin domain-containing protein; NFκB, nuclear factor κB; PI9, proteinase inhibitor 9; PYD, pyrin domain; TLR, Toll-like receptor.

implies that these irritants might directly activate NALP3.<sup>39</sup> These findings demonstrate an involvement of the NALP3 inflammasome in the T-cell-dependent contact-hypersensitivity response and provide further support for a role of NLRs in linking innate and adaptive immune responses.

### INTERLEUKIN 1 $\beta$

One of the main functions of IL-1 $\beta$  is as a pyrogenic cytokine, produced mainly by blood monocytes. IL-1 $\beta$  is normally produced in response to infection, injury, or immunologic challenge;<sup>28</sup> at minimal concentrations, it causes fever, hypotension, and production of additional proinflammatory cytokines, such as IL-6. The IL-1 family has expanded from the three founding members (IL-1 $\alpha$ , IL-1 $\beta$ , and the IL-1 receptor antagonist [IL-1Ra]) to include IL-18, IL-33, and five other members (on the basis of amino acid sequence conservation and identity of either the gene or the three-dimensional structure).<sup>22–24,41</sup> The synthesis and release of IL-1 $\beta$  is very tightly regulated (unlike that of other cytokines, such as tumor necrosis factor);<sup>28</sup> the immune system has evolved several mechanisms to regulate excessive production or dysregulation of IL-1 $\beta$ , from transcription of the *IL1B* gene to cleavage of the 35 kDa pro-IL-1 $\beta$  precursor to generate the mature 17 kDa product.<sup>42</sup> Several proteins—in particular, some CARD-containing proteins, such as the CARD-only protein (COP), Iceberg, the caspase 1 inhibitor proteinase inhibitor 9 (PI-9), and pyrin—are believed to regulate IL-1 $\beta$  production by interfering with the recruitment of caspase 1 or directly neutralizing caspase 1 activity.<sup>43–45</sup> Other putative negative regulators of inflammasome activity have been described, such as pyrin-only protein 1 (POP1; also known as ASC2) and POP2.<sup>46,47</sup> Much current research is devoted to understanding the mechanisms of action of these molecules, considering their potential as therapeutic agents.

### INFLAMMATORY DISORDERS AND INFLAMMASOMES

A growing number of systemic inflammatory diseases, characterized by fever, anemia, and elevated levels of acute-phase proteins, have been linked to excessive production and bioactivity of IL-1 $\beta$ ; all these conditions respond, to varying degrees, to specific blockade of the IL-1R.<sup>48</sup> Furthermore, several of these

disorders are associated with abnormalities in NLR signaling pathways, as exemplified by the ‘cryopyrinopathies’, which are also termed ‘the CIAS1-associated periodic syndromes’.

### Cryopyrinopathies

The cryopyrinopathies constitute a subfamily of the hereditary periodic fever syndromes, and the clinical presentation includes unexplained episodes of fever and severe localized inflammation.<sup>49</sup> This entire family of autoinflammatory syndromes is characterized by unprovoked systemic inflammation in the absence of high titers of autoantibodies or antigen-specific T cells.<sup>50</sup> MWS, FCAS, and CINCA/NOMID were originally thought to be distinct clinical entities but are actually part of a spectrum of symptoms, with CINCA/NOMID being the most severe and FCAS (previously described as familial cold urticaria [FCU]) being the mildest. The majority of these disorders are caused by missense mutations in the NACHT domain of the *NALP3/CIAS1* gene and are prime examples of dysregulated processing and secretion of IL-1 $\beta$ .<sup>51–53</sup> MWS, CINCA/NOMID, and FCAS usually develop during childhood and are typically inherited from an affected parent as autosomal-dominant traits, although an appreciable percentage of cases might also arise spontaneously. The *NALP3/CIAS1* mutations are thought to result in a gain-of-function effect, probably through the loss of a regulatory step associated with NALP3 inflammasome activation that causes excessive production of IL-1 $\beta$ .<sup>25,54</sup> Fortunately, all these patients respond favorably to IL-1Ra therapy, despite having undetectable circulating levels of IL-1 $\beta$ .<sup>55,56</sup>

### FMF and PAPA

Two additional autoinflammatory diseases, FMF and PAPA, which map to distinct genetic loci, also have abnormalities in the NALP3 inflammasome pathway. FMF, an autosomal-recessive disorder caused by mutations in the pyrin-encoding gene (*MEFV*), is the most prevalent of the hereditary periodic fever syndromes worldwide. PAPA, a rare autosomal-dominant autoinflammatory disorder characterized by the accumulation of sterile, pyrogenic, neutrophil-rich material in the joints and disfiguring skin lesions, is caused by mutations in *CD2BP1/PSTPIP1*, which encodes proline-serine-threonine-phosphatase-interacting protein 1. This protein is involved in actin reorganization during cytoskeletal-mediated

events and interacts with pyrin through its Src homology 3 domain.<sup>57,58</sup>

Although these systemic autoinflammatory disorders are relatively rare, identification of the mutated genes has been fundamental in characterizing the role of IL-1 $\beta$  in systemic inflammation, regardless of the cause.<sup>59</sup>

### Gout and pseudogout

Gout is caused by abnormal purine metabolism and is associated with deposition of monosodium urate (MSU) crystals in joints and periarticular tissues. Similarly, pseudogout arises from deposition of calcium pyrophosphate dihydrate crystals, owing to unknown causes. Martinon *et al.* have shown that MSU and calcium pyrophosphate dihydrate crystals activate the NALP3 inflammasome, which causes the production of active IL-1 $\beta$  and IL-18.<sup>5</sup> IL-1 $\beta$  blockade reduced MSU-crystal-induced inflammation in a mouse model.<sup>5</sup> In a subsequent pilot study of 10 patients with gout who had failed to respond to standard anti-inflammatory therapies, all patients responded to treatment with 100 mg/day of the IL-1Ra anakinra for 3 days.<sup>60</sup> Refractory pseudogout has also been successfully treated with anakinra.<sup>61</sup>

### Systemic juvenile idiopathic arthritis and adult-onset Still's disease

Systemic juvenile idiopathic arthritis (sJIA), a destructive, systemic inflammatory disease in children, shares many clinical, hematologic, and biochemical manifestations with the autoinflammatory syndromes; this has led to speculation over whether sJIA should be reclassified as an autoinflammatory, rather than an autoimmune, disease.<sup>62</sup> Children suffering from sJIA present with systemic symptoms, including fever and/or rashes, that might precede the development of arthritis by months or years,<sup>63</sup> and dysregulated production of IL-1 $\beta$  has been proposed to underlie the pathogenesis of this disorder. Pascual *et al.* demonstrated that serum from sJIA patients could upregulate the expression of *IL1A*, *IL1B*, and other innate-immunity genes in healthy controls.<sup>63</sup> Furthermore, peripheral blood mononuclear cells from these patients produced excessive levels of IL-1 $\beta$  compared with healthy controls *in vitro*, and anakinra was effective in treating the disease,<sup>63</sup> which supported data from an earlier study.<sup>64</sup>

No mutations that affect IL-1 $\beta$  regulation have so far been identified in sJIA patients.

Nevertheless, speculation remains that susceptibility to sJIA might also involve mutations in particular inflammasome components. Considering the tight regulation of the synthesis, processing, and secretion of IL-1 $\beta$ , dysregulation of IL-1 $\beta$  production, or indeed any of the naturally occurring IL-1Ra proteins, IL-1 type II decoy receptor proteins,<sup>65</sup> or the soluble IL-1R accessory protein (IRAP),<sup>66</sup> might contribute to increased activity of IL-1 $\beta$  in sJIA.

Significant elevation of IL-18 levels has been reported in the sera and synovial fluid of sJIA patients compared with other JIA patients;<sup>67,68</sup> however, it remains unclear whether this increase is a cause, or an effect, of the disease. IL-18 is also elevated in adult-onset Still's disease (AOSD),<sup>69,70</sup> a systemic inflammatory disease of unknown etiology that shares some clinical similarities with sJIA.<sup>71</sup> AOSD presents with intermittent fevers, rashes, leukocytosis, increased levels of liver enzymes and lactate dehydrogenase, high levels of serum ferritin, lymphadenopathy, and splenomegaly. The use of anakinra in AOSD patients who are refractory to conventional therapies (estimated to be approximately 15%) has met with favorable results; several reports have documented its efficacy,<sup>64,72,73</sup> and, in some cases, complete remission has been obtained.<sup>74</sup> Interestingly, the levels of IL-18 usually remain elevated during disease remission,<sup>72</sup> which supports a specific role for IL-1 $\beta$  in AOSD.

### Schnitzler syndrome

Schnitzler syndrome is a disorder of unknown pathogenesis characterized by chronic, nonpruritic urticaria, monoclonal gammopathy, intermittent fevers, arthralgias/arthritis, bone pain, and lymphadenopathy; lymphoplasmacytic malignancy occurs in at least 15% of patients. Early studies indicate that anakinra is an effective therapy for this disorder, because it has induced remission in most patients that have so far received the drug.<sup>75</sup> Follow-up studies are in progress to establish how IL-1 blockade might affect possible evolution to lymphoplasmacytic malignancy.

### CONCLUSIONS

Inflammasomes and IL-1 $\beta$  are involved in the pathogenesis of several inflammatory disorders. The remarkable progress in this field has offered new hope for many patients with these disorders and also highlighted the role IL-1 $\beta$  might have

in other inflammatory disorders, such as sJIA, AOSD, and rheumatoid arthritis (RA). The efficacy and efficiency of IL-1 blockade with anakinra in patients with MWS, FCAS, and CINCA/NOMID are countered by its short half-life (requiring daily subcutaneous injections) and diurnal variation in concentration. However, anakinra is a proof-of-principle for IL-1 $\beta$  blockade in these disorders, and a new generation of IL-1 $\beta$  antagonists can be anticipated in the near future. The development of antagonists with higher affinities and longer half-lives will facilitate patient management and also assist patient compliance. It will also be necessary to determine whether disruption by anakinra of the vicious circle of IL-1 $\beta$  production induced by IL-1 $\beta$  is the major cause of decreased secretion of this cytokine following treatment or whether some other mechanism is involved.

The new generation of compounds that has been developed includes a long-acting fully humanized IL-1 $\beta$  antibody, a soluble IRAP, and IL-1 Trap (a combination of IL-1R type I and IRAP). An IL-1 $\beta$  monoclonal antibody is currently in phase II trials for both MWS and RA, and IL-1 Trap has received orphan drug designation by the US FDA for the treatment of cryopyrinopathies. A gene-therapy approach is also being developed to deliver IL-1 $\beta$  inhibitors. In a phase I clinical trial of nine postmenopausal women affected by treatment-resistant RA, synoviocytes were transduced *ex vivo* with a recombinant retrovirus expressing an IL-1Ra and reinjected into multiple joints.<sup>76</sup> The gene was expressed in all joints that received the transgene, and the procedure was well tolerated by the patients. However, this regimen is currently too complex for routine use and the levels of IL-1Ra expression *in vivo* were not sufficiently high to ensure long-term anti-inflammatory levels.

In addition to these specific IL-1 $\beta$ -targeting agents, the development of caspase 1 inhibitors has shown encouraging results. In studies using the orally available prodrug VX-765, a potent, selective, competitive inhibitor of caspase 1, IL-1 $\beta$  secretion was blocked in lipopolysaccharide-stimulated peripheral blood mononuclear cells from FCAS patients and control subjects.<sup>77</sup> VX-765 also reduced disease severity in a collagen-induced arthritis mouse model.<sup>78</sup>

Despite the increasing evidence for the involvement of IL-1 $\beta$  in tissue destruction and disease persistence in RA, and the benefit of blocking this pathway in animal models of

RA, anakinra has provided little therapeutic benefit to RA patients. IL-1 $\beta$  is an extremely potent cytokine and must, therefore, be blocked continuously, which might explain, in part, the limited efficacy of anakinra in RA. In systemic autoinflammatory disorders, anakinra has direct 'access' to its IL-1 $\beta$  target in the blood; this is not the case in RA, in which the deleterious effects of IL-1 $\beta$  are mediated primarily in the joints. Constitutively blocking cytokines might interfere with the efficiency of the immune system to cope with infection. This difficulty has been most publicized with the use of anti-tumor necrosis factor therapies and consequent increase in rates of *Mycobacterium tuberculosis* infection. To date, few opportunistic infections have been reported with the long-term use of anakinra, although the first case of tuberculosis reactivation in an RA patient treated with anakinra has recently been reported.<sup>79</sup> The results of clinical trials of other IL-1 $\beta$  inhibitors will, therefore, provide valuable information on the use of IL-1 $\beta$  inhibition in the treatment of RA and other rheumatic diseases.

**Supplementary information** in the form of a table is available on the *Nature Clinical Practice Rheumatology* website.

#### KEY POINTS

- The NALP1 and NALP3 inflammasomes, both located in the cytoplasm, detect intracellular infection and cooperate with Toll-like receptor-mediated pathways to induce a rapid and appropriate response to invading pathogens and genotoxic stress
- Mutations in either pyrin or NALP3 are associated with susceptibility to innate immune-mediated diseases; aberrant processing of interleukin (IL)-1 $\beta$  occurs in all the 'cryopyrinopathies', as well as in gout and pseudogout
- IL-1 $\beta$  blockade is remarkably effective for many of these conditions; however, IL-1 $\beta$  antagonists with higher affinities and longer half-lives than anakinra are required
- Further investigations into the role of inflammasomes in the pathogenesis of several autoimmune conditions, such as type 1 diabetes and neoplastic conditions, can be expected

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**Competing interests**

The authors declared no competing interests.

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