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The NLRP3 inflammasome in health and disease: the good, the bad and the ugly

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Summary

While interleukin (IL)-1β plays an important role in combating the invading pathogen as part of the innate immune response, its dysregulation is responsible for a number of autoinflammatory disorders. Large IL-1β activating platforms, known as inflammasomes, can assemble in response to the detection of endogenous host and pathogen-associated danger molecules. Formation of these protein complexes results in the autocatalysis and activation of caspase-1, which processes precursor IL-1β into its secreted biologically active form. Inflammasome and IL-1β activity is required to efficiently control viral, bacterial and fungal pathogen infections. Conversely, excess IL-1β activity contributes to human disease, and its inhibition has proved therapeutically beneficial in the treatment of a spectrum of serious, yet relatively rare, heritable inflammasomopathies. Recently, inflammasome function has been implicated in more common human conditions, such as gout, type II diabetes and cancer. This raises the possibility that anti-IL-1 therapeutics may have broader applications than anticipated previously, and may be utilized across diverse disease states that are linked insidiously through unwanted or heightened inflammasome activity.

Keywords: infections, inflammasome, innate immunity, interleukin-1, NLRP3

Introduction

Several families of germline encoded pattern recognition receptors (PRRs) have been identified that mediate critical aspects of the innate and protective immune responses required for control of microbial and viral infection. These include the Toll-like receptor (TLR) family, the retinoid-inducible gene 1 (RIG-I) like receptors (RLRs), the C-type lectin receptors and the nucleotide binding domain (NOD)-like receptor (NLR) family. Activation of PRRs results from the recognition of a number of conserved microbial and viral components, such as cell wall proteoglycans, pore-forming toxins and pathogen RNA and DNA [pathogen-associated molecular patterns (PAMPs)]. In addition, several host PRR activators [damage-associated molecular patterns (DAMPs)] have been identified, such as extracellular adenosine 5′-triphosphate (ATP), host DNA, hyaluronan and monosodium urate crystals. DAMPs can accumulate as a result of metabolic disorders or may be released upon cellular damage caused by trauma (i.e. myocardial infarction) and infection. They can therefore contribute to sterile-inflammation and wound responses, as well as pathogen-associated immune responses.

While TLRs detect extracellular and intracellular vacuolar stimuli, NLRs appear to respond to cytosolic disturbances. The NLR family contains several proteins (see below) that act as scaffolds and oligomerize into large protein complexes (~700 kDa) to induce inflammasome formation via activation of the inflammatory caspase, caspase-1, which proteolyses and thereby activates precursor interleukin (IL)-1β and IL-18, and can also lead to the release of IL-1α [1,2]. Activated IL-1β is a potent endogenous pyrogen and induces flu-like symptoms such as chills, rigors, fever, nausea, vomiting, headache and fatigue when injected into humans at 1–10 nanograms/kg of body weight [3,4]. Both IL-1β and IL-1α bind to the IL-1 receptor (IL1-R) and induce the formation of a high-affinity ternary complex with the IL-1R accessory protein. The resulting downstream signalling cascade leads to transcription factor induction of proinflammatory cytokines and chemokines, and includes genes required for angiogenesis and the recruitment of immune effector cells into the extravascular space. It can also result in the activation of lymphocytes and epithelial cells. While these responses to IL-1β are critical for host protection from many types of viruses and microbes and may aid in cellular and tissue repair responses as discussed below, the

dysregulation of IL-1β activity is now implicated in a variety of seemingly divergent diseases such as type II diabetes and gout. Clinical blockade of IL-1 has not only proved to be beneficial in the treatment of these conditions, but is surprisingly well tolerated, which will hopefully expedite the clinical evaluation of IL-1 activity in other pathologies in the near future.

In this review we highlight the benefits of nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome function in the host defence against invading pathogens (the good), the relatively rare heritable inflammasomopathies that cause excessive IL-1β activation and a number of related diseases (the bad) and the experimental and clinical evidence for unwarranted inflammasome activity contributing to common pathologies affecting millions of people, such as cancer and diabetes (the ugly).

Inflammasome structure

Twenty-two human NLRs exist that have been delineated based on their domain structure and phylogenetic relationships [5,6] (Fig. 1). In general, NLRs contain a C-terminal region made up of a variable number of leucine-rich repeats (LRRs) that are likely to autoinhibit NLR protein function in the resting state, and undergo a conformational change following the detection of an activating stimuli [7]. A central nucleotide binding and oligomerization (NACHT) domain, common to all NLRs, oligomerizes upon inflammasome activation in the presence of nucleotides such as ATP and is essential for function [8,9]. An N-terminal effector domain consisting of either a caspase activation and recruitment domain (CARD), Pyrin or baculoviral inhibitor of apoptosis protein repeat (BIR) domain precedes the NACHT domain. These N-terminal domains initiate specific downstream signalling cascades through homotypic protein interactions. In the case of inflammasome formation, the Pyrin domain containing inflammasomes (i.e. NLRP3) can bind the Pyrin domain of apoptosis speck protein (ASC), which subsequently recruits pro-caspase-1 through CARD–CARD homotypic interactions

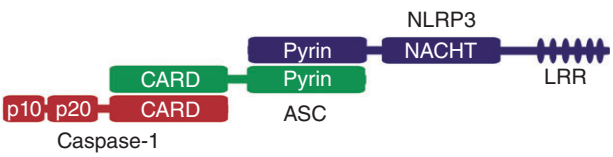

Fig. 1. Structure of the nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome. NLRP3 activation leads to homotypic interactions between the NLRP3 and apoptosis speck protein (ASC) pyrin domains and complex oligomerization. The caspase activation and recruitment domain (CARD) domains of ASC and caspase-1 interact and caspase-1 dimerization results in proximity-induced autoactivation and generation of the active tetrameric caspase-1 p20 and p10 fragments.

(Fig. 1). Other inflammasomes that lack a Pyrin domain (i.e. NLRC4) appear able to directly recruit caspase-1 through a C- or N-terminal CARD domain, although they may depend on ASC for optimal function [8]. Pro-caspase-1 recruitment results in proximity-induced caspase-1 oligomerization and autocatalysis, resulting in the release of the active catalytic p20 and p10 caspase-1 fragments and subsequent processing of precursor IL-1β into its biologically active 17 kDa fragment. Notably, basal levels of IL-1β are low and a nuclear factor kappa B (NF-κB)-dependent priming signal [often provided by TLR family members or tumour necrosis factor (TNF)] is required to induce precursor IL-1β expression before it can be cleaved by caspase-1, and can also enhance the expression of other inflammasome components such as NLRP3 [10]. While inflammasomes are not involved directly in the secretion of cytokines such as TNF or IL-6 (although IL-1R signalling can modulate their transcription), caspase-1 is required for non-conventional protein secretion of a variety of leaderless proteins involved in inflammation, cytoprotection and tissue repair [11]; however, any extracellular function for most of these proteins remains to be determined.

Cleavage of IL-1β by caspase-1 is highly specific and other caspases, such as apoptotic caspases, are unlikely to activate IL-1β directly [12]. It has been suggested that a number of serine proteases may cleave IL-1β near the caspase-1 cleavage site, thus generating active IL-1β (reviewed in [13]). Similarly, activation of the TNF superfamily death receptor Fas can also induce IL-1β maturation in caspase-1 knock-out neutrophils [14]. While the relevance of IL-1β cleavage and activation by caspase-1-independent mechanisms *in vivo* has yet to be fully addressed, caspase-1-independent IL-1β activation can occur in murine models of arthritis, *Mycobacterium tuberculosis* infection and following tissue damage, suggesting that alternate protease processing of IL-1β is physiologically relevant [15–19].

The good: inflammasome protection against pathogen infection

To date, potentially five inflammasome scaffold proteins that respond to different pathogenic stimuli to activate caspase-1 and IL-1β *in vivo* have been characterized. The inflammasomes belonging to the NLR family include NLRP1, NLRC4 and NLRP3. The NLRP1 (NALP1/CARD7) inflammasome is activated following the detection of anthrax lethal toxin, the agent responsible for shock-death following systemic infection by *Bacillus anthracis* (reviewed in [6]). NLRC4 (IPAF/CARD12) detects flagellin and components of the type 3 secretion system from pathogenic bacteria such as *Shigella flexneri*, *Salmonella typhimurium*, *Listeria monocytogenes* and *Legionella pneumophila* (reviewed in [20]). Outside the NLR family, absent in melanoma 2 (AIM2) is capable of forming a caspase-1 inflammasome through its recognition of cytosolic dsDNA from viruses and bacteria,

as well as the host itself [21–23], while the RIG-I inflammasome can detect cytosolic viral RNA species such as 5′-triphosphate RNA and dsRNA [24]. While we focus upon the NLRP3 inflammasome in this review, Table 1 lists the different inflammasomes involved in PAMP recognition, and whether gene knock-out murine models have established a role for inflammasome function in pathogen immunity *in vivo*.

The best-characterized NLR capable of forming an inflammasome complex is NLRP3 (Cryopyrin/Nalp3/Cias1/Pypaf1). The extraordinary number of NLRP3 activators suggests that it may be a general detector of cellular stresses resulting from sterile trauma, intrinsic metabolic disturbances or pathogen infection (Fig. 2). Some of the host-derived DAMPs that activate NLRP3 include hyaluronan, cholesterol crystals, extracellular ATP, β-amyloid, DNA and gout-associated monosodium urate crystals, while environmental DAMPs include asbestos, silica, nanoparticles, skin irritants and alum adjuvant. PAMPs that stimulate NLRP3 can include pathogen-associated RNA, DNA, pore-forming toxins and peptidoglycans. While potassium efflux from the cell is a general requirement for the activation of the NLRP3 inflammasome, this is not required for other inflammasomes such as the one assembled around NLRC4 [25].

Stress-induced reactive oxygen species (ROS) production has been hypothesized as a common denominator that may determine NLRP3 activation status either directly via oxidation, or through an as-yet undetermined intermediate (Fig. 2) (reviewed in [26]). Other data suggest that lysosomal rupture and release of intracellular proteases, such as cathepsins, may activate NLRP3 (reviewed in [27]). This 'frustrated phagocytosis' scenario has been implicated in NLRP3 activation from particulate or crystalline stimulants, where their uptake leads to lysosomal damage and release of potential NLRP3 activating proteases [28,29]. While cathepsin B has been reported as taking part in NRLP3 activation based on chemical inhibitor studies, mice lacking this gene show normal NLRP3 activity in response to several NLRP3 stimuli [30]. Therefore, how lysosomal protease release/activation could induce NLRP3 activity remains unclear, although in theory it could result from the cleavage of a NLRP3 ligand or inhibitory protein [27].

While most inflammasome activators induce cellular ROS and, conversely, ROS scavenging compounds inhibit NLRP3 inflammasome function, the specificity and targets of these compounds is often questionable. Further, many ROS inducing cellular processes do not result in inflammasome activation, and the targeted deletion of ROS-producing or inhibitory genes, arguably the gold standard in analysing cellular function, has yet to result in a block in NRLP3 inflammasome function. In fact, it was demonstrated that deletion of the ROS scavenger superoxide dismutase (SOD)

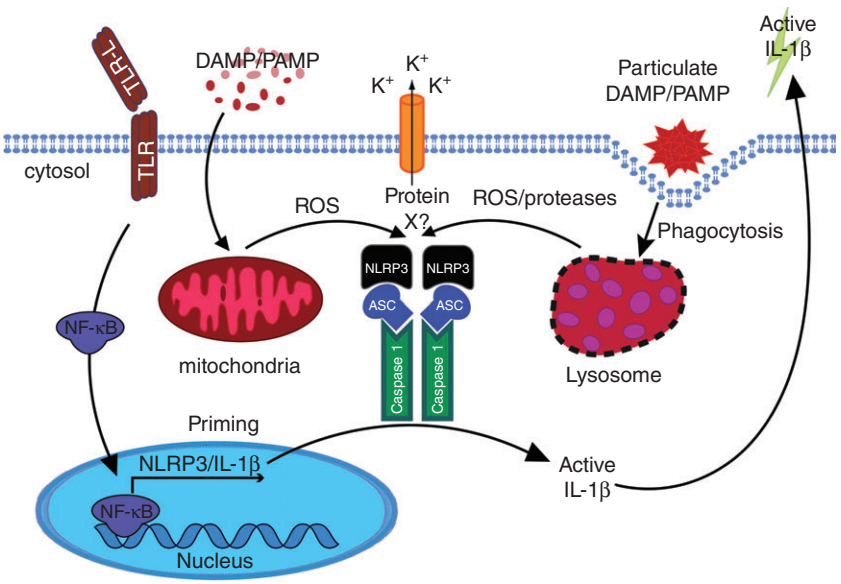

Fig. 2. Models for nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome activation. Cells, typically macrophages or dendritic cells, must first be 'primed' by an appropriate nuclear factor kappa B (NF-κB) transcription factor activating stimuli to induce precursor interleukin (IL)-1β expression. This often occurs by activation of a Toll-like receptor (TLR) family member (depicted), tumour necrosis factor (TNF) receptor activation, or even IL-1R activation (not depicted). NLRP3 stimulants all induce K^+ efflux. Although this is essential for NLRP3 activity, why and how this occurs remains a mystery. Pore-forming toxins and cell permeable NLRP3 activators can also result in mitochondrial reactive oxygen species (ROS) production that may amplify or induce NLRP3 activity, possibly via an undetermined intermediate (protein X). Particulate or crystalline matter is phagocytosed and leads to endosomal/lysosomal damage, resulting in the activation/release of lysosomal proteases (i.e. cathepsins) that can cause NLRP3 induced caspase-1 activity, which may also depend on mitochondrial ROS induction and/or processing of a NLRP3 inhibitory or activating ligand.

Table 1. The good: inflammasome control of pathogen infection.

Organism	PAMPS identified	Inflammasome activated	Inflammasome importance established *in vivo*?	Refs
Helminths				
Schistosoma mansoni	n.d.	NLRP3	Yes	[138]
Bacteria				
Mycobacterium tuberculosis	ESX-1 secretion system	NLRP3-dependent and -independent mechanism	Yes. *In vivo* IL-1 production is independent of caspase-1	[17,139–142]
Streptococcus pneumoniae	Pneumolysin	NLRP3	Yes	[143,144]
Streptococcus pyogenes	Streptolysin O	NLRP3	Yes. Not important *in vivo*	[145]
Streptomyces hygroscopicus	Nigericin	NLRP3	n.a.	[146]
Klebsiella pneumoniae	n.d.	NLRP3	Yes	[147]
Chlamycia pneumoniae	n.d.	NLRP3	Yes	[148]
Salmonella typhimurium	Flagellin and type III secretion system	NLRP3 and NLRC4	Yes	[149,150]
Francisella tularensis	DNA	AIM2	Yes	[146,151,152]
Legionella pneumophila	Flagellin	NLRC4	Yes	[153]
Listeria monocytogenes	Flagellin, Listeriolysin O, DNA	AIM2, NLRP3, NLRC4	Yes*	[146,154,155]
Pseudomonas aeruginosa	Flagellin, Type III secretion system	NLRC4	Yes	[156–158]
Shigella flexneri	Type III secretion system	NLRC4	Yes	[157,159]
Neisseria gonorrhoeae	Lipo-oligosaccharide	NLRP3	No	[160]
Staphylococcus aureus	Peptidoglycan Haemolysin	NLRP3	Yes	[146,161–165]
Virbrio vulnificus and *Vibrio cholerae*	Haemolysins	NLRP3	No	[166]
Bacillus anthracis	Anthrax lethal toxin	NLRP1	Yes	[167–170]
Escherichia coli	Type III secretion system, flagellin	NLRC4	No	[157]
Chlamydia trachomatis	Type III secretion system	NLRP3	No	[171]
Protozoa				
Toxoplasma gondii	n.d.	NLRP1	No	[172]
Plasmodium species; falciparum, berghei, chabaudi	Haemozoin, MSU	NLRP3	Yes†	[30,136,173]
Fungal				
Candida albicans	Hyphae, β-glucan	NLRP3	Yes	[174]
Aspergillus fumigatus	n.d., β-glucan	NLRP3	No	[175,176]
Saccharomyces cerevisiae	n.d., β-glucan	NLRP3	n.a.	[174]
Viruses				
Sendai virus	RNA	NLRP3	No	[177]
Influenza virus	RNA, M2 ion channel	NLRP3	Yes	[177–181]
Adenovirus	DNA	NLRP3	Yes	[182]
Vaccinia virus	DNA, RNA	AIM2	No	[23,155]
Mouse cytomegalovirus	DNA	AIM2	Yes	[155]
Vesicular stomatis virus	5′-triphosphate ssRNA	RIG-I‡, NLRP3	Yes. Not important *in vivo*	[24,183]
Encephalomyocarditis virus	RNA	NLRP3	Yes. Not important *in vivo*	[24,183]

*Flagellin importance only determined. †In a *Plasmodium berghei* mouse model, NLRP3 has been suggested to protect from cerebral malaria in a NLRP3-dependent, but caspase-1, apoptosis speck protein (ASC) and interleukin (IL)-1β-independent manner [184]. ‡The requirement of retinoid-inducible gene 1 (RIG-I) for vesicular stomatis virus (VSV)-induced IL-1 is unclear as, unlike the initial finding, it was reported recently to not be required [183]. PAMP: pathogen-associated molecular pattern; ESX: early secreted antigenic target, 6 kDa secretion system; MSU: monosodium urate; n.d.: not determined; n.a.: not applicable.

resulted in enhanced IL-1β activation, and it was suggested that ROS oxidizes specific caspase-1 cysteine residues resulting in caspase-1 inhibition [31]. Similarly, monocytes from chronic granulomatous disease patients who lack NADPH oxidase activity, and its associated ROS production, display increased IL-1β maturation in response to NLRP3 stimulants [32,33].

Recently it has been proposed that the mitochondria, and not NADPH oxidase activity, may be the source of ROS required for NLRP3 activation (Fig. 2) [34]. In support of this, it was reported that monocytes from patients who harbour missense mutations in TNFR1 and suffer from an autoinflammatory condition termed TNF-receptor-associated periodic syndrome (TRAPS) display increased mitochondrial respiratory capacity and ROS generation compared to normal monocytes, leading to enhanced cytokine, including IL-1β, production [35]. It will be interesting to determine if monocytes from patients harbouring activating NLRP3 mutations also display enhanced mitochondrial respiration and ROS and if this effects IL-1β maturation [35].

Understandably, a variety of both host and pathogen mechanisms have evolved to inhibit inflammasome activity. Several viral POPs (Pyrin domain-only proteins) and serpins (protease inhibitors) have been identified that can bind and inhibit caspase-1, while bacteria have been shown to interfere with caspase-1 function via type III secretion effector molecules or pore-forming virulence factors (reviewed in [36]). Host inhibitors include a secreted IL-1 receptor antagonist (Il-1Ra) that competes for receptor binding with IL-1, and an IL-1 decoy receptor (IL-1RII). Deletion of IL-1Ra in mice increases IL-1β serum levels and leads to severe inflammatory distress and disease phenotypes resembling rheumatoid arthritis [37–39]. Mutations in Pyrin cause familial Mediterranean fever and increased IL-1β activation is also observed in Pyrin knock-out mice [40]. The exact mechanism for Pyrin inhibition of inflammasome function remains unclear, although it is likely to compete with caspase-1 for binding to ASC [40]. Sequestration or inhibition of ASC and caspase-1 can also be achieved through the Pyrin or CARD-only protein families in humans (reviewed in [41]). TNF superfamily ligand stimulation, autophagy and type I IFN treatment can also result in diminished inflammasome function, although how they do so is still being unravelled [42–45].

The bad: cryopyrin-associated periodic syndromes and autoinflammatory disorders

The NLRP3 inflammasome has attracted considerable attention ever since its initial characterization due to its implication in the pathogenesis of several human inflammatory diseases [6]. In particular, mutated NLRP3 has been identified as the cause of a group of inflammatory diseases known as the cryopyrin-associated periodic syndromes (CAPS).

Cryopyrin-associated periodic syndromes

Gain of function mutations in the NACHT domain of NLRP3 were identified as being responsible for three chronic aseptic inflammatory diseases: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and neonatal onset multi-systemic inflammatory disease/chronic infantile neurological cutaneous articular syndrome (NOMID/CINCA) [46]. These closely related conditions form the family of cryopyrin-associated periodic syndromes (CAPS), a name derived from the original designation of the NLRP3-encoding gene, then known as *cryopyrin*. Together, they constitute a spectrum of diseases with increasing severity, with FCAS, MWS and NOMID/CINCA representing the mildest, intermediate and most severe forms, respectively [47]. Clinically, they are characterized by recurrent fevers, urticarial-like skin rashes, joint and ocular symptoms, amyloidosis and, in the case of NOMID/CINCA, severe neurological complications [47,48] (Table 2).

In FCAS, MWS and NOMID/CINCA, several point mutations target the NACHT domain of the NLRP3 protein, resulting in gain-of-function mutations that constitutively activate the NLRP3 inflammasome [49,50]. In accordance, monocytes and macrophages isolated from MWS patients display a basal, spontaneous secretion of mature IL-1β in the absence of any external stimulus [49]. Collectively, these observations provided a convincing rationale for a novel therapeutic approach to these patients, namely through the inhibition of inflammasome activity. Strikingly, treating these patients with anakinra, a non-glycosylated recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra) which blocks inflammasome-dependent IL-1β signalling, resulted in a complete cessation of clinical symptoms and biochemical changes within hours of administration [51,52]. The efficacy of anti-IL-1β therapy was demonstrated across the CAPS spectrum, even in children with the more severe phenotype of NOMID/CINCA [53,54].

The clinical availability of IL-1 inhibitors has thus been critical to the identification of the NLRP3 inflammasome as a critical regulator of inflammation *in vivo*. The prototypic anti-IL-1β therapy has been based so far on the daily subcutaneous injection of anakinra [55] (Table 3). Anakinra was first developed as a promising therapy for sepsis and septic shock [56], but subsequent large-scale studies have been disappointing in that regard [57–59]. However, in 2001 it was approved by the Food and Drug Administration (FDA) as a second-line treatment for rheumatoid arthritis patients suffering from a moderate to severe form of the disease that is unresponsive to at least one disease modifying anti-rheumatic drug (DMARD) therapy.

In preliminary clinical studies, anakinra has been widely successful in treating CAPS patients. Indeed, all cases

Table 2. The bad I: cryopyrin-associated periodic syndromes.

	FCAS	MWS	NOMID/CINCA
Inheritance	Autosomal dominant	Usually autosomal dominant, rare sporadic cases	Mostly sporadic, rarely autosomal dominant
Onset of disease	Neonatal or infancy (< 6 months)	Variable, usually infancy, up to adolescence	Neonatal or early infancy
Flares	Cold-triggered, usually 1–2 h after exposure, episode < 24 h	No clearly identified trigger (possibly cold exposure, stress). Spectrum of continuous symptoms to recurrent flares lasting 1–3 days	Usually continuous symptoms, with aggravation during flares
Relative severity	Low	Medium	High
Cardinal symptoms	Cold-induced fever, urticarial-like skin rash, arthralgia, conjunctivitis, sweating, fatigue, extreme thirst, nausea	Recurrent low-grade fever, urticarial-like skin rash, sensorineural hearing loss, arthritis, conjunctivitis, AA amyloidosis	Inconstant mild fever, urticarial-like skin rash, chronic aseptic meningitis, sensorineural hearing loss
Skin	Maculopapular, migratory, urticarial-like, usually non-pruritic skin rash		
Joints	Arthralgia	Arthralgia, arthritis	Arthralgia, arthritis, bony overgrowth arthropathy of the knees (25–50%)
Eyes	Conjunctivitis	Conjunctivitis, uveitis	Conjunctivitis, uveitis (75%), chronic papilledema possibly progressing to blindness
Sensorineural hearing loss	Rare	Frequent (75%), onset during adolescence	Frequent (50%), onset during childhood
Central nervous system	None	None	Severe headaches, high intracranial pressure, chronic aseptic meningitis, possibly leading to mental retardation
Amyloidosis	Rare (< 2%)	Frequent (25–50%), adult-onset	Frequent (25%), adult-onset

FCAS: familial cold autoinflammatory syndrome; MWS: Muckle–Wells syndrome; NOMD/CINCA: neonatal onset multi-systemic inflammatory disease/chronic infantile neurological cutaneous articular syndrome; AA amyloidosis: amyloid AA amyloidosis.

reported in the literature to date responded to the therapy, albeit with various dosage requirements [47]. Overall, anakinra has a perhaps surprisingly robust record of safety [60,61], considering the prominent role of IL-1β in inflammatory and immunological responses. Conversely, patient tolerance for anakinra is often poor, due to substantial morbidity associated with injection-site reactions and upper respiratory tract infections.

Recently, two additional IL-1 antagonists have been approved for clinical use in CAPS patients (Table 3). Rilonacept is

Table 3. Current approved anti-interleukin (IL)-1 therapies.

	Anakinra (Kineret)	Rilonacept (Arcalyst)	Canakinumab (Ilaris)
Nature	Recombinant IL-1Ra	Cytokine trap (fusion protein including IL-1R and IL-1Ra)	Humanized monoclonal antibody against IL-1β
Target	IL-1R	IL-1β (and IL-1α, IL-1RAcP)	IL-1β
Half-life	4–6 h	8·6 days	26 days
Administration	100 mg, daily, subcutaneous	320 mg loading dose then 160 mg maintenance, weekly, subcutaneous	150 mg, every 8 weeks, subutaneous (or intravenous)
Common side-effects	Major injection site reactions, URI, infections	Minor injection site reactions, URI, infections	URI, vertigo (MWS patients), negligible injection site reactions,
Indications	Second-line therapy for RA (FDA 2001, EMEA 2002). CAPS (off-label use)	FCAS and MWS patients aged more than 12 years (FDA 2008, EMEA 2009)	FCAS and MWS patients aged more than 4 years (FDA and EMEA 2009)

IL-1Ra: IL-1 receptor antagonist; IL-1R: IL-1 receptor; IL-1RAcP: IL-1 receptor accessory protein; URI, upper respiratory tract infections; CAPS; cryopyrin-associated periodic syndromes; RA: rheumatoid arthritis; FCAS: familial cold autoinflammatory syndrome; MWS: Muckle–Wells syndrome; FDA: Food and Drug Administration; EMEA: European Medicines Agency. Regarding NOMID/CINCA: the only currently approved therapy is Canakinumab (approved by the EMEA but not the FDA).

a dimeric fusion glycoprotein that acts as a soluble decoy receptor with high affinity for both IL-1α and IL-1β [62]. It has proved effective in treating FCAS and MWS patients in two clinical studies [62,63]. Rilonacept is administered subcutaneously once-weekly due to its longer half-life, and presents a safety profile comparable to that of anakinra.

Canakinumab is a fully humanized monoclonal antibody against IL-1β with a half-life of about 4 weeks that has proved safe and effective in treating CAPS patients [64]. Both the above compounds are attractive additional anti-IL-1β therapies because of their weekly (rilonacept) or bimonthly (canakinumab) schedule of administration, in contrast to the requirement for daily injections of anakinra.

Autoinflammatory syndromes

Cryopyrin-associated periodic syndromes are part of the greater family of hereditary autoinflammatory syndromes, a concept first proposed in 1999 to describe a group of inherited disorders characterized by recurrent attacks of fever and multi-systemic inflammation [65]. In contrast to autoimmune diseases, autoinflammatory disorders lack high-titre autoantibodies or antigen-specific T cells [66]. The NLRP3 inflammasome has been implicated in the pathogenesis of several additional autoinflammatory syndromes aside from CAPS, on the basis of their favourable response to anti-IL-1β therapy [6,50] (Table 4).

Familial Mediterranean fever (FMF) and pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome are caused by mutations in the genes encoding for Pyrin and PSTPIP1, respectively [50]. While FMF is an autosomal recessive disease characterized by episodes of fever lasting 1–3 days associated with severe abdominal pain, pleuritic chest pain, arthritis and a skin rash [67], PAPA syndrome is inherited in a dominant manner, and characterized by recurrent pyogenic but sterile arthritis coupled to skin manifestations such as pyoderma gangrenosum and acne [68,69]. Interestingly, Pyrin has been shown to interact with NLRP3 inflammasome components, and the mutated form responsible for FMF was found to result in NLRP3 inflammasome activation [70]. Moreover, PSTPIP1 was shown to associate with Pyrin, and mutated forms responsible for PAPA syndrome had a higher affinity for Pyrin [71]. Taken together, these findings suggest that both FMF and PAPA syndrome might be inflammasome-dependent pathologies, and the term of 'extrinsic inflammasomopathies' has thus been proposed [50]. Accordingly, IL-1 antagonism has proved to be an effective treatment for both conditions [72–74]. Other autoinflammatory disorders have been linked to dysregulated inflammasome activity on the basis of their favourable response to anti-IL-1 therapy; however, in most of these

Table 4. Additional autoinflammatory syndromes possibly linked to dysregulated inflammasome activity.

Disease	Cause	Cardinal symptoms	Current treatment	Successful anti-IL-1 therapy
Hyper IgD with periodic fever syndrome	Mutations in mevalonate kinase	Recurrent fever, lymphadenopathy, abdominal pain, diarrhoea, headaches, hepatosplenomegaly, arthralgia, skin rash (< 1 week)	None, supportive care	[185–187]
TNF receptor-associated periodic syndrome	Mutations in TNR receptor I	Recurrent fever, abdominal pain, severe myalgia, painful skin rash (> 1 week)	NSAIDs, corticosteroids, etanercept	[188]
Systemic juvenile idiopathic arthritis	Unknown	Daily recurring fever, anaemia, hepatosplenomegaly, macular salmon-coloured skin rash of trunk and extremities, myalgia, arthritis (late symptom)	NSAIDs, corticosteroids, DMARDs	[189]
Adult-onset Still's disease	Unknown	Daily recurring fever, hepatosplenomegaly, arthritis, salmon-colored skin rash of trunk and extremities, myalgia	NSAIDs, corticosteroids, DMARDs	[189]
Relapsing polychondritis	Unknown	Intermittent fever, skin rash, auricular / nasal / respiratory tract chondritis, ocular inflammation, arthritis, audiovestibular damage	Systemic corticosteroids, methotrexate	[190,191]
Schnitzler's syndrome	Unknown	Chronic urticarial skin rash, recurrent fever, arthralgia, myalgia	Anakinra	[192]
Sweet syndrome	Unknown, neutrophil-dependent	Fever, skin lesions (violet papules, plaques or nodules), pulmonary symptoms (dyspnoea, cough)	Corticosteroids	[193]
Behçet's disease	Unknown	Painful oral aphtous ulcers, painful genital ulcers, uveitis	Corticosteroids	[194,195]
Anti-synthetase syndrome	Unknown	Myositis, interstitial lung disease, arthritis, fever, Raynaud's phenomenon	Corticosteroids	[196]

NSAIDs: non-steroidal anti-inflammatory drug; DMARD: disease-modifying anti-rheumatic drug; IL: interleukin; IgD: immunoglobulin D; TNF: tumour necrosis factor; TNR: tenascin R.

cases the molecular basis for the putative link is largely unclear (Table 4).

The ugly: common human diseases linked to NLRP3 inflammasome activity

In addition to its central role in the pathogenesis of autoinflammatory disorders, the NLRP3 inflammasome has emerged recently as an unexpected sensor for metabolic danger and stress [75,76]. Indeed, it has been implicated in the development of major diseases such as gout, type 2 diabetes and obesity-induced insulin resistance. Moreover, the NLRP3 inflammasome is increasingly suspected of playing a major role in other human pathologies such as cancer, asbestosis and Alzheimer's disease.

Gout

Gout is a sterile inflammatory disease caused by monosodium urate (MSU) crystal deposition in various tissues. The prototypical clinical manifestation is acute monoarthritis, where MSU crystals precipitate in the joint, triggering an acute local inflammatory response [77]. MSU crystals were demonstrated to specifically activate the NLRP3 inflammasome, both *in vitro* and *in vivo* [78]. Uric acid is normally produced as the end result of the metabolic pathway governing the degradation of purines, and hyperuricaemia is thus a main risk factor for the development of gout [77]. Taken together, this suggests that the NLRP3 inflammasome has evolved as a sensor of metabolic endogenous danger, in addition to its pathogen-detecting functions.

Excitingly, preliminary clinical trials involving *in vivo* IL-1β blockade by anakinra or rilonacept in gout patients demonstrated high efficacy and the absence of adverse effects [79,80]. These findings require confirmation in large-scale controlled studies, and it will be interesting to see whether long-acting therapies such as canakinumab are able to tame chronic gout flares over time. Of special interest, anti-IL-1 therapy might be attractive to patients for which mainstream gout therapies are inefficient or contraindicated [81].

Type II diabetes

Another key metabolic danger signal resides in chronically elevated blood sugar levels and associated insulin resistance, which are hallmarks of type 2 diabetes. During recent years there has been a growing interest in the inflammatory component of the disease [75], and in particular in the role of IL-1β [82]. Indeed, IL-1β has been proposed to play a critical role in the loss of β cell mass in the course of type 2 diabetes [83], and a current hypothesis suggests that the relative balance between IL-1β and endogenous IL-1Ra regulates pancreatic islet inflammation associated with the disease [84]. Remarkably, a recent clinical trial supports the notion that IL-1β is indeed a key player in type 2 diabetes, as patients receiving IL-1β antagonists featured improved glycaemic control and β cell mass [85]. Notably, diabetic markers such as increased levels of saturated fatty acids and islet-derived amyloid polypeptide have been reported as capable of activating the NLRP3 inflammasome [86,87], and NLRP3- and ASC-deficient mice fed a high-fat diet display improved insulin sensitivity when compared to control mice [86].

Obesity-induced insulin resistance

Further experimental data suggest that the NLRP3 inflammasome is an important regulator of adipocyte differentiation and insulin sensitivity [88]. Adipocytes are rendered more metabolically active and insulin-sensitive upon NLRP3 inflammasome inhibition in murine models of obesity [88]. Strikingly, calorie restriction and exercise-mediated weight loss in obese type 2 diabetes patients is associated with a decreased NLRP3 expression in adipose tissue, coupled to decreased inflammation and improved insulin sensitivity [89]. Collectively, these findings suggest that the NLRP3 inflammasome is able to sense obesity-associated danger signals and contribute to the development of inflammation and insulin resistance [89].

Cancer

The tumour microenvironment has been likened to a non-resolving wound response, with an inflammatory milieu capable of stimulating tumour survival, growth, angiogenesis, invasion and metastasis, immune suppression and genetic mutation [90,91]. Studies suggest that IL-1, like the other key proinflammatory cytokine TNF, is often associated with tumour promotion. An evaluation of several clinical trials using recombinant IL-1β or IL-1α showed that neither had any significant therapeutic benefit when used alone against ovarian cancer, renal cell carcinoma or melanoma, and the toxicity associated with IL-1 administration is likely to outweigh any potential benefits [4].

However, immune-mediated anti-tumour responses resulting from the production of IL-1β or IL-1α have been documented. Early reports showed that IL-1 treatment (alone or in combination with chemotherapeutic treatment) of cancer cell lines or murine syngenic tumours resulted in decreased tumour cell growth and often promoted tumour regression [92–94]. Similarly, when IL-1α transgenic mice expressing 17 kDa IL-1α under the keratin 14 promoter were treated with DMBA/TPA (7,12-dimethylbenzanthracene/12-*O*-tetradecanoylphorbol-13-acetate), or crossed to mutant Ha-Ras expressing mice, the IL-1α expressing mice were completely resistant to papilloma and carcinoma formation due to enhanced acute inflammatory responses [95]. More recently it was also demonstrated that the NRLP3 inflammasome and subsequent IL-1β priming of T cells is critical

for immune-mediated eradication of tumours following chemotherapy [96].

Several groups have also examined the role of NLRP3 and caspase-1 in inflammatory bowel diseases using the dextran sulphate sodium (DSS) mouse model of colitis. Ulcerative colitis and Crohn's disease predispose to colorectal cancer, where an inappropriate inflammatory response to commensal bacteria is believed to play a major role in the neoplastic transformation of the intestinal epithelium. Two studies have suggested that caspase-1 or NLRP3 deficiency leads to reduced colitis severity in DSS-treated mice when compared to wild-type mice [97,98]. However, opposing results reported by several groups showed that NLRP3, ASC and caspase-1 knock-out mice are all more susceptible to DSS-induced colitis and death [99–101]. In inflammasome-deficient mice, it was reported that a lack of IL-18 activation prevented the repair of the mucosal barrier following DSS-induced damage, resulting in systemic commensal bacterial spread [101]. It was also demonstrated that colitis-associated cancer, induced by DSS and azoxymethane, is enhanced significantly upon genetic deletion of either NLRP3, caspase-1 or ASC, while the role of NLRC4 remains controversial [102–104]. It has been observed previously that other TLR/IL-1R family signalling members, such as myeloid differentiation factor 88 (MydD88), also protect from DSS-associated colitis and intestinal tumorigenesis [105–107]. Therefore, the accumulative evidence suggests that appropriate innate immune signalling responses to commensal bacteria, mediated at least in part by the NLRP3 inflammasome, are a general requirement for intestinal homeostasis. Consistent with this notion, single nucleotide polymorphisms (SNPs) within the NLRP3 region that result in decreased NLRP3 expression have been identified as contributing to Crohn's disease susceptibility, suggesting that the NRLP3 inflammasome may also play a protective role in inflammatory bowel disease in humans [108].

Ulcerative colitis results from hyper-responsive inflammation, and in this context it has been demonstrated that excessive IL-1β and IL-18 production can also contribute to DSS-induced colitis and possibly cancer, as was observed when the autophagy gene ATG16L1, or the caspase-1 negative regulator, caspase-12, were deleted [43,101]. Therefore, the NLRP3 inflammasome may play an important role in cellular repair and regeneration following acute tissue damage, but if tissues are exposed to chronic or excessive inflammasome activity, NLRP3 stimulation is likely to enhance neoplastic processes.

Despite its ability to promote an immune cell-mediated anti-tumour response, high levels of IL-1 in the tumour microenvironment often correlate with a poor prognosis (reviewed in [109]). Tumour-associated macrophages and dendritic cells are likely to contribute to IL-1β levels within the tumour infiltrate, while some cancer cell lines, such as those derived from myeloma, melanoma and acute myeoblastic leukaemia, can produce active IL-1β constitutively which can contribute towards tumour cell growth and invasiveness [110–112]. It is notable that some common oncogenes, such as Ras, can induce IL-1β expression [113] and IL-1β is a known target for the transcription factor NF-κB, which is activated in many neoplastic malignancies.

IL-1 receptor signalling can induce either directly or indirectly the production genes that stimulate tumour growth, angiogenesis and metastasis [i.e. IL-6, IL-8, TNF, matrix metalloproteinases (MMPs), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1), CXCL-2]. Melanoma cells expressing high levels of IL-1β show reduced tumour growth and metastases when treated with IL-1Ra in murine xenograft experiments [114]. Similarly, Lewis lung cell carcinoma cells engineered to produce IL-1β showed increased tumour growth and increased expression of angiogenic factors when implanted into mice [115]. In other mouse models, murine B16 melanoma growth, invasiveness, lung metastasis and stimulation of angiogenesis is severely attenuated in IL-1β, and to a lesser extent IL-1α, knock-out mice [116], an affect which anakinra treatment appears to recapitulate somewhat in B16 melanoma injected wild-type mice [117]. Similarly, chemically induced skin carcinogenesis is severely compromised in IL-1β knock-out mice and, conversely, tumour growth accelerated upon genetic deletion of IL-1Ra [118]. The mechanisms and potential contribution of different inflammasome(s) in IL-1β activation in murine cancer models has yet to be examined in detail, although caspase-1 function does contribute to B16 melanoma hepatic metastasis [119].

Cells from acute myeloid leukaemia (AML) patients can produce and secrete IL-1β and show substantially reduced proliferation and decreased growth factor levels [i.e. granulocyte–macrophage colony-stimulating factor (GM-CSF)] when treated with IL-1Ra, although in a subpopulation of patients AML cells may also proliferate when exposed to IL-1Ra [112,120–123]. A Phase I safety trial reported no responses in patients with refractory or relapsed AML when treated with soluble decoy human IL-1R [124]. However, it was noted that the decoy IL-1R serum levels were below those that completely blocked AML cell growth *in vitro* and were likely to be even lower within marrow. It may therefore be worth revisiting the effects of IL-1 blockade on AML in the clinic using more efficacious IL-1 inhibitors.

Evidence for the tumorigenic role of IL-1β also comes from its association with gastric cancer, the second deadliest form of cancer worldwide after lung cancer [125]. IL-1β is induced by *Helicobacter pylori* within the gastric mucosa and is a potent inhibitor of gastric acid secretion, which may lead to gastric atrophy, a precursor of gastric cancer. In 2000, Rabkin *et al*. described IL-1 gene cluster polymorphisms that correlated with a predisposition to hypochlorhydria, gastric

atrophy and gastric cancer in humans infected with *H. pylori* [126]. Several studies in different human populations have since confirmed these observations (reviewed in [127]), and mice engineered to express IL-1β in the stomach develop gastric inflammation and cancer [128]. However, it is still unclear how the human polymorphisms affect IL-1β production and which, if any, inflammasomes are involved.

The expression of IL-1β by either myeloma cells or innate immune cells has been associated for some time with the induction of IL-6, a key growth factor that promotes myeloma cell survival and proliferation. Recent clinical trials using IL-1Ra (combined with low-dose dexamethasone) demonstrated that IL-1 inhibition induced a chronic disease state in smouldering or indolent multiple myeloma patients, and substantially improved progression-free survival by preventing the transition to active multiple myeloma [129]. This represents the first demonstration of the therapeutic benefit of IL-1 inhibition in a human cancer.

Given the general safety of inhibiting IL-1 *in vivo*, and its probable role in cancer metastasis, future clinical trials examining IL-1 inhibition in cancer are deemed warranted [130]. It will also be important to determine the mechanisms and inflammasomes by which cancer cells directly or indirectly modulate IL-1β activity.

Other diseases

Numerous NLRP3 inflammasome activators have been identified and characterized *in vitro* [6]. In some cases, they have pointed to the unexpected implication of the NLRP3 inflammasome in the pathogenesis of various inflammatory diseases. For example, asbestosis and silicosis have been shown to activate the NLRP3 inflammasome in murine models of chronic pulmonary fibrotic disorders [131,132], raising the intriguing possibility that IL-1β may contribute to inflammation-induced lung cancer, and that anti-IL-1β therapy might be beneficial for patients suffering from these diseases. The fibrillar peptide amyloid-β, which plays a key function in the development of Alzheimer's disease, was also shown to activate the NLRP3 inflammasome [28]. Moreover, the NLRP3 inflammasome was suggested to be instrumental in the inflammatory component of the disease and its associated brain tissue damage [28]. In the skin, NLRP3 inflammasome activation has been linked to UVB-induced damage [133,134] and contact hypersensitivity [133,135]. Recent studies have shown that haemozoin, a crystal produced by plasmodium species in the course of malarial infection, activates the NLRP3 inflammasome [30,136]. More surprising still, non-coding NLRP3 mutations were linked to essential hypertension susceptibility, possibly due to increased expression of the protein [137].

In most of theses cases, including cancer, the evidence pointing to an involvement of the NLRP3 inflammasome in disease development *in vivo* remains preliminary and awaits further confirmation. Collectively, however, they stand as a testimony to the impressive versatility of the NLRP3 inflammasome as a danger-detection system with potentially far-reaching implications for human health.

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Disclosure

The authors have no conflicts of interest to declare.

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