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Inflammasomes: mechanism of action, role in disease, and therapeutics

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Abstract

The inflammasomes are innate immune system receptors and sensors that regulate the activation of caspase-1 and induce inflammation in response to infectious microbes and molecules derived from host proteins. They have been implicated in a host of inflammatory disorders. Recent developments have greatly enhanced our understanding of the molecular mechanisms by which different inflammasomes are activated. Additionally, increasing evidence in mouse models, supported by human data, strongly implicates an involvement of the inflammasome in the initiation or progression of diseases with a high impact on public health, such as metabolic disorders and neurodegenerative diseases. Finally, recent developments pointing toward promising therapeutics that target inflammasome activity in inflammatory diseases have been reported. This review will focus on these three areas of inflammasome research.

Subject terms: Chronic inflammation Immunological disorders Inflammasome Inflammatory diseases

Introduction

Inflammation is a protective immune response mounted by the evolutionarily conserved innate immune system in response to harmful stimuli, such as pathogens, dead cells or irritants, and is tightly regulated by the host. Insufficient inflammation can lead to persistent infection of pathogens, while excessive inflammation can cause chronic or systemic inflammatory diseases. Innate immune function depends upon the recognition of pathogen-associated molecular patterns (PAMPs), derived from invading pathogens, and danger-associated molecular patterns (DAMPs), induced as a result of endogenous stress, by germline-encoded pattern-recognition receptors (PRRs). Activation of PRRs by PAMPs or DAMPs triggers downstream signaling cascades and leads to production of type I interferons (interferon-α and interferon-β) and proinflammatory cytokines. Of note, DAMP-triggered inflammation, which is particularly important in inflammatory diseases, is termed sterile inflammation when it occurs in the absence of any foreign pathogens[1].

Activation of the inflammasome is a key function mediated by the innate immune system, and recent advances have greatly increased our understanding of the macromolecular activation of inflammasomes. Several families of PRRs are important components in the inflammasome complex, including the nucleotide-binding domain, leucine-rich repeat containing proteins (also known as NOD-like receptors, NLRs) and the absent in melanoma 2 (AIM)-like receptors (ALRs) in both mice and humans[2]. Upon sensing certain stimuli, the relevant NLR

or AIM2 can oligomerize to be a caspase-1–activating scaffold. Active caspase-1 subsequently functions to cleave the proinflammatory IL-1 family of cytokines into their bioactive forms, IL-1β and IL-18, and cause pyroptosis, a type of inflammatory cell death[3, 4].

Inflammasomes have been linked to a variety of autoinflammatory and autoimmune diseases, including neurodegenerative diseases (multiple sclerosis, Alzheimer's disease and Parkinson's disease) and metabolic disorders (atherosclerosis, type 2 diabetes and obesity)[4]. In the initiation of inflammatory disease, inflammasomes play either causative or contributing roles, and also exaggerate the pathology in response to host-derived factors. This review will focus on the current understanding of inflammasome activation; on the roles of inflammasomes in several prevalent diseases that are increasingly recognized as having an inflammatory contribution, such as neurodegenerative diseases and metabolic disorders; and on advances in potential therapies targeting inflammasomes.

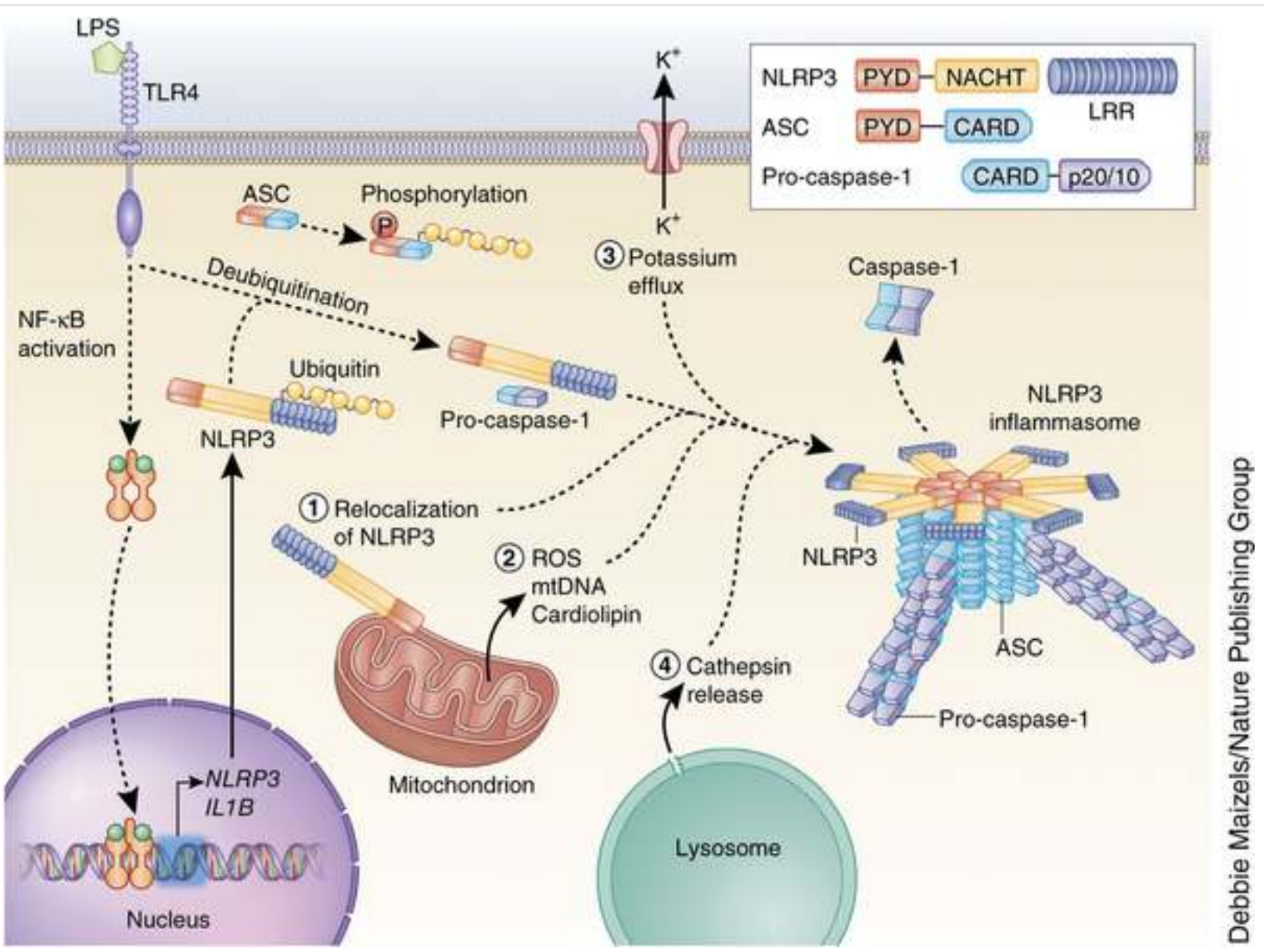
Mechanisms of inflammasome activation

General principles of inflammasome activation.

Recent developments in our understanding of the mechanisms of inflammasome activation have been expertly reviewed in depth[4, 5, 6, 7, 8]. Here, however, we give a brief overview of recent advances in the mechanisms of inflammasome activation in order to best explain their link with disease.

Inflammasomes are multimeric protein complexes that assemble in the cytosol after sensing PAMPs or DAMPs[7, 9]. Although there are fundamental differences between inflammasomes dependent upon stimuli, in general, canonical inflammasomes serve as a scaffold to recruit the inactive zymogen pro-caspase-1 (Figs. 1 and 2). Oligomerization of pro-caspase-1 proteins induces their autoproteolytic cleavage into active caspase-1 (ref. 10). Active caspase-1 is a cysteine-dependent protease that cleaves the precursor cytokines pro-IL-1β and pro-IL-18, generating the biologically active cytokines IL-1β and IL-18, respectively[11, 12, 13]. Active caspase-1 is also able to induce an inflammatory form of cell death known as pyroptosis[5, 6, 7].

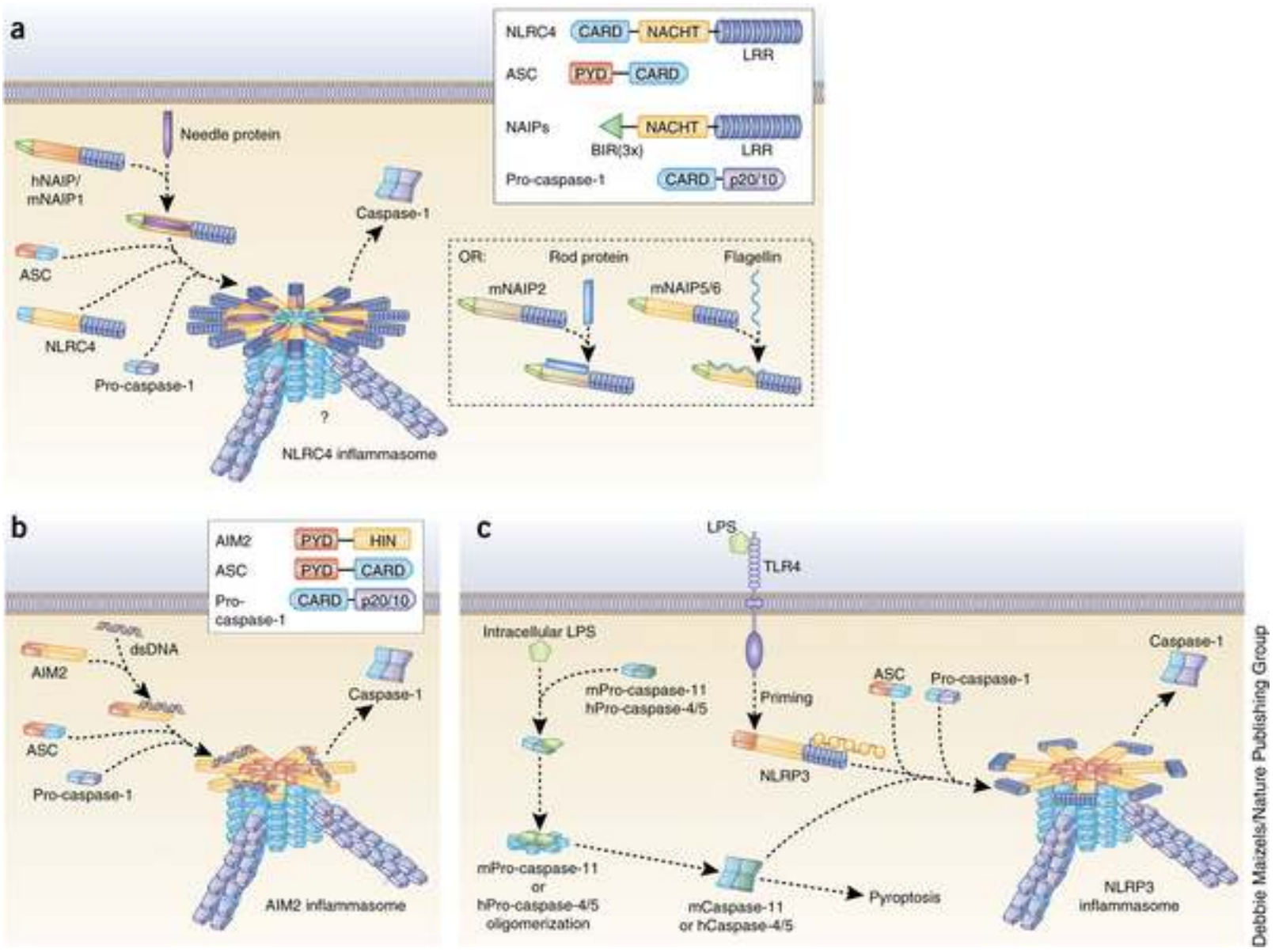
Figure 1: Mechanisms of NLRP3 inflammasome activation.



NLRP3 must be primed before activation. Priming involves two distinct steps. First, an NF-κB–activating stimulus, such as LPS binding to TLR4, induces elevated expression of *NLRP3* (as well as *IL1B*), which leads to increased expression of NLRP3 protein. Additionally, priming immediately licenses NLRP3 by inducing its deubiquitination. The adaptor protein ASC must become linearly ubiquitinated and phosphorylated for inflammasome assembly to occur. After priming, canonical NLRP3 inflammasome activation requires a second, distinct signal to activate NLRP3 and lead to the formation of the NLRP3 inflammasome complex. The most commonly accepted activating stimuli for NLRP3 include relocalization of NLRP3 to the mitochondria, the sensation of mitochondrial factors released into the cytosol (mitochondrial ROS, mitochondrial DNA, or cardiolipin), potassium

efflux through ion channels, and cathepsin release following destabilization of lysosomal membranes. Recent studies have determined that activated NLRP3 nucleates ASC into prion-like filaments through PYD-PYD interactions. Pro-caspase-1 filaments subsequently form off of the ASC filaments through CARD-CARD interactions, allowing autoproteolytic activation of pro-caspase-1. Inset shows domain arrangement of the NLRP3 inflammasome components. Pro-caspase-1 and caspase-1 domains are simplified for clarity, the CARD domain is actually removed by cleavage, and two heterodimers form with the p20 and p10 effector domains (p20/10).

Figure 2: Mechanisms of NLRC4, AIM2 and noncanonical NLRP3 inflammasome activation.



(**a**) NLRC4 inflammasome agonists such as the bacterial needle protein bind directly to regions within the NACHT domains of the NAIP subfamily of proteins. hNAIP and mNAIP1 bind needle protein, mNAIP2 binds rod protein, and both mNAIP5 and mNAIP6 bind flagellin. Ligand-bound NAIP proteins then oligomerize with NLRC4 to form a caspase-1–activating inflammasome. Though NLRC4 can directly oligomerize with caspase-1 through CARD-CARD interactions, ASC is required for caspase-1 activation by the NLRC4 inflammasome, possibly through the formation of prion-like filaments (blue) by ASC. However, ASC is dispensable for the induction of pyroptosis. Inset shows domain arrangement of NLRC4 inflammasome components. NAIP proteins have three N-terminal BIR domains. hNAIP, human NAIP; mNAIP, mouse NAIP. (**b**) The mechanism of AIM2 inflammasome activation is well defined. The HIN domain of AIM2 directly binds cytosolic dsDNA, displacing the PYD and relieving autoinhibition. This allows oligomerization of AIM2 PYD with ASC PYD, converting ASC into its prion form. Prion-like filaments of pro-caspase-1 (violet) are then able to form off of the ASC filaments, inducing caspase-1 activation. Inset shows domain arrangement of AIM2 inflammasome components. (**c**) Studies have determined that mouse pro-caspase-11 (mPro-caspase-11) and human pro-caspases-4 and -5 (hPro-caspase-4/5) can directly bind intracellular LPS and activate a noncanonical NLRP3 inflammasome. This induces oligomerization of these pro-caspases, leading to their proximity-induced activation. This is sufficient for the induction of pyroptosis but not for the processing of pro-IL-1β. However, active mCaspase-11 and hCaspase-4 can promote full assembly and activation of the NLRP3 inflammasome following a priming signal.

Inflammasome names denote the protein forming the scaffold. Most inflammasomes are formed with one or two NLR family members, and NLRC4 requires interaction with an NLR member of the NAIP subfamily of proteins[6, 14] (Figs. 1 and 2a). However, non-NLR proteins such as AIM2 (Fig. 2b) and pyrin can also form inflammasomes. NLRC4 can directly associate with caspase-1 through CARD-CARD interactions[15]. NLRs containing an N-terminal pyrin domain (PYD) have been shown to associate with apoptosis-associated speck-like protein containing a CARD (ASC) in order to recruit pro-caspase-1 to the inflammasome[9, 16] (Fig. 1).

Inflammasome activation occurs when the scaffold protein senses or binds its activating stimuli. How this occurs is starting to be clarified for certain inflammasome proteins[6]; prominent among these are the roles of ASC, AIM2, and NAIP and NLRC4. For example, AIM2 can directly bind its stimulus, double-stranded DNA (dsDNA)[17]. However, many questions remain regarding inflammasome activation. We will now briefly

discuss the mechanism of activation of the best-characterized inflammasomes, an area in which major advances have been made. The readers can refer to recent reviews in which all of the NLR inflammasomes have been discussed[5, 6, 7], including evidence supporting the existence of less-characterized inflammasomes such as NLRP6, NLRP7, NLRP12 and IFI16 inflammasomes. It should also be noted that although NLRP1, which has many genetic variants in mice and rats, forms well-defined inflammasomes in these rodent models, the activation of the single human NLRP1 paralog into an inflammasome is less well understood[18].

NLRP3 inflammasome.

The NLRP3 inflammasome (Fig. 1) is activated in response to the widest array of stimuli, leading to the theory that the dissimilar agonists induce similar downstream events that are sensed by NLRP3 (refs. 8,19,20). The mechanisms of NLRP3 activation supported by the most studies include potassium efflux out of the cell, the generation of mitochondrial reactive oxygen species (ROS), the translocation of NLRP3 to the mitochondria, the release of mitochondrial DNA or cardiolipin, and the release of cathepsins into the cytosol after lysosomal destabilization[6, 7, 8] (Fig. 1). However, not all of these events are induced by all NLRP3 agonists, so the precise mechanism of NLRP3 activation is still debated. Additionally, increases in intracellular calcium can activate the NLRP3 inflammasome[21, 22], but this is also not a requirement of all NLRP3 agonists[23]. Though many published studies support the involvement of lysosomal cathepsins, proteases that degrade internalized proteins, in NLRP3 inflammasome activation, it is important to note that this is not without some controversy[24].

In most cell types, NLRP3 must be primed, and a prototypical example of such a priming event is the binding of lipopolysaccharide (LPS) to TLR4. Priming has long been known to increase cellular expression of NLRP3 through NF-κB signaling[25]. However, recent findings have shown that priming rapidly licenses mouse NLRP3 inflammasome activation by inducing the deubiquitination of NLRP3 independent of new protein synthesis, whereas inhibition of deubiquitination inhibits human NLRP3 activation[26, 27]. Once primed, NLRP3 can respond to its stimuli and assemble the NLRP3 inflammasome. Additionally, ASC must be linearly ubiquitinated for NLRP3 inflammasome assembly[28]. Current stimuli recognized as NLRP3 agonists that induce NLRP3 inflammasome formation include ATP, pore-forming toxins, crystalline substances, nucleic acids, hyaluronan, and fungal, bacterial or viral pathogens[6, 7]. These stimuli can be encountered during infection, either produced by pathogens or released by damaged host cells. Additionally, pathologic conditions in the body may promote the formation of these stimuli in the absence of infection; an example is the formation of inflammatory cholesterol crystals, as discussed in more detail later.

Recent studies showed that the NLRP3 NBD oligomerizes the NLRP3 PYD, which serves as a scaffold to nucleate ASC proteins through PYD-PYD interactions[29, 30]. This causes ASC to convert to a prion-like form and generate long ASC filaments that are crucial to inflammasome activation. Pro-caspase-1 then interacts with ASC through CARD-CARD interactions and forms its own prion-like filaments that branch off of the ASC filaments. The close proximity of pro-caspase-1 proteins then induces autoproteolytic maturation of pro-caspase-1 into active caspase-1.

Additionally, increasing evidence has identified a crucial role for caspase-8 in inflammasome activation and pro-IL-1β processing. Caspase-8 is a proapoptotic protease that initiates the external apoptosis pathway in response to external stimuli, such as FasL and TNF, and protects against an inflammatory form of cell death termed necroptosis[31]. It is now also recognized that caspase-8 is required for both the transcriptional priming and activation of the canonical and noncanonical NLRP3 inflammasomes in mice in response to pathogenic stimuli and ligands stimulating various different TLRs[32, 33, 34]. Thus, inflammatory diseases in which TLR ligands are generated could lead to caspase-8–mediated NLRP3 priming or activation.

Additionally, caspase-8 was shown to bind and localize to ASC specks, further suggesting that caspase-8 is an important component of inflammasome complexes[35]. However, the exact molecular mechanism by which caspase-8 promotes caspase-1 activation has yet to be elucidated. Importantly, caspase-8 also has an identified role in NLRC4 and AIM2 inflammasome activation[35, 36] and has even been shown to directly promote pro-IL-1β processing in a noncanonical caspase-8 inflammasome induced by the binding of certain extracellular pathogens to dectin-1 (ref. 37). Notably, the exact role of caspase-8–mediated inflammasome activation is somewhat controversial[38].

NLRC4 inflammasome.

In contrast to the diverse stimuli that activate NLRP3 inflammasomes, the NLRC4 inflammasome responds to a more limited set of stimuli. A major advance in our understanding of the NLRC4 inflammasome is the recognition that NLRC4 forms a complex with various NAIP proteins, and NLRC4-activating ligands are bound by these NAIP components rather than by NLRC4 (Fig. 2a). This raises the question of whether NLRC4 is a scaffolding protein and not a receptor[14, 39]. In mice, NAIP1 binds the bacterial type III secretory system (T3SS) needle

protein[40, 41], NAIP2 binds the bacterial T3SS rod protein[42] and both NAIP5 and NAIP6 bind bacterial flagellin[42, 43]. T3SS is found in several Gram-negative bacteria and allows the bacteria to inject effector molecules into infected host cells. By contrast to mice, in humans only one NAIP protein has been characterized, and it was found to bind only the T3SS needle protein[40], suggesting a far more restrictive repertoire of ligands for the NLRC4 inflammasome in human cells than for the NLRP3 inflammasome, which responds to a plethora of stimuli.

Once NAIP proteins bind their ligands, they can oligomerize with NLRC4 and form a NAIP/NLRC4 inflammasome[14]. In order for NLRC4 to be activated, its autoinhibition must be relieved to allow oligomerization with NAIP proteins, but how this occurs is unclear[14]. However, two new gain-of-function mutations of NLRC4 have recently been identified in humans that cause severe spontaneous autoimmune syndrome, suggesting that the helical domain is responsible for this autoinhibition[44, 45]. Though some reports indicate that mouse NLRC4 must be phosphorylated before inflammasome activation[46, 47], there are also conflicting reports indicating that phosphorylation is dispensable[14].

Though NLRC4 contains a CARD domain, ASC is required for maximal inflammasome activation[7] (Fig. 2a). A possible explanation might be the formation of ASC filaments off of NLRC4, as there is evidence that the CARD domain can convert ASC to its prion-like form[31].

AIM2 inflammasome.

The non-NLR AIM2 can also form a caspase-1–containing inflammasome, but, unlike the NLRs, the HIN-200 domain of AIM2 can directly bind its stimulus, cytosolic dsDNA, which may be encountered in the cytosol during pathogenic infection (Fig. 2b)[17]. The autoinhibitory conformation of AIM2 is created by interactions of its two domains and relieved by the sugar phosphate backbone of dsDNA[48]. DNA binding displaces the PYD domain[48], freeing the PYD domain to recruit ASC to the complex[17, 49]. AIM2 cannot interact with ASC unless autoinhibition is relieved[50], and thus AIM2 maintains itself in an inactive state until its ligand binds.

Interestingly, AIM2 does not appear to recognize a specific sequence or structure of dsDNA but instead requires a dsDNA strand of at least 80 base pairs for optimal inflammasome activation[48]. Similar to NLRP3, oligomerized AIM2 nucleates ASC through PYD-PYD interactions and converts ASC to its prion form, leading to the development of long PYD-PYD ASC filaments[29, 30].

Recently, a noncanonical AIM2 inflammasome was shown to mediate protection against *Francisella novicida*[51]. *F. novicida* infection is detected by cGAS and STING, inducing the expression of the transcription factor IRF1. IRF1 increases the expression of guanylate-binding proteins, which increase the intracellular killing of the bacterium. This releases dsDNA into the cytosol and induces AIM2 inflammasome activation.

Noncanonical inflammasomes

A developing area of interest in the inflammasome field is the noncanonical inflammasome formed by caspase-11 in mice (Fig. 2c). Caspase-11 was initially found to be important for the activation of caspase-1 and caspase-3 (ref. 52). Recently, it was shown to promote NLRP3 inflammasome activation to indirectly enhance processing of pro-IL-1β or pro-IL-18 (ref. 53). More remarkably, caspase-11 detects intracellular LPS and some intracellular bacteria, directly mediating cell death and IL-1α secretion, but not IL-1β secretion, in a mechanism independent of the traditional LPS receptor TLR4 (refs. 7,54,55). Though humans do not express caspase-11, recent studies indicate that caspase-4 and caspase-5 in human cells serve a similar function[56, 57] (Fig. 2c). Notably, active caspase-4 can promote the activation of the primed NLRP3 inflammasome without a need for a canonical NLRP3 activating stimulus[57]. As caspase-11–deficient mice are known to be protected from endotoxic shock[53], further study of the noncanonical inflammasome in human cells is of great interest.

Mechanisms of inflammasome spreading.

ASC has long been recognized to redistribute upon inflammasome activation from the nucleus to the cytosol and form a large perinuclear aggregate in cells[58, 59]. In a recent breakthrough, ASC specks were reported to be released by dying cells, leading to cleavage of extracellular pro-IL-1β and activating caspase-1 in macrophages internalizing the specks[60]. Importantly, as activation of all major inflammasomes is associated with speck formation[59], this suggests that inflammasome activation propagates inflammation from cell to cell. The buildup of specks at sites of inflammation has serious implications for inflammatory diseases, as injection of purified ASC specks into mice *in vivo* has been shown to propagate inflammation[60].

Additionally, phosphorylation of ASC was recently shown to be a key checkpoint in ASC speck formation. The kinases Syk and JNK, which activate in response to a vast array of stimuli and lead to the phosphorylation of many downstream targets, mediate phosphorylation of ASC upon NLRP3 inflammasome activation, and inhibition of these kinases prevented ASC speck formation and blocked caspase-1 activation[61].

Importantly, phosphorylation was dispensable for NLRP3 and ASC oligomerization. This suggests that phosphorylation of ASC may be necessary for ASC to switch to its prion-like form and form self-propagating filaments. This also suggests that kinase inhibition may have potential therapeutic use against inflammatory diseases in the absence of more targeted inhibitors.

Inflammasomes in disease

Here we focus on neurologic disorders and metabolic diseases, neither of which are traditionally considered to be inflammatory diseases but which are increasingly recognized as having an inflammatory component that contributes significantly to the disease process. Misfolded protein aggregates and aberrant accumulation of certain metabolites accompanying those diseases are endogenous DAMPs that have been proved to be direct activators of the NLRP3 inflammasome, which plays a critical role in the initiation and progress of those diseases.

The inflammasome and multiple sclerosis.

Multiple sclerosis (MS), one of the most common autoimmune inflammatory diseases, is characterized by myelin-reactive $CD4^+$ T cells that infiltrate the central nervous system (CNS), attack oligodendrocytes and induce demyelination[62]. Demyelination partially disrupts the communication of the nervous system, resulting in physical, mental and psychiatric challenges, among other problems. Presently, MS has no cure and shortens the lifespan of affected individuals by approximately 5–10 years[63].

Experimental autoimmune encephalomyelitis (EAE) is an animal model commonly used to mimic MS. To induce EAE, mice are immunized with the peptide myelin oligodendrocyte glycoprotein (MOG) emulsified in adjuvant, inducing infiltration of MOG-specific T cells and other inflammatory cells into the CNS[64]. Prior to the discovery of NLRs, the inflammasome products caspase-1, IL-1β and IL-18 had been shown to contribute to EAE progression. *Casp1* $^{-/-}$, *Il1a* $^{-/-}$, *Il1b* $^{-/-}$ and *Il18* $^{-/-}$ mice are resistant to EAE and show concomitant reductions in interferon (IFN)-γ and/or IL-17 levels[65, 66, 67]. It has recently been shown that *Nlrp3* expression increases in the spinal cord during EAE progression and that *Nlrp3*-deficient mice have a dramatically delayed course and reduced severity of disease, accompanied by fewer infiltrating inflammatory cells and reduced astrogliosis[64, 68]. In addition, a study using a cuprizone model of MS also showed that *Nlrp3*-deficient mice had delayed demyelination and oligodendrocyte loss[69]. Additionally, EAE mice show increased IL-18 levels compared with controls, and *Il18*-deficient mice phenocopy the reduced disease seen in *Nlrp3*-deficient mice, suggesting that NLRP3 functions through IL-18 to promote EAE[64, 68].

Despite these findings, the role of NLRP3 in EAE progression is complicated. Expression of *Nlrp3* in antigen-presenting cells (APCs) was required to stimulate T helper type 1 (T_H1) and T_H17 cells to respond to brain autoantigen in one study[64]. Additionally, *Nlrp3* and *Asc* (also known as *Pycard*) deficiency caused reduced expression of many chemokines and chemokine receptors, such as *Ccr2* and *Ccr6*, in both APCs and T_H cells, reducing migration of T_H1 and T_H17 cells into the CNS of *Nlrp3*- and *Asc*-deficient mice following EAE induction by MOG peptide immunization. However, direct delivery of $CD4^+$ T cells from EAE-induced WT, *Nlrp3* $^{-/-}$ or *Asc* $^{-/-}$ mice into the brain and spinal cord of recipient *Rag2* $^{-/-}$ mice, which lack mature T cells, induced the same degree of disease[68]. In summary, although these results suggest that the NLRP3 inflammasome contributes to both T_H1 and T_H17 cell responses and migration during EAE, the function of the NLRP3 inflammasome is not an inherent function of T cells. In the clinic, peripheral blood mononuclear cells (PBMCs) from patients with relapsing-remitting MS had higher levels of NLRP3, IL-1β and caspase-1 than were found in PBMCs from healthy controls. Intriguingly, soluble factors secreted by human PBMCs upon NLRP3 activation skew the cytokine profile of $CD4^+$ T cells toward a proinflammatory T_H17 phenotype, supporting a link between MS and the NLRP3 inflammasome[70].

However, a role for NLRP3 and ASC in EAE is not found in all studies and varies with variations in the disease model. Aggressive immunization of mice with heat-killed mycobacteria (Mtb) was able to induce EAE even in the absence of NLRP3 or ASC, whereas lower-dose Mtb immunization required NLRP3 and ASC for EAE induction[71]. Another study found no difference in MOG-induced EAE disease between WT and *Nlrp3*-deficient mice. In the same study, ASC promoted EAE progression in an inflammasome-independent manner through a mechanism that involved maintaining $CD4^+$ T cell survival. In agreement with this, *Asc*-deficient mice were even more resistant to EAE than were *Casp1*-deficient mice[72]. Part of the difference in inflammasome dependency may be explained by recent findings showing that IFN-β inhibits IL-1β production by macrophages, and only NLRP3-dependent EAE is ameliorated by IFN-β treatment. This suggests that IFN-β may therapeutically inhibit the NLRP3 inflammasome–IL-1β–IL-18 axis in MS[71]. Though IFN-β has been used therapeutically for more than 15 years, one-third of MS patients fail to respond to IFN-β, reflecting heterogeneity in the disease.

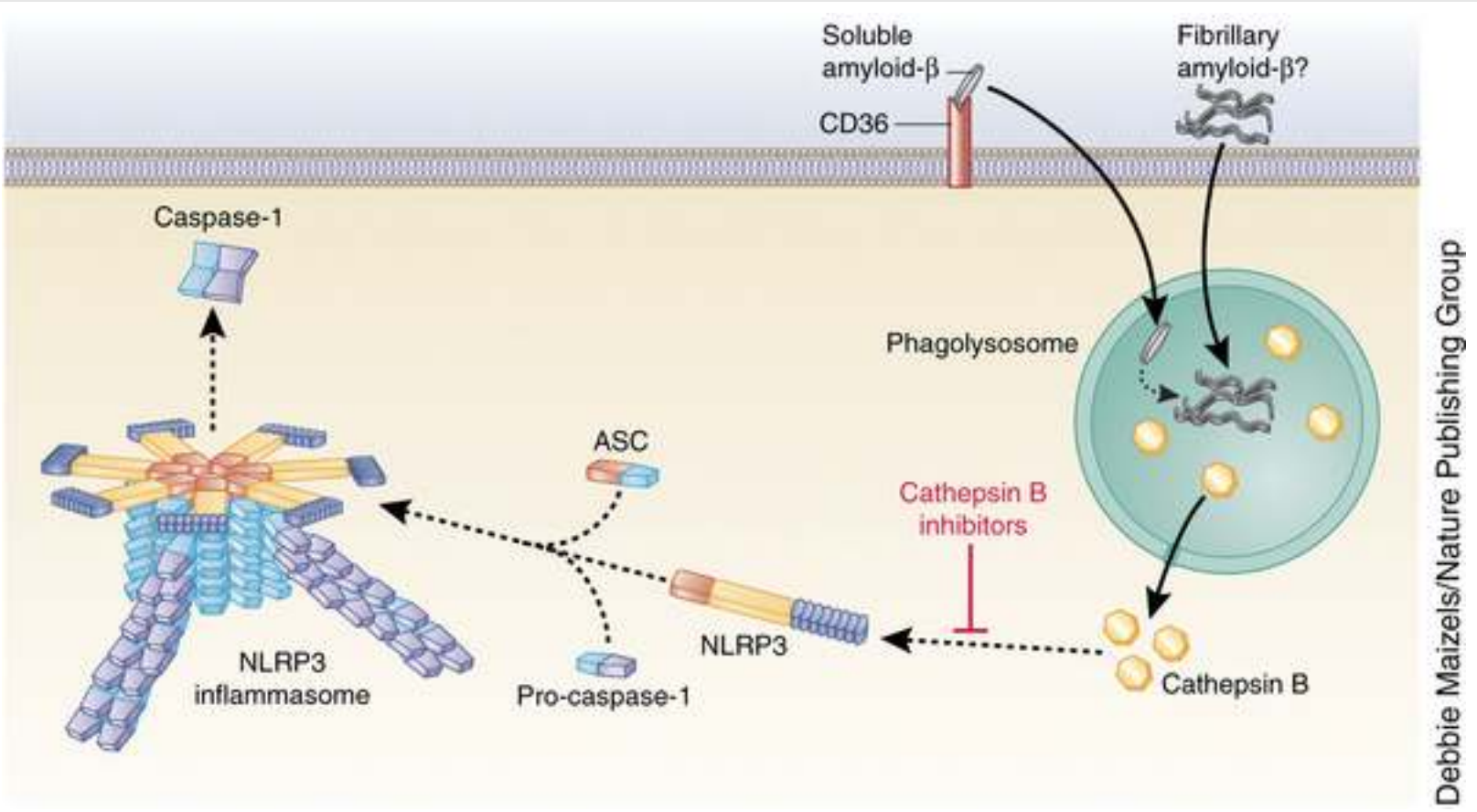
In addition to the NLRP3 inflammasome, a recent study using the pertussis toxin (PTX)-induced EAE model showed that TLR4 was required

for pro-IL-1β induction, and the pyrin-dependent inflammasome contributed to bioactive IL-1β formation. IL-1β stimulated nearby stromal cells to secrete IL-6, which can promote leukocyte adhesion and migration. *Pyrin* (also known as *Mefv*)-deficient 2D2 mice (MOG-specific T cell receptor transgenic mice) had lower EAE incidence and delayed and less severe disease following PTX injection. However, the pyrin inflammasome functions only at the initial stage of EAE induced by PTX, as comparable infiltration of $CD3^+$ cells was observed in the spinal cord of mice with similar clinical scores regardless of their genotype. In line with this, adoptive transfer of MOG-specific T cells into WT and *pyrin*-deficient mice induced similar EAE[73].

The inflammasome and Alzheimer's disease (AD).

Accumulation of amyloid-β plaques in the cerebrum is a characteristic of AD. Amyloid-β peptide is regularly formed in cerebral tissue by cleavage of the amyloid precursor protein, but it can form prion-like misfolded oligomers in the case of AD[74]. Amyloid-β was the first molecule associated with neurodegenerative disease models that was found to activate the mouse NLRP3 inflammasome, resulting in IL-1β production[75]. Fibrillary amyloid-β induces NLRP3 inflammasome–dependent activation of caspase-1 through a mechanism dependent on endosomal rupture and cathepsin B release in LPS-primed mouse macrophages[75] (Fig. 3). Interestingly, administration of cathepsin B inhibitors significantly improved memory deficit and reduced amyloid plaque load in the brain in the AD mouse model, suggesting a potential therapeutic approach for treating AD in which the inflammasome is targeted[76]. Importantly, a recent pivotal study in mice showed that the cell-surface receptor CD36 mediates the internalization of soluble amyloid-β, which then undergoes intracellular conversion to fibrillary amyloid-β to activate the NLRP3 inflammasome[77]. A direct link between the NLRP3 inflammasome and the development of AD has been shown in APP/PS1 mice (transgenic mice that develop chronic deposition of amyloid-β) with NLRP3 and caspase-1 deficiency. These mice have reduced AD-related pathogenesis, reflected by reduced chronic amyloid-β secretion, neuronal inflammation and cognitive impairment. In these mice, NLRP3 inflammasome deficiency skewed microglial cells to an M2 phenotype (characterized by elevated expression of arginase-1 and IL-4), resulting in the reduced deposition of amyloid-β and enhanced tissue remodeling in the AD mouse model[78]. In addition to the mouse study, a recent study found enhanced active caspase-1 expression in the brains of people with AD, suggesting that there is a link between inflammasome activation and AD in humans[78]. Therefore, *in vitro* and *in vivo* studies suggest a potentially important role for the NLRP3 inflammasome in the pathogenesis of AD and identify the NLRP3–caspase-1 axis as a potential target for AD therapy.

Figure 3: Mechanisms of NLRP3 inflammasome action in Alzheimer's disease.



In Alzheimer's disease, CD36 mediates the internalization of soluble amyloid-β and its intracellular conversion to fibrillary amyloid-β. This leads to disruption of the phagolysosome and activation of the NLRP3 inflammasome due to cathepsin B release. However, this does not exclude the possibility that phagocytosis of extracellular fibrillary amyloid-β also activates the NLRP3 inflammasome. Cathepsin B inhibition prevents amyloid-β–induced NLRP3 activation.

Inflammasome and Parkinson's disease (PD) model.

PD results in the death of dopamine-generating neurons in the substantia nigra and the presence of aggregated inclusions composed mainly of α-synuclein (αSyn) in neurons[79]. αSyn can form fibrils with a cross–β-sheet structure, morphologically similar to the amyloid fibrils from

AD[80]. Through multiple mechanisms, intracellular αSyn can be released into extracellular spaces[81]. Extracellular αSyn activates primary microglia and astrocytes as well as transformed microglia and astrocyte cell lines and induces the production of the cytokine IL-1β[81, 82]. In a rat model of PD, chronic expression of exogenous IL-1β introduced in an adenoviral vector in the region of the substantia nigra was shown to induce cell death in dopamine neurons and to promote PD progression[83]. Recently it was found that both fibrillary and monomeric αSyn induce pro-IL-1β expression via TLR2 signaling in human primary monocytes, but only fibrillary αSyn fully activates the inflammasome by inducing caspase-1 activation and mature IL-1β production[84]. This activation of caspase-1 required phagocytosis, cathepsin B and ROS. Cathepsin B and ROS are thought to lie upstream of NLRP3 activation, suggesting that αSyn activates the NLRP3 inflammasome[84]. However, this study did not use the more relevant microglial cells and astrocytes, and the involvement of NLRP3 was not directly proven by an *in vivo* animal model.

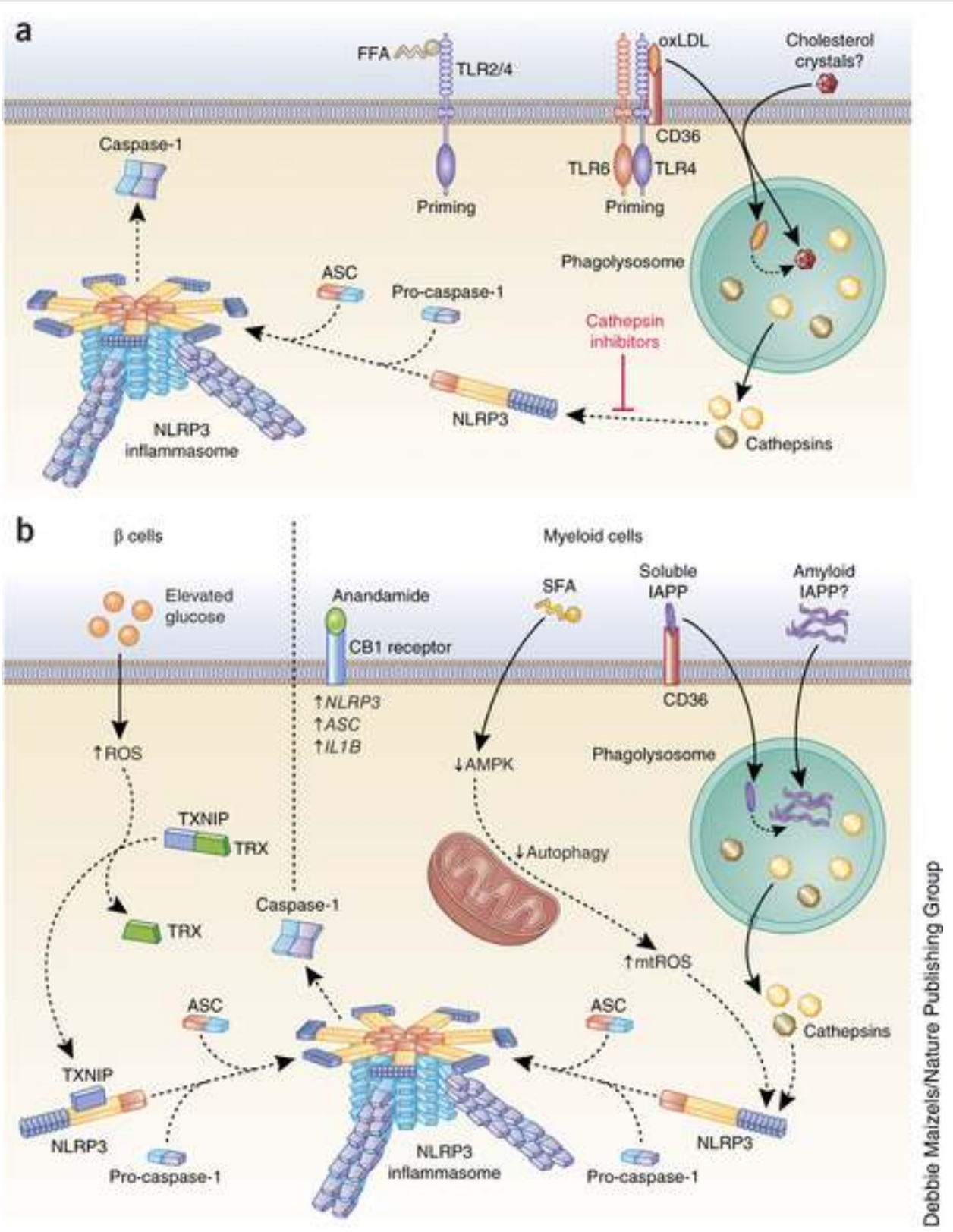
In a PD mouse model in which PD is induced by loss of nigral dopaminergic neurons caused by treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), mice lacking Nlrp3 are resistant to developing PD. This provides *in vivo* evidence for a link between the NLRP3 inflammasome and PD[85]. Interestingly, dopamine was found to negatively regulate NLRP3 activation in both primary microglia and astrocytes via a dopamine D_1 receptor (DRD1)–cyclic adenosine monophosphate (cAMP) signaling pathway[85]. Moreover, cAMP was found to directly bind NLRP3 and promote its ubiquitination-dependent degradation via the E3 ubiquitin ligase MARCH7 (ref. 85). Furthermore, mice lacking DRD1 are more susceptible to MPTP-induced neuroinflammation, as reflected by enhanced NLRP3 activation–dependent IL-1β and IL-18 production and increased loss of dopaminergic neurons[85]. These studies suggest that dopamine-producing neurons and the NLRP3 inflammasome regulate each other in a bidirectional fashion, whereby the inflammasome can damage these neurons, while dopamine from these neurons can inhibit NLRP3 function.

NLRP3 inflammasome and atherosclerosis.

Chronic inflammation plays an essential role in the initiation and progression of metabolic disorders such as type 2 diabetes (T2D), obesity, gouty arthritis and atherosclerosis[86]. Atherosclerosis accounts for 70% of morbidity in T2D patients and is a chronic disease that results in progressive narrowing of arterial vessels due to imbalanced lipid metabolism. Cholesterol crystals and white blood cells accumulate on the arterial wall, limiting the flow of oxygen-rich blood to the organs[87]. Atherosclerosis is commonly referred to as a hardening or furring of the arteries and can lead to life-threatening complications such as heart attack and stroke.

It has long been suggested, on the basis of evidence from mouse models[88, 89, 90], that IL-18, a product of inflammasome activation, may have crucial roles in the initiation and progression of atherosclerosis. Furthermore, human atherosclerotic plaques have elevated concentrations of IL-18 and IL-18 receptors compared to disease-free arterial tissues. Apolipoprotein E (ApoE) is important for proper cholesterol metabolism. In ApoE-deficient mice, which spontaneously develop atherosclerotic lesions, elevated IL-18 levels have been shown to cause vascular inflammation and enhance the instability of atherosclerotic plaques, while IL-18 deficiency resulted in reduced atherosclerotic lesion size[89, 91, 92]. Elevation of low-density lipoprotein (LDL) and free fatty acids (FFAs) in human blood due to imbalanced lipid metabolism is able to induce pro-IL-1β production through TLRs, providing the first signal for inflammasome activation[93] (Fig. 4a). Recent studies indicate that the cell surface receptor CD36 facilitates internalization of oxidized LDL (ox-LDL) and intracellular conversion of ox-LDL to cholesterol crystals[77]. These intracellularly formed cholesterol crystals activate the NLRP3 inflammasome *in vitro* in both mouse and human cells through phagolysosomal damage, a mechanism dependent on both cathepsin B and cathepsin L[88] (Fig. 4a). *In vivo*, intraperitoneal injection of cholesterol crystals in mice induced acute inflammation that was attenuated by the deficiency of NLRP3 inflammasome components, cathepsin B, and cathepsin L. In this model, IL-1β was released through NLRP3 inflammasome activation and in turn promoted rupture of atherosclerotic plaques.

Figure 4: Mechanism of inflammasome activation in inflammatory disease.



(**a**) In atherosclerosis, free fatty acids (FFA) can prime the NLRP3 inflammasome through TLR2-TLR4 signaling. Additionally, oxidized low-density lipoprotein (oxLDL) primes the NLRP3 inflammasome through a CD36-TLR4-TLR6 signaling complex. CD36 also facilitates the internalization of oxLDL and its intracellular conversion to cholesterol crystals, which disrupt the phagolysosome and activate the NLRP3 inflammasome through cathepsin release. Phagocytosis of extracellular cholesterol crystals may also contribute to inflammasome activation. Cathepsin inhibition prevents the NLRP3 inflammasome activation induced by cholesterol crystals. (**b**) In type 2 diabetes (T2D), the NLRP3 inflammasome is activated in both islet β-cells and myeloid cells. In β-cells, elevated glucose increases thioredoxin (TRX)-interacting protein (TXNIP). Intracellular ROS also causes a conformational change in TXNIP, leading to its dissociation from TRX. TXNIP then binds NLRP3 and promotes NLRP3 inflammasome activation. In myeloid cells, the endocannabinoid anandamide binds the CB1 receptor to increase the expression of *NLRP3*, *ASC* and *IL1B*. Saturated fatty acid (SFA) inhibits intracellular AMP-activated protein kinase (AMPK). This decreases autophagy, which leads to an increase in mitochondrial ROS (mtROS), a known NLRP3 inflammasome stimulus. CD36 facilitates the internalization of soluble islet amyloid polypeptide (IAPP), which is converted intracellularly to its amyloid form. This disrupts the phagolysosome and activates the NLRP3 inflammasome due to cathepsin release. As the amyloid form of IAPP builds up in the pancreatic islets of individuals with T2D, phagocytosis of extracellular amyloid IAPP may also contribute to NLRP3 inflammasome activation.

Mice lacking the LDL receptor are prone to developing atherosclerotic plaques. When these mice are fed a high-cholesterol diet, they have markedly reduced lesion size if the bone marrow cells lack *Nlrp3*, *Asc*, or *Il1a and Il1b*[88]. Similarly, in the ApoE-deficient mouse model of atherosclerosis, lack of IL-1β significantly decreases the size of atherosclerotic lesions[94]. In line with this, another study showed that blockade of IL-1β inhibited atherosclerotic plaque formation in the ApoE-deficient mouse model[95]. However, other studies have failed to link NLRP3 and IL-1β to atherosclerosis but instead found that IL-1α played an essential role in mice[96, 97]. Further studies are required to clarify the contributions of IL-1α and IL-1β to atherogenesis.

NLRP3 inflammasome and type 2 diabetes.

T2D is a major global health threat resulting in insulin resistance and is a chronic inflammatory disease characterized by elevated circulating

levels of TNF, interleukins and cytokine-like proteins known as adipokines released from adipose tissue[98]. IL-1β in particular has been strongly linked to the pathogenesis of T2D through promotion of insulin resistance and induction of β-cell functional impairment and apoptosis. In cell culture, IL-1β dampens insulin sensitivity by inducing JNK-dependent serine phosphorylation of insulin receptor substrate-1 (IRS-1), resulting in the disruption of insulin-induced PI3K-Akt signaling in insulin-targeted cells. At the same time, IL-1β induces the expression of TNF-α[99], which could independently impair insulin signaling[100]. Together with elevated FFAs in circulation due to imbalanced lipid metabolism, IL-1β induces metabolic stressors, such as ER stress and oxidative stress, both of which are involved in induction of inflammation and β-cell loss, thereby leading to the pathogenesis of T2D[86, 101]. Furthermore, clinical trials reported that either IL-1 receptor antagonist (IL-1RA) or anti-IL-1β neutralizing antibody improved control of glucose levels and β-cell function[102, 103]. Data also show that fatigue in T2D patients was reduced by IL-1β blockade. Trials with larger patient numbers should strengthen the argument for IL-1β–targeted therapy in T2D[104].

Elevation of NLRP3 inflammasome activity in myeloid cells from T2D patients when compared with those from unaffected individuals has been described[105]. Multiple studies have found that mice deficient in NLRP3, ASC and/or caspase-1 show improved glucose tolerance and insulin sensitivity when exposed to a high-fat diet (HFD)[99, 106, 107, 108, 109]. This is accompanied by reduced inflammatory cytokine levels in the serum and in metabolic tissues such as liver and adipose tissue in conjunction with increased insulin-PI3K-Akt signaling[99, 106, 107, 108]. These studies provide a direct link between the NLRP3 inflammasome, chronic inflammation and insulin resistance.

As regards the role of the NLRP3 inflammasome and IL-1β in T2D pathogenesis, extensive studies have identified endogenous and exogenous stimulators of the NLRP3 inflammasome during T2D. Islet amyloid polypeptide (IAPP), a 37-amino-acid peptide hormone secreted from β-cells along with insulin, can form an amyloid structure that builds up in the pancreatic islets of patients with T2D[110]. As in the conversion of oxLDL to cholesterol crystals, the surface receptor CD36 also facilitates the conversion of soluble IAPP to its amyloid form (Fig. 4b). *In vitro*, IAPP induces NLRP3 activation through a mechanism involving phagolysosome perturbation as well as cathepsin-B and cathepsin-L that leads to IL-1β production in macrophages and dendritic cells in culture [111] (Fig. 4b). In a transgenic mouse model in which human IAPP is overexpressed in mouse β-cells, pancreatic macrophages showed strong induction of IL-1β[111, 112]. Elevated blood glucose was reported to induce IL-1β expression in β-cells, possibly through inflammasome activation mediated by thioredoxin (TRX)-interacting protein (TXNIP)[108, 113]. Glucose can upregulate TXNIP expression in islets, and increased ROS due to oxidative stress in T2D has been proposed to cause conformational changes in TXNIP, leading to its dissociation from thioredoxin and, in turn, association with NLRP3 for inflammasome activation[108] (Fig. 4b). Even though those studies could link oxidative stress with NLRP3 activation and IL-1β production in islets, the data were not reproducible in *Txnip*-deficient macrophages by another research group [111].

The neuromodulatory lipids known as endocannabinoids were recently found to induce NLRP3 inflammasome–dependent IL-1β production by pancreatic infiltrating macrophages through the peripheral CB1 receptor (CB_1R), resulting in pancreatic β-cell death in a paracrine manner[114] (Fig. 4b). The endocannabinoid anandamide increased ASC protein levels and caspase-1 activation in rat islets and markedly increased IL-1β secretion from a mouse macrophage cell line, RAW264.7. Anandamide-induced IL-1β production is dependent on *Nlrp3* and *Cb1r* (also known as *Cnr1*). Intriguingly, blockade of CB_1R by an inhibitor delayed the progress of T2D in the Zucker diabetic fatty rat, which carries a spontaneous mutation of the leptin receptor gene and with aging develops progressive hyperglycemia accompanied by reduced β-cell apoptosis and hyperglycemia. This finding implicates CB_1R as a potential therapeutic target in T2D[114].

Finally, saturated fatty acids such as palmitate and ceramide that arise from a high-fat diet and induce type 2 diabetes can induce NLRP3 inflammasome activation[99, 107] (Fig. 4b). In mouse macrophages, palmitate inhibits AMP-activated protein kinase (AMPK) activity, leading to defective autophagy and the generation of mitochondrial ROS, which is a proposed mechanism of NLRP3 inflammasome activation[99]. Ceramide is also sensed by NLRP3, resulting in NLRP3-dependent caspase-1 activation in both mouse bone marrow–derived macrophages (BMDM) and mouse epididymal adipose tissue explants[107]. Interestingly, replacement of saturated fatty acids with monounsaturated fatty acids in HFDs improves insulin sensitivity by reducing IL-1β production via preserved AMPK activity in the mouse model[115]. Recently, omega-3 fatty acids (ω-3 FAs), which are polyunsaturated fatty acids, have been shown to inhibit NLRP3 inflammasome activity through a G protein–coupled receptor (GPR120)–GPR40–β-arrestin-2 signaling pathway[116]. More importantly, ω-3 FAs prevented insulin resistance in a HFD-induced model of T2D, suggesting that dietary use of ω-3 FAs could be used to ameliorate T2D and other inflammatory diseases[116]. Using the human THP-1 cell line, others have shown that unsaturated fatty acid can prevent NLRP3 activation, presenting another way to reduce inflammation[117].

NLRP3 inflammasome and obesity

Obesity is characterized by excessive expansion of adipose tissue due to adipocyte hypertrophy and immune cell infiltration[98]. Obesity-associated inflammation leads to functional abnormality of adipocytes, resulting in elevated circulating levels of FFAs and ectopic lipid accumulation[118]. This can subsequently give rise to multiple metabolic disorders, such as atherosclerosis and T2D, as discussed previously. In this section, we will focus on discussing the involvement of inflammasome components in the development of obesity and adipose inflammation.

The expression of human *NLRP3* and *ASC* (*PYCARD*) is upregulated in adipocytes from obese patients [119]. Caspase-1 expression has been found in both human and mouse adipose tissues and increases with adipocyte differentiation and obesity development[120]. Blockade of caspase-1 and IL-1β, but not IL-18, improves adipogenic gene expression *in vitro*, indicating that caspase-1 regulates adipogenesis, potentially via IL-1β. Differentiated adipocytes with caspase-1 deficiency also have better adipogenesis and insulin sensitivity than wild-type control cells [120].

To establish the direct link between inflammasome activity and the development of obesity, HFD-induced or genetically induced obese animals lacking inflammasome components have been studied[106, 120]. It was initially reported that caspase-1 contributes to adipose tissue formation, as mice lacking *Casp1* have reduced adipocyte size, reduced fat mass, increased adipogenic gene expression and improved insulin sensitivity. Furthermore, in the HFD-induced model of obesity, mice lacking *Casp1* gained less weight than did wild-type controls. In the spontaneously obese mouse model (*ob*/*ob* mice), caspase-1 inhibition reduced mouse body weight. Interestingly, caspase-1 blockade resulted in decreased lipogenesis and higher fat oxidation in *ob*/*ob* mice than in control mice but did not affect food intake, suggesting the potential mechanism by which caspase-1 promotes obesity [120]. Similarly, it was also observed that NLRP3, ASC and caspase-1 deficiency protected from HFD-induced obesity[106]. However, a recent study reported the contradictory results that mice lacking *Casp1* were more obese than control mice, having greater fat mass than controls [121]. The difference may be due to the variation in intestinal microbiota in mice raised in different animal facilities, as the intestinal microbiota has been demonstrated to have a significant role in metabolic diseases[122]. Additionally, IL-18, one of the products of inflammasome activation, has been shown to protect mice from obesity, as mice lacking *Il18* developed obesity due to increased food intake [123]. This provides another possibility for the discrepancy in obesity phenotypes observed in *Casp1*-deficient mice.

Recently, it was shown that the lack of inhibitor of κB kinase epsilon (IKBKE), a downstream mediator of TLR and cytokine signals, in ApoE-deficient mice fed a Western-type diet (high in saturated fat) caused enhanced expression of inflammasome-related genes and low-grade chronic inflammation[124]. Hence, IKBKE functions as an endogenous negative regulator of the NLRP3 inflammasome under an obesity-inducing condition.

As regards the role of caspase-1 in obesity, studies have shown that it is likely that caspase-1 contributes to obesity through various mechanisms. It was previously thought that macrophages accumulate within inflamed adipose tissue to produce caspase-1 (ref. 125). However, recent studies in mice have shown that a major source of caspase-1 in adipose tissue is independent of infiltrating macrophages[120]. Recently, caspase-1 was shown to prevent lipid clearing in non-hematopoietic cells by an NLRP3-dependent but IL-1α/β– and IL-18–independent mechanism[126]. Furthermore, sirtuin 1 (SIRT1), a deacetylase that can regulate metabolism and protect from obesity, was recently shown to be a caspase-1 substrate. Adipocyte-specific knockout of the gene *Sirt1* resulted in spontaneous obesity, and SIRT1 protein was cleaved and inactivated in adipose tissues by active caspase-1 under the HFD stress [127]. However, the mechanism of inflammasome and caspase-1 activation in adipocytes needs clarification.

A strong association between obesity and leukocytosis exists, and inflamed adipose tissue from obese mice was recently found to induce monocytosis in recipient wild-type mice[128]. NLRP3 played an essential role in obesity-induced leukocytosis, as *Nlrp3*$^{-/-}$ bone marrow reconstituted in *ob*/*ob* recipient mice resulted in significantly reduced numbers of circulating leukocytes [128].

Therapies that target inflammasomes

Inappropriate inflammasome activity has been incriminated in the pathogenesis of neurodegenerative disease and metabolic disorders. Many reagents that target the inflammasome products IL-1β and IL-18, including the recombinant IL-1RA anakinra, the neutralizing IL-1β antibody canakinumab, the soluble decoy IL-1 receptor rilonacept, IL-18–binding protein, soluble IL-18 receptors and anti–IL-18 receptor monoclonal antibodies, have been developed to treat autoinflammatory diseases such as cryopyrin-associated autoinflammatory syndrome

(CAPS)[129, 130]. However, independently of IL-1β and IL-18, inflammasome-dependent pyroptosis is a type of inflammatory cell death that will release DAMPs to induce more inflammation and also is important in the pathology of CAPS[131]. Therefore, inhibitors of the inflammasomes could offer greater therapeutic promise for this condition.

A small-molecule inhibitor, glyburide, that is commonly used for treatment of T2D was the first compound identified to inhibit NLRP3- but not NLRC4- and NLRP1-dependent IL-1β production[132]. Glyburide is able to inhibit ATP-, nigericin- and IAPP-induced NLRP3 inflammasome activation[111]. However, glyburide's mechanism of action remains elusive, though it is known to function downstream of the P2X7 receptor and upstream of NLRP3. Importantly, glyburide has been shown to efficiently prevent endotoxic shock–induced lethality in the animal model of this disease[132]. A recently identified group of NLRP3 inhibitors targeting P2X7 signaling is the nucleoside reverse transcriptase inhibitors (NRTIs), which are mainly used to block retrovirus replication. NRTIs have shown efficacy against several inflammatory and autoimmune diseases in mouse models[133]. Several other small-molecule inhibitors targeting NLRP3, NLRP1, NLRC4 or AIM2, including parthenolide[134], Bay 11-708 (ref. 134), CRID3 (ref. 135), auranofin[136], isoliquiritigenin[137], 3,4-methylenedioxy-β-nitrostyrene[138], cyclopentenone prostaglandin 15d-PGJ_2 (ref. 139) and 25-hydroxycholesterol (25-HC)[140], have been characterized, even though their potency for *in vivo* usage needs more evaluation. The large majority of these are pharmacologic inhibitors that have been repurposed to target the inflammasome.

Recently, two additional small-molecule inhibitors that reduce NLRP3 activation have been reported. The ketone body β-hydroxybutyrate (BHB), which serves as an alternative source of ATP during energy-deficit status, was found to specifically inhibit a variety of stimuli triggering NLRP3 inflammasome activation but not NLRC4 or AIM2 inflammasome activation[141]. Importantly, in animal models of NLRP3-mediated diseases such as Muckle-Wells syndrome, familial cold autoinflammatory syndrome and urate crystal–induced peritonitis, BHB-complexed nanolipogels and a ketogenic diet strikingly attenuated caspase-1 activation and IL-1β secretion. It was shown that BHB inhibits the NLRP3 inflammasome by preventing potassium efflux and reducing ASC oligomerization and speck formation, although the direct target of BHB is still under exploration[141].

Another study found that the compound MCC950 is a highly selective inhibitor of the NLRP3 inflammasome[142]. MCC950 blocked both canonical (ATP, nigericin and monosodium urate) and noncanonical (cytosolic LPS) NLRP3-dependent inflammasome activation at nanomolar concentrations, with no effect on NLRC4, NLRP1 or AIM2 inflammasomes. *In vivo*, MCC950 has been shown to reduce IL-1β production and attenuate the severity of EAE, a disease model of multiple sclerosis described earlier that is known to be exacerbated by the NLRP3 inflammasome[64, 68, 71]. MCC950 rescued the neonatal lethality in a mouse model of CAPS, whereas blockade of IL-1β alone did not, providing evidence for a benefit of inflammasome inhibitors beyond just the inhibition of IL-1β. Even though the mechanism of NLRP3 inhibition by MCC950 is not fully understood, an extensive assessment of the *in vitro* and *in vivo* pharmacokinetics of MCC950 has been performed, providing significant strides toward therapeutic application[142].

Type I interferon has been shown to suppress inflammasome activation with a poorly understood mechanism[143]. Recent studies showed that an IFN-stimulated gene product, cholesterol 25-hydroxylase (Ch25h), antagonizes both *Il1b* transcription and NLRP3, NLRC4 and AIM2 inflammasome activation, suggesting Ch25h has a broad inhibitory activity of different inflammasomes. More importantly, the Ch25h substrate 25-hydroxycholesterol is able to inhibit NLRP3 inflammasome activation and IL-1β production[140].

Conclusions and perspectives

The new understanding of how inflammasomes are activated in health and disease raises new questions. Can post-translational modifications of inflammasome components be targeted to modulate inflammasome activation? For example, therapies that specifically promote NLRP3 ubiquitination could quell pathologic inflammation driven by NLRP3 inflammasome activation by promoting NLRP3 degradation. What are the contributory roles of inflammasomes in the myeloid lineage compared to other cell types such as endothelial cells, epithelial cells or even adipocytes in inflammatory diseases? Can drugs that directly target inflammasome components, rather than those that target the end products of inflammasomes such as IL-1β, be identified? Two new gain-of-function mutations of NLRC4, Val341Ala and Thr337Ser, that cause severe spontaneous autoimmune syndromes have recently been identified in humans[44, 45]. Establishment of a mouse model with similar mutations in NLRC4 will be a powerful tool to study the mechanism of NLRC4 autoactivation-induced autoimmune diseases and evaluate NLRC4 inhibitors *in vivo*.

Importantly, a greater understanding of the balance between beneficial and detrimental inflammasome activation is also needed. Indeed,

inflammasome activity is critical for host response to microbial pathogens and possibly for optimal response to vaccine adjuvants, as cytokine production by the innate immune system shapes the adaptive immune response. Thus, not all inflammasome activation can be considered harmful, and the therapeutic inhibition of this pathway has to be balanced against its beneficial contribution. As the mechanistic insight of the inflammasomes increases, opportunities to create new therapies for patients with inflammatory diseases are expected to enhance proportionately.

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