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Review

The role of inflammasome-derived IL-1 in driving IL-17 responses

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ABSTRACT

NLRs are members of the PRR family that sense microbial pathogens and mediate host innate immune responses to infection. Certain NLRs can assemble into a multiprotein complex called the inflammasome, which activates casapse-1 required for the cleavage of immature forms of IL-1β and IL-18 into active, mature cytokines. The inflammasome is activated by conserved, exogenous molecules from microbes and nonmicrobial molecules, such as asbestos, alum, or silica, as well as by endogenous danger signals, such as ATP, amyloid-β, and sodium urate crystals. Activation of the inflammasome is a critical event triggering IL-1-driven inflammation and is central to the pathology of autoinflammatory diseases, such as gout and MWS. Recent studies have also shown IL-1 or IL-18, in synergy with IL-23, can promote IL-17-prduction from Th17 cells and γδ T cells, and this process can be regulated by autophagy. IL-1-driven IL-17 production plays a critical role in host protective immunity to infection with fungi, bacteria, and certain viruses. However, Th17 cells and IL-17-seceting γδ T cells, activated by inflammasome-derived IL-1 or IL-18, have major pathogenic roles in many autoimmune diseases. Consequently, inflammasomes are now major drug targets for many autoimmune and chronic inflammatory diseases, as well as autoinflammatory diseases. *J. Leukoc. Biol.* 93: 489–497; 2013.

Introduction

IL-1 has a broad range of functions, in particular, in mediating inflammation in protective immunity to infectious diseases but also in diseases involving dysregulated immune responses [1]. Indeed, there is convincing evidence that IL-1 is critical to the pathology of most autoinflammatory and many autoimmune and chronic inflammatory diseases [2, 3]. Furthermore, evidence is emerging to suggest that IL-1 has a major role in the pathology of type 2 diabetes [4, 5], atherosclerosis [6], Alzheimer's disease [7], osteoarthritis [8], allergic asthma [9], and epilepsy [10]. IL-1 is released by cells of the innate immune system in response to activation of PPRs with PAMPs, released by pathogens during infection, and by DAMPs or alarmins, released from dead or damaged cells during sterile inflammation [11–13].

Prior to the introduction of the IL nomenclature, IL-1 had also been called lymphocyte-activating factor on the basis of its ability to induce lymphocyte proliferation [14], a property that was not fully appreciated until very recently. Exciting data have emerged over the last few years, demonstrating that IL-1 plays a major role in prompting adaptive immunity during infection and in autoimmunity [15, 16]. In particular, there is convincing evidence that IL-1 plays a nonredundant role in driving Th17 cells and also by certain populations of the innate lymphocyte [15, 17], and this may explain the pathogenic role of IL-1 in many T cell-mediated autoimmune diseases.

IL-1 functions in synergy with IL-23 to promote the production of IL-17 and related cytokines from Th17 cells but also from subpopulations of γδ T cells [17], invariant NK T cells [18], and ILCs (unpublished results). Another IL-1 family member, IL-18, can also synergize with IL-23 to promote IL-17 production by γδ T cells and memory CD4 T cells [19], and these cells are now considered to be the major mediators of pathology in many autoimmune diseases. The production of IL-1 and IL-18 by cells of the innate immune system is mediated by a combination of signaling pathways downstream of TLRs and NLRs, in particular, NLRs that form part of an inflammasome complex. Procaspase-1 is recruited to the inflammasome complex and processed to active caspase-1, which processes IL-1 and IL-18 into their active forms [20, 21]. As a consequence, activation of the inflammasome is now emerging as a critical step in the driving Th17 responses and IL-17 production by innate lymphocytes (**Fig. 1**).

Abbreviations: $^{-/-}$=deficient/defective, ASC=apoptosis-associated speck-like protein containing a caspase recruitment domain, CAPS=cryopyrin-associated periodic syndromes, CIA=collagen-induced arthritis, DAMP=damage-associated molecular pattern, DIRA=deficiency of the IL-1R antagonist, EAE=experimental autoimmune encephalomyelitis, IL-1RI/II=IL-1 type I/II receptor, IL-1Ra=IL-1R antagonist, IL-18Bp=IL-18 binding protein, ILC=innate lymphoid cell, MS=multiple sclerosis, MWS=Muckle-Wells syndrome, NLR=nucleotide-binding oligomerization-like receptor, NLRP3=nucleotide-binding oligomerization-like receptor pyrin domain-containing 3, RA=rheumatoid arthritis, SAA=serum amyloid A, SLE=systemic lupus erythematosus, Th17 cells=IL-17-producing by CD4 T cells, TIR=Toll/IL-1R homology, Treg=regulatory T cell, TRIF=Toll/IL-1R homology domain-containing adapter-inducing IFN-β

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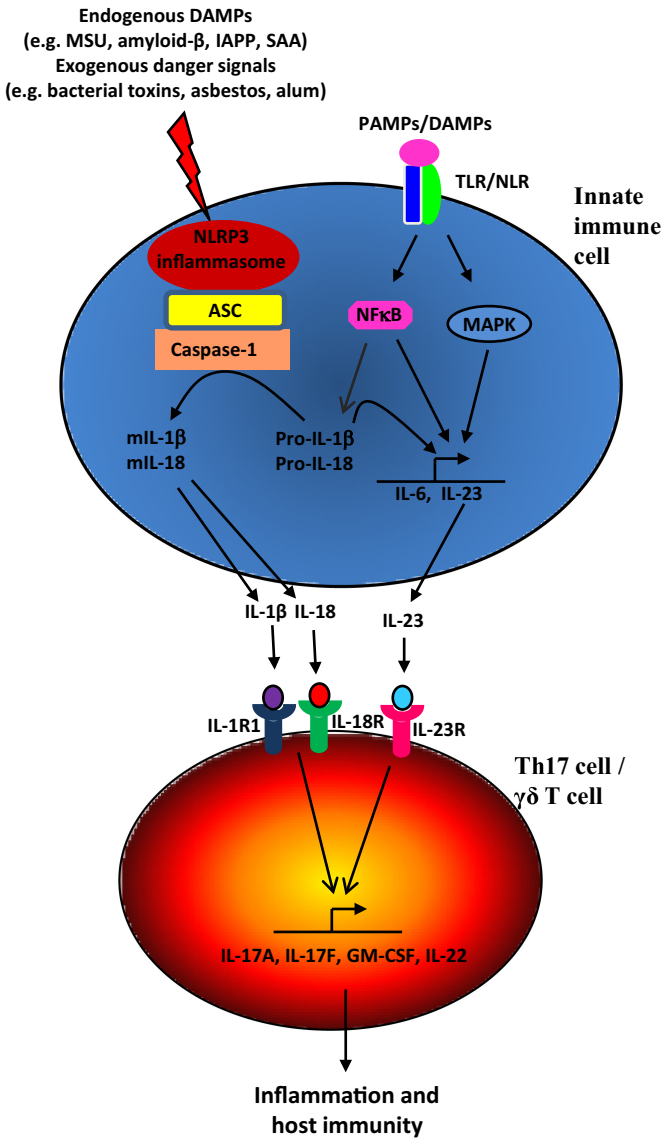

Figure 1. Inflammasome-processed cytokines induce IL-17. The NLRP3 inflammasome is activated by endogenous DAMPs, such as monosodium urate crystals (MSU), amyloid-β, islet amyloid polypeptide (IAPP), and SAA, and exogenous PAMPs, such as bacterial toxins, asbestos, and alum. Pro-IL-1β and pro-IL-18 are induced via activation of TLR or NLR signaling pathways by PAMPS and DAMPs. Phosphorylation of ERK promotes transcription of IL-23p19 and IL-23 production. IL-23 production is also enhanced by IL-1β. The NLRP3 and associated adapter protein ASC activate caspase-1, which cleaves pro-IL-1β and pro-IL-18 into mature (m) IL-1β and IL-18. IL-1β, IL-18, and IL-23 bind to their respective receptors on Th17 and γδ T cells and induce production of IL-17A, IL-17F, GM-CSF, and IL-22. These cytokines are involved in inflammatory responses during autoimmunity and in host protective immune responses during infection.

IL-1 CYTOKINE FAMILY AND THE INFLAMMASOME

IL-1 cytokine family

The IL-1 superfamily of cytokines encompasses at least 11 members, which include IL-1α, IL-1β, and IL-18 [1]. The first identified members of the family, IL-1α and IL-1β, have long been recognized as pivotal mediators of inflammation during infection, as well as having a damaging role in driving pathology in autoinflammatory and autoimmune diseases [22, 23]. IL-1α and IL-1β function by binding to the IL-1RI, in association with the coreceptor, IL-1R accessory protein. This cytokine receptor–coreceptor complex recruits the adaptor molecule MyD88 through its TIR domains. Consequently, NF-κB is phosphorylated, translocates to the nucleus, and induces the transcription of proinflammatory cytokines. The functional activities of IL-1α and IL-1β are regulated by the naturally occurring IL-1Ra, which can bind to the receptor and inhibit the binding of IL-1β and IL-1α. Target cells can also express a decoy receptor, the IL-1RII, which binds IL-1α and IL-1β but lacks a TIR domain and therefore, cannot recruit MyD88. IL-1RII binds IL-1 with a greater affinity than IL-1RI and serves to sequester the active IL-1 cytokines and control IL-1-mediated inflammatory responses [24].

IL-18 binds to the IL-18Rα chain and recruits a coreceptor, IL-18Rβ, forming a complex that can promote transcription of proinflammatory molecules. IL-18Bp is a potent and specific endogenous inhibitor that binds to IL-18 with a high affinity and neutralizes it [25, 26]. IL-18 mediates inflammatory responses and together with IL-12, promotes IFN-γ production by NK cells and $CD4^+$ Th1 cells [27]. More recently, it has been shown that IL-18 synergizes with IL-23 to promote IL-17 production by Th17 cells and IL-17-secreting γδ T cells [19].

Processing of IL-1 and IL-18 by the inflammasome

IL-1β and IL-18 are synthesized as biologically inactive precursor proteins that require cleavage to produce the biologically active cytokines. IL-1α is constitutively expressed and cleaved by calpain, elastase, and granzyme B to produce a more biologically active cytokine [28]. Conversely, pro-IL-1β and pro-IL-18, induced in innate immune cells in responses to PAMP activation of TLRs, are cleaved by the cysteine protease caspase-1 into mature, active cytokines [29] (Fig. 1). However, there is evidence that extracellular serine proteases released from neutrophils at the site of inflammation may also be capable of processing these cytokines [30].

Caspase-1 is synthesized as an inactive precursor that requires cleavage inside a multiprotein inflammasome to become biologically active. Caspase-1 is activated following assembly of the inflammasome complex, which contains members of the NLR family, such as NLRP3 [29]. The inflammasome is assembled in response to a wide range of conserved, exogenous molecules from microbes, including bacterial toxins and nonmicrobial molecules, including asbestos, alum, or silica, as well as by endogenous danger signals, such as ATP and amyloid-β [16, 31–35].

INFLAMMASOME-INDUCED IL-1 PROMOTES IL-17 RESPONSES

IL-1-induced IL-17 production by Th17 T cells

The discoveries of the proinflammatory cytokine, IL-17, and subsequently, the different subtypes of T cells that secrete this

cytokine, have significantly enhanced our understanding of the role of T cells in autoimmune and other inflammatory diseases. Although Th1 cells were initially thought to be the key pathogenic T cell in many autoimmune diseases, mice deficient in IFN-γ or IL-12 signaling have exacerbated symptoms during the course of certain autoimmune diseases [36–39]. It was then demonstrated that mice lacking IL-23p19 were resistant to induction of EAE, a mouse model for MS [38]. Furthermore, autoantigen-specific T cells polarized in vitro to secrete IL-17 (Th17 cells) were more efficient than Th1 cells at inducing EAE, following adoptive transfer into naive mice, and administration of neutralizing anti-IL-17A antibody reduced but did not completely attenuate the severity of EAE in C57BL/6 mice [40].

The differentiation of naive T cells into Th17 cells was initially reported to be stimulated by IL-23 [38, 40–43]. However, naïve, murine T cells do not express the IL-23R and do not develop into Th17 cells following stimulation with IL-23 [40, 44]. Conversely, naïve, murine T cells do secrete IL-17A in response to IL-6 and TGF-β when costimulated with anti-CD3 and anti-CD28 or with APCs in vitro [45–47]. Furthermore, IL-23 does play an important role in expansion and survival of Th17 cells [45–47]. Studies performed in our own laboratory have demonstrated that IL-1α or IL-1β can synergize with IL-23 to induce secretion of IL-17A from murine T cells in the presence or absence of TCR stimulation. IL-23-induced IL-17A secretion was absent in IL-1RI$^{-/-}$ mice [15]. Furthermore, like IL-23$^{-/-}$ mice, IL-1RI$^{-/-}$ mice are resistant to the development of EAE [15, 38]. There is also evidence that IL-1 and IL-23 can promote induction and activation of human Th17 cells [48, 49]. Furthermore, IL-1 can induce IL-6 production from innate immune cells, which stimulates the differentiation of naive T cells into Th17 cells [50].

IL-1- and IL-18-induced IL-17 secretion by γδ T cells

γδ T cells are an unconventional T cell subset and are rapid and potent producers of cytokines in lymphoid and mucosal tissues [51]. They are an important early mediator of inflammatory responses and for the protection against infection at mucosal surfaces. A large body of evidence, mainly in mouse models, has shown that γδ T cells play a pathogenic role in autoimmune diseases, including EAE [17]. TCRγ$^{-/-}$ mice have less-severe EAE, especially in the later disease stages [52] and γδ T cells are found in the chronically demyelinated areas of the CNS of patients with MS [53], and IL-17-secreting γδ T cells accumulate in the brain and spinal cord of mice with EAE [17]. Furthermore, depletion of γδ T cells reduced the severity and delayed the onset of EAE induced by T cell transfer [17, 54]. IL-17-producing γδ T cells are also pathogenic in CIA and uveitis [55, 56].

γδ T cells develop in the thymus by divergence from αβ T cell progenitors at the CD4$^-$CD8$^-$ double-negative stage of T cell development [57]. In contrast to the processes for αβ T cell maturation, γδ T cells do not necessarily undergo positive selection via antigen recognition and can be released into the periphery as cells that are "antigen-experienced" and therefore, positively selected or "antigen-naive" and have therefore not been subjected to selection processes. Antigen-experienced γδ T cells produce IFN-γ, whereas antigen-naive γδ T cells secrete IL-17A [58]. γδ T cells express a variety of chemokine receptors, cytokine receptors, and PRRs, which are involved in their activation and the induction of IL-17. In particular, γδ T cells express IL-1RI on their cell surface, and it has been reported that IL-1α or IL-1β, in synergy with IL-23, plays a crucial role in the induction of IL-17 from γδ T cells without TCR engagement in mice and humans [17]. γδ T cells also express high levels of IL-18R on their cell surface, and it has been demonstrated recently that IL-18 can synergize with IL-23 to promote IL-17 production by γδ T cells [19]. Thus, it appears that the activation of the inflammasome in DCs and macrophages, with the consequent processing of the cytokines IL-1β and IL-18 as a result of inflammasome-triggered pathways, is important for the generation of IL-17-secreting γδ T cells [19]. The regulation of IL-1 expression and release is therefore a critical point of control against the induction and progression of IL-17-dependent inflammatory disorders, particularly as we have shown recently that IL-1 can drive the expression of IL-23 [59].

Regulation of IL-1-induced IL-17 by autophagy

In addition to the suppressive role of anti-inflammatory cytokines and Tregs, the release of IL-1 by macrophages and DCs is regulated by autophagy, which is a highly conserved mechanism for the catabolism of cytosolic constituents, including macromolecules and damaged or surplus organelles. Autophagy represents a cellular survival mechanism during periods of nutrient starvation but is also involved in other cellular processes, including specific responses by immune cells. Autophagy is regulated by numerous growth factors, hormones, and cytokines [60]. In particular, Th1 cytokines, including IFN-γ and TNF-α, induce autophagy in macrophages [61, 62], whereas the Th2/regulatory cytokines IL-4, IL-13, and IL-10 are inhibitory [63–66]. Autophagy also has an important role to play in macrophage responses to pathogens, including *Mycobacterium tuberculosis* [67], and is linked to MHC class I and class II antigen-presentation pathways [68].

Autophagy also plays a pivotal role in the regulation of inflammatory responses, particularly, the production, processing, and release of IL-1 family cytokines (**Fig. 2**). Disruption of normal, autophagic pathways in human and mouse macrophages and DCs, by inhibition with PI3K inhibitors or by small interfering RNA knockdown of autophagy proteins, leads to the increased release of IL-1α, IL-1β, and IL-18 in response to LPS and other TLR ligands [69–74]. In mice, this is dependent on signaling via TRIF, at least partially dependent on NLRP3, and requires the release of mitochondrial ROS and mitochondrial DNA into the cytosol [70, 72–74], whereas in human PBMCs, it may be independent of TRIF but dependent on p38 MAPK [69]. Conversely, the induction of autophagy has been shown to limit IL-1β release. Autophagosomes can sequester pro-IL-1β and inflammasome components, including NLRP3, ASC, and absence in melanoma 2, but not caspase 1, for lysosomal degradation [70, 75]. These studies suggest that autophagy can influence IL-1β/IL-18 release through effects on more than one inflammasome or by directly limiting IL-1β availability.

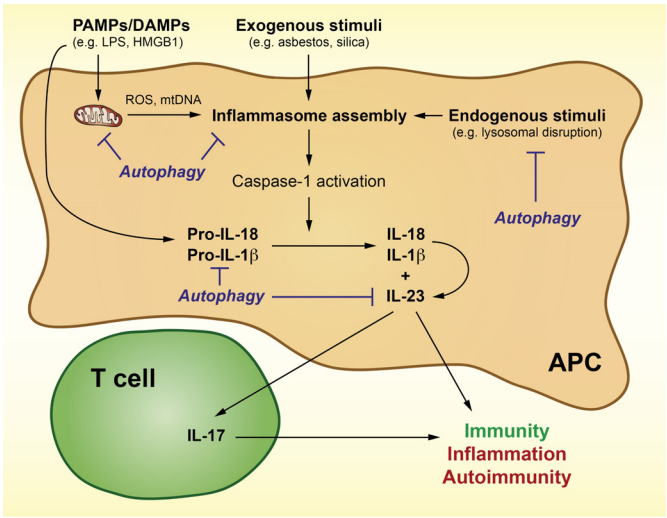

Figure 2. Inflammasome-processed cytokines that induce IL-17 are regulated by autophagy. Autophagy intersects with inflammasome-dependent generation of IL-1β and IL-18 at different stages: autophagosomes can remove many of the endogenous inflammasome-activating stimuli, including mitochondrial DNA (mtDNA), ROS, and damaged lysosomes, as well as pro-IL-1β and inflammasome components. In addition, through its effects on IL-1β, autophagy inhibits IL-23 secretion. HMGB1, High-mobility group box 1.

Given the important role of IL-1 in promoting IL-17 production by T cells, regulation of IL-1 by autophagy in macrophages and DCs would be expected to subsequently exert control over IL-17 secretion by T cells. Further evidence of a regulatory role for autophagy in IL-17 secretion was provided by the demonstration that autophagy also regulates IL-23 secretion by macrophages and DCs. Similar to IL-1, inhibition of autophagy leads to increased IL-23 secretion, whereas induction of autophagy has the opposite effect [59]. An earlier study demonstrated that IL-1β can drive IL-23 secretion [76], and this appears to be the mechanism through which autophagy exerts its effects on IL-23 [59]. Thus, autophagy regulates IL-1 and IL-23 in macrophages and DCs. Moreover, supernatants from DCs treated with LPS and the autophagy inhibitor 3-methyladenine potently induce IL-17, IL-22, and IFN-γ secretion by $\gamma\delta$ T cells in vitro [59]. A more recent study suggests this also applies in vivo; in a model of infection with *M. tuberculosis*, mice with a selective deletion of autophagy protein 5 in myeloid cells demonstrated greater inflammatory responses, including increased secretion/release of IL-1α, IL-12p70, CXCL1, and IL-17, than their autophagy-competent littermates [77]. These data indicate that autophagy in innate immune cells has the potential to influence T cell polarization, suggesting an important role in the control of inflammation and innate/adaptive immune responses. In this context, it is particularly interesting that polymorphisms in autophagy genes have been linked with a number of inflammatory conditions, including Crohn's disease [78–82] and SLE [83–86].

INFLAMMASOME-MEDIATED IL-17 IN DISEASE

IL-1 and the inflammasome in autoinflammatory diseases

Mutations in NLRP3 lead to dysregulation of IL-1β production and result in CAPS, rare autoinflammatory diseases that include familial cold autoinflammatory syndrome and MWS. These are diseases that affect an array of tissues and organs, such as the lungs, gastrointestinal tract, skin, and CNS [3, 87]. Furthermore, patients with DIRA as a result of mutations in *IL1RN*, develop an autoinflammatory disease, characterized by systemic inflammation, including pustular rash, joint swelling, and bone abnormalities [88]. These patients are hyper-responsive to endogenous IL-1, but the symptoms resolve completely following treatment with rIL-1Ra (anakinra). Interestingly, patients with DIRA have a higher percentage of Th17 cells and enhanced IL-17 expression in the inflamed skin [88]. Furthermore, studies in mice with targeted gain-of-function mutations in NLRP3, identical to those in MWS, have demonstrated that constitutive inflammasome activation leads to Th17-dominated immune responses, and these animals develop spontaneous skin inflammation [89]. These studies pointed to a role for the inflammasome in promoting the development of Th17 cells (**Table 1**).

TABLE 1. Examples of Inflammatory and Infectious Diseases Where Activation of the Inflammasome and IL-1 Production Is Associated with IL-17 Production

Disease	Inflammasome activator	Identified product(s)	T cell induction	Role in disease	Reference
MWS	DAMPs?	IL-1β	Th17 cells	Skin inflammation	[20, 89]
DIRA	DAMPs?	IL-1β	Th17 cells	Skin inflammation	[88]
Allergic asthma	SAA	IL-1β	Th17 cells	Pulmonary neutrophilic inflammation	[9]
EAE	Killed myobacteria (PAMPs)	IL-1β + IL-18	Th17 cells + IL-17$^+$ $\gamma\delta$ T cells	CNS inflammation and demyelination	[19, 90]
Bordetella pertussis infection	Adenylate cyclase toxin	IL-1β + IL-18	Th17 cells + IL-17$^+$ $\gamma\delta$ T cells	Neutrophil recruitment and protective immunity	[16]
Candida infection	?	IL-1β + IL-18	Th17 cells + Th1 cells	Neutrophil recruitment and protective immunity	[91]
Lyme disease	?	IL-1β + IL-18	Th17 cells + Th1 cells	Protective immunity to *Borrelia burgdorferi*	[92]

Inflammasome-processed cytokines drive IL-17 responses in autoimmune diseases

Studies in mouse models of autoimmunity, along with indirect evidence from patients, have demonstrated that IL-1 plays a pathogenic role in many autoimmune diseases [1]. IL-1Ra$^{-/-}$ mice have uncontrolled IL-1 production and spontaneously develop arthritis, characterized by overexpression of IL-1β, IL-6, and TNF-α at the joints [93]. Conversely, IL-1RI$^{-/-}$ mice are resistant to the development of EAE [15]. Furthermore, in EAE and MS patients, treatment with two front-line MS therapeutics, IFN-β and glatiramer acetate, is associated with an increase in serum levels of IL-1Ra [94, 95].

The role of IL-18 in autoimmune diseases is more controversial. Excessive production of IL-18 is found in the blood and inflamed joints of patients with RA [23]. Inhibition of IL-18 attenuated disease symptoms in an animal model of arthritis, and this is associated with reduced IL-1 and TNF-α in the synovial fluid [96]. Furthermore, IL-18 concentrations in serum positively correlate with disease activity and renal damage in SLE [97, 98]. IL-18 is also expressed in brain lesions of patients with MS and is increased in cerebrospinal fluid and serum of patients during relapse, although conflicting results have been obtained in the EAE model [99, 100]. Overexpression of IL-18Bp, a natural inhibitor of IL-18, in the CNS led to a marked reduction of Th17 responses and inhibition of EAE [101]. In addition, IL-18$^{-/-}$ mice are resistant to EAE [99]. However, another study showed that IL-18$^{-/-}$ mice were fully susceptible to EAE, whereas loss of the IL-18R induced resistance to the disease [100]. In addition, IL-18$^{-/-}$ mice develop arthritis when immunized with methylated BSA [102], whereas soluble IL-18Rβ, an IL-18 inhibitor, promoted CIA by inhibiting Tregs, thus allowing persistence of activated Th17 cells [103].

Studies in our laboratory have directly addressed the contribution of the inflammasome and caspase-1-processed cytokines in autoimmunity using the EAE model. The findings demonstrated that activation of the inflammasome and caspase-1 in innate immune cells induced IL-1β and IL-18 production by DCs, which in turn, promoted Th17 cells and $\gamma\delta$ T cells [19]. $\gamma\delta$ T cells secreted IL-17A in response to IL-18 and IL-23 or IL-1β and IL-23 in the absence of TCR stimulation. Passive induction of EAE through the administration of DCs pulsed with myelin oligodendrocyte glycoprotein and heat-killed mycobacteria was attenuated significantly when the DCs were pretreated with a caspase-1 inhibitor. This inhibition could be reversed by the in vivo administration of IL-1β, IL-18, or both cytokines [19]. Furthermore, in vivo administration of a caspase-1 inhibitor to mice with actively induced EAE significantly reduced the number of Th17 cells and IL-17-secreting $\gamma\delta$ T cells and attenuated the course of disease. Caspase-1$^{-/-}$ mice had a reduced incidence and severity of EAE, and this reduction was even more pronounced in mice lacking ASC, an adaptor molecule in the NLRP3 (and other) inflammasomes [90, 104]. These data demonstrate that the inflammasome-processed innate cytokines IL-1β and IL-18 play a crucial role in the activation of T cells that secrete IL-17 and related cytokines and mediate autoimmunity.

Inflammasome-processed cytokines drive IL-17 responses in allergic asthma

Asthma has traditionally been considered a Th2-mediated disease; however, evidence is emerging from mouse models to suggest that IL-17 cells may also be involved [105, 106]. Allergic sensitization through the airway primes strong Th17 responses that promote airway neutrophilia and acute airway hyper-responsiveness [107]. It has also been reported that IL-17A production by Th17 cells can act directly on airway smooth muscle to enhance allergen-induced airway hyper-responsiveness [106]. In contrast, transfer of IL-17-seceting $\gamma\delta$ T cells at the peak of acute allergic responses suppressed Th2-driven eosinophilic recruitment and attenuated airway hyper-responsiveness [108]. Subjects with allergic asthma have elevated levels of IL-1β and IL-17 [109] but also, the acute-phase proteins, including C-reactive protein and SAA [110]. SAA is induced by colonization of mice with segmented filamentous bacteria and has been implicated in promoting the development of intestinal Th17 cells [111]. It has been reported recently that SAA can activate the NLRP3 inflammasome and in combination with TLR2 activation, promote IL-1β production by DCs [9]. Furthermore, SAA-sensitized mice develop an IL-1RI-dependent Th2/Th17 allergic airway disease. These findings suggest that SAA may promote antigen-specific Th17 responses through inflammasome activation and IL-1 production.

Protective role of inflammasome-driven IL-17 in infection

IL-1β and IL-1α have a long-established role in protective responses to bacterial and fungal infection. Until recently, the mechanism was thought to involve the general innate inflammatory response to infection, including recruitment of neutrophils. It has also been reported that IL-18 has a role in protective immunity to infection through activation of NK cells and Th1 responses [112]. However, recent evidence has suggested that inflammasome-processed innate inflammatory cytokines may also function in immunity to infection by promoting IL-17 production by Th17 cells [16]. NLRP3 and caspase-1 are activated by a number of bacteria that produce pore-forming toxins, such as maitotoxin, nigericin, and aerolysin and adenylate cyclase toxin [16, 21]. In addition, the murine NLRP1 homolog, NLRP1b, is activated by the pore-forming toxin anthrax lethal toxin [113]. It has also been demonstrated that the NLRP3 inflammasome is activated by fungal pathogens and is critical in host defense against *Candida albicans* [114].

Th17 cells are also important in host protection against infection [115, 116]. IL-17A promotes recruitment of neutrophils to the site of infection; stimulates local epithelial cells to secrete antimicrobial proteins, such as lipocalins and calgranulins; and induces the production of structural proteins important in tight junction stability [117–129]. IL-22, which is produced by Th17 cells, $\gamma\delta$ T cells, and ILC, stimulates antimicrobial peptide production and increases barrier function, thereby mediating immunity against bacteria in the gastrointestinal tract [130].

There have been a small number of studies that have made the link between inflammasome-induced cytokines and protec-

tive IL-17 responses against infection. Studies from our own laboratory, for example, have shown that adenylate cyclase toxin from *B. pertussis* is capable of driving robust IL-1β production by DCs through activation of caspase-1 and the NLRP3 inflammasome [16]. Furthermore, inflammasome-mediated IL-1β plays a critical role in promoting antigen-specific Th17 cells and in generating protective immunity against *B. pertussis* infection. The course of *B. pertussis* infection was exacerbated significantly in IL-1RI$^{-/-}$ mice, and this was associated with reduced IL-17 production and neutrophil recruitment [16]. It has also been demonstrated that caspase-1 and ASC protect against *Candida* through IL-1β and IL-18 production and consequent induction of antifungal Th1 and Th17 responses [91]. Furthermore, inflammasome-driven IL-1β and IL-18 were found to, respectively, promote Th17 and Th1 responses in immunity to *B. burgdorferi*, the spirochete that causes Lyme disease [92]. Collectively, these findings demonstrate that inflammasomes has a critical role in controlling protective adaptive immune responses during certain infections.

CONCLUDING REMARKS

Inflammasomes, caspase-1, and the cytokines that they process are major drug targets in many diseases where IL-1β or IL-18 is directly involved in inflammatory pathology, and evidence is emerging that they may also play a crucial role in diseases mediated by IL-17-producing T cells. It has already been demonstrated that anakinra, a recombinant form of the naturally occurring human IL-1Ra, is highly effective in treating several autoinflammatory disorders, including gout, CAPS, and DIRA [1, 88, 131]. Furthermore, an anti-IL-1β mAb, canakinumab, has been licensed for treating CAPS [132] and was effective in controlling inflammation, pain, and new flares in patients with gouty arthritis [133]. Inflammasomes have a more indirect role in autoimmunity, where they promote pathogenic Th17 and/or Th1 cells. Therefore, inflammasomes, caspase-1, and IL-1β are emerging as drug targets for human autoimmune diseases. Indeed, anakinra (IL-1Ra) has been approved for the treatment of RA, where it has moderate efficacy, although it is very effective against systemic-onset juvenile idiopathic arthritis [134]. Inhibitors of caspase-1 are effective in IL-1-mediated diseases in animal models, including EAE, colitis, pancreatitis, and seizures [19, 104, 135–137]. A caspase-1 inhibitor, pralnacasan (VX-740), has been tested in Phase II clinical trials in RA, and although anti-inflammatory effects were observed, its use had to be discontinued as a result of liver toxicity in long-term animal studies [138]. Another caspase-1 inhibitor, VX-765, has been evaluated in a Phase II clinical trial in psoriasis patients [138]. As caspase-1 processes IL-18 as well as IL-1β, both of which can synergize with IL-23 to drive Th17 responses, nontoxic drugs that specifically target caspase-1 or inflammasomes may have greater potential for the treatment of autoimmune diseases than those that target IL-1 signaling alone. It is also important to understand the relative contribution of different inflammasome complexes to different diseases and infections, as they could lead to the development of more specific drugs. However, IL-1-driven Th17 cells play a critical role in protective immunity to fungal and bacterial infections; therefore, blocking these pathways should be approached with caution.

AUTHORSHIP

All authors contributed to the writing of this article. The overall integration of the article was performed by K.H.G.M.

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KEY WORDS:
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