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INNATE AND ADAPTIVE EFFECTS OF INFLAMMASOMES ON T CELL RESPONSES

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Running title:

INFLAMMASOMES AND ADJUVANTICITY

Summary

Inflammasomes are protein complexes that form in response to pathogen- or host-derived stress signals. Their activation leads to the production of inflammatory cytokines and promotes a pyrogenic cell death process. The massive release of inflammatory mediators that follows inflammasome activation is a key event in alarming innate immune cells. Growing evidence also highlights the role of inflammasome-derived cytokines in shaping the adaptive immune response, as exemplified by the capacity of IL-1β to support Th17 responses, or by the finding that IL-18 evokes antigen-independent IFN-γ secretion by memory $CD8^+$ T cells. A deeper understanding of these mechanisms and on how to manipulate this powerful inflammatory system therefore represents an important step forward in the development of improved vaccine strategies.

Highlights:

- inflammasome activation leads to production of bioactive IL-1β and IL-18
- IL-1β promotes Th17 differentiation, IL-18 supports IL-12-driven Th1 polarization
- IL-18 drives non-cognate lymphocyte activation, thereby improving immunity
- manipulation of inflammasome activity and substrates can ameliorate vaccine strategies

Keywords:

NLR; inflammasome; IL-1; IL-18; adjuvant; antigen-dependent T cell response; antigen-independent T cell response

Glossary:

AIM2, absent in melanoma 2; **ASC**, apoptosis speck protein with caspase recruitment domain; **DAMP**, danger-associated molecular pattern; **ICSBP**, interferon consensus sequence binding protein; **NLR**, NOD-like receptor; **NLRC**, NLR family, caspase recruitment domain containing; **NLRP**, NLR family, pyrin domain containing; **PAMP**, pathogen-associated molecular pattern; **TCR**, T cell receptor

Introduction

Sensing of different PAMPs or DAMPs can lead to activation of inflammasomes [1,2]. The huge inflammatory potential liberated upon inflammasome assembly is a basic defense mechanism employed to control different infections and its central role in innate immune responses has been largely demonstrated over the past years. Mounting evidence suggests that inflammasomes might be important for adaptive immune responses as well. We will therefore present here the current understanding on how inflammasomes tailor adaptive immune responses.

Inflammasomes: intracellular platforms for caspase-1 activation

Inflammasomes are intracellular caspase-1 activating multiprotein complexes that are induced by different PAMPs or DAMPs (as schematically represented in Figure 1; for general review on inflammasome function, see [1,2]). They are formed by association of NLR family members with the adaptor protein ASC and procaspase-1 through homotypic domain interactions. Their formation results in the proteolytic activation of caspase-1, which in turn processes different substrates. Several NLRs, such as NLRP1, NLRP3 and NLRC4 have been shown to form functional inflammasomes in response to a wide array of stimuli. Furthermore AIM2, a member of the PYHIN family, can recruit ASC and caspase-1 in response to double-stranded DNA [2].

Regulation of caspase-1-dependent cytokines

Active caspase-1 has several known targets, including cytokines from the interleukin (IL)-1 family. In addition, its activity is implicated in the unconventional secretion of other danger signals, such as the alarmin high-mobility group box 1 (HMGB1), and in a process of inflammatory cell death called pyroptosis [3-5].

IL-1β and IL-18, the two best-characterized inflammasome-dependent cytokines, are cleaved by caspase-1 from their inactive intracellular precursors, pro-IL-1β and pro-IL-18 [6]. IL-1α, another IL-1 family member, does not however require cleavage for its activity. It is often secreted concomitantly with IL-1β, though its release in response to certain stimuli and *in vivo* can be independent of the inflammasome [7,8]. Since IL-1α and IL-1β both signal through the IL-1R complex, the contribution *in vivo* of both cytokines is not always clear. It is therefore important to keep in mind that dependency on IL-1R does not yet imply caspase-1 dependency. IL-18 signals via a distinct receptor, the IL-18R, which belongs to the IL-1 receptor superfamily and is structurally very similar to IL-1R.

In contrast to IL-1, whose expression requires an NF-κB activating signal, *IL-18* mRNA is considered to be constitutively expressed in many cell types and therefore largely regulated through caspase-1-dependent cleavage [9]. However, LPS treatment of macrophages strongly augments *IL-18* transcript abundance [10]. Notably, a PU.1 and an ICSBP binding site have been located in the promoter of *IL-18*, which suggests its upregulation also by IFNs [11,12]. As type I IFNs can significantly reduce pro-IL-1α and pro-IL-1β levels [13], it is plausible that IFNs shift the balance of the two major caspase-1 substrates in favor of pro-IL-18.

Main effects of IL-1β and IL-18 on T helper cell polarization

The most prominent feature of IL-1β with regard to the adaptive immune response is to favor T helper type 17 (Th17) differentiation (as summarized in Figure 2) [14-16]. This lymphocyte subset secretes IL-17 and participates in host defense against extracellular bacteria and fungi, but is also involved in autoimmunity.

IL-18 acts instead as an amplifier of IFN-γ production by Th1 cells (Figure 2) [11]. IL-18R is poorly expressed on naïve T cells, but is upregulated upon priming, allowing enhanced Th1 polarization of activated T lymphocytes. Furthermore, IL-18R expression is increased following exposure to IL-12, the major Th1-polarizing cytokine. IL-18, in turn, helps induce the IL-12 high affinity receptor, establishing a feed-forward Th1-amplifying loop [11,17]. Surprisingly, in the absence of a Th1-polarizing environment, IL-18 can promote the differentiation of Th2 cells, a $CD4^+$ T cell subset dominating allergic responses and characterized by the expression of IL-4 and IL-13 [11,17,18].

Although the effects of IL-1β and IL-18 on adaptive immune cells have been well characterized, the *in vivo* relevance of inflammasomes in adaptive immune responses remains more elusive. The following sections will therefore summarize the recent data on their *in vivo* effects and pinpoint the drawbacks of the models that have been used.

INFLAMMASOMES AND ADJUVANTICITY

Inflammasome activation and adjuvants

It was long known that DAMPs can activate dendritic cells (DCs), thereby favoring T cell priming. Uric acid was identified, in a study by Rock and coworkers, as a danger signal released from dying cells that acts as an efficient T cell adjuvant [19]. Interestingly, DAMPs such as uric acid, ATP, or mitochondrial DNA activate the NLRP3 inflammasome, raising the question on whether or not its activity is important for T cell priming under such conditions. Indeed, uric acid crystals were shown to promote Th17 responses in an ASC- and caspase-1-dependent manner when applied subcutaneously [20]. However, in a uric acid-mediated asthma model Th2-polarized responses proceeded independently of the inflammasome [21].

This is reminiscent of what has been observed for alum, a clinically approved adjuvant that is routinely used in human vaccines. Alum has unanimously been shown to activate the NLRP3 inflammasome *in vitro*, but the *in vivo* role of the inflammasome in alum-induced adjuvanticity remains controversial [22-26]. IL-18 and IL-1 preferentially drive Th1/Th17 responses, whereas alum rather polarizes Th2 type immunity, which – by some groups – was found to be unaltered in the absence of caspase-1 or Nlrp3 [24,25]. Along this line, whereas IL-1 signaling and inflammasome activity have been implicated in allergic reactions, the importance of the latter in the establishement of such Th2 responses has not been unambiguously delineated [26-28]. Therefore, the definitive role of the NLRP3 inflammasome in adjuvanticity might occur through indirect mechanisms, be strongly influenced by the context, and still remains to be clarified.

Of note, it has been shown that tumor cells treated with chemotherapeutic agents can act as effective adjuvants to prime anti-tumor T cell responses through release of ATP and subsequent P2X7-dependent inflammasome activation [29]. As illustrated hereafter, additional implications of inflammasomes in the development of adaptive immunity come from the study of naturally occurring immune responses.

Lessons from autoimmune and autoinflammatory conditions

Recent reports link the inflammasome to Multiple Sclerosis (MS), a demyelinating inflammatory disease of the central nervous system, where autoreactive T cells target oligodendrocytes [30,31]. IL-1 signaling has been implicated in the development of

MS, a Th1- and Th17-driven pathology [30-32]. Inflammasome-deficient mice are protected from disease progression in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS (Table 1) [33-36]. The exact function of the inflammasome in this process is however unclear, since two recent reports describe the implication of Nlrp3 and ASC in EAE progression [34,36], whereas another study finds an inflammasome-independent role for ASC [35]. These divergent findings could be due to differences in the immunization protocols used for EAE induction, as suggested in [33,36].

A second example is cryopyrin-associated periodic syndromes (CAPS), human disorders which present with recurrent fever and inflammation and are in many cases due to gain-of-function mutations in NLRP3 [37]. Knock-in (KI) mice harboring constitutively active NLRP3 mutations have been established and recapitulate several aspects of the human disease, such as skin and systemic illness together with increased IL-1β production in the myeloid compartment [38,39]. The NLRP3-R258W KI mouse develops skin inflammation with neutrophil infiltration and predominant Th17 differentiation, whereas in the NLRP3-A350V KI mouse the autoinflammatory process was shown to be T and B cell-independent. The reason for these different observations in the two KI models remains unclear. Interestingly, a recent study showed increased IL-17 serum levels as well as Th17 frequency in CAPS patients, which could be reduced by blocking IL-1β *in vivo*, suggesting that inflammasome-derived IL-1β is important in the differentiation of Th17 in human autoinflammatory conditions (Table 1) [40].

Inflammasomes and T cell responses in infections

IL-1 has been shown to promote Th17 polarization in the context of different types of infections (Table 1) [41-46]. The use of knockout mouse strains highlighted the role of caspase-1 and ASC in Th17 priming during *Candida albicans* infection [42]. *C. albicans*-induced IL-1β drives the differentiation of Th17 cells secreting IL-17 alongside with IFN-γ [47]. In line with this observation, the absence of IL-1 often leads to decreased numbers of IL-17- as well as IFN-γ-producing cells [41-44]. Moreover, IL-1 can promote T cell proliferation, and its suppressive effects on regulatory T cells and IL-10 production by T cells provide a mechanistic interpretation for the former observation [47,48]. It is therefore not surprising that in some infectious models, inflammasome deficiency leads to a generalized reduction of T cell responses [42,44]. In addition, it has recently been demonstrated that upon influenza A infection, IL-1R signaling in DCs is necessary to promote $CD8^+$ T cell responses, illustrating how paracrine IL-1 can contribute to mature DCs [49]. Since this study was based on *IL-1RI*-knockout mice, the precise contribution by inflammasomes, however, remains to be determined.

Bordetella pertussis infection of *IL-1RI*-deficient animals showed decreased protection and diminished Th17 responses [43]. Yet, because both IL-1β and IL-1α promote Th17 polarization, the contribution by the inflammasome in the priming phase was shown using a selective caspase-1 inhibitor. The use of *Nlrc4*- and *Nlrp3*- further suggested inflammasome relevance in inducing Th17 responses upon *Legionella pneumophila* and *Schistosoma mansoni* infection, respectively [44,45]. In contrast, caspase-1 ablation did not reduce IL-17 production in the context of *Helicobacter pylori* infection, while IL-18 deficiency promoted it, pinpointing the relevance of inflammasome substrates in modulating the adaptive immune response [41].

IL-18 has been shown to promote IFN-γ production in several infectious models, including *Propionibacterium acnes*, *Mycobacterium bovis*, *Leishmania major*, and the intracellular fungal parasite *Cryptococcus neoformans* [11,50]. However, it was noticed early on that the effects of IL-18 on Th1 polarization are different from those of IL-12. While IL-12 is a crucial factor for Th1 polarization, IL-18 only has the ability of acting on IL-12-primed cells to strengthen their Th1 differentiation [50].

Infectious models make a strong case for the *in vivo* Th17/Th1 polarizing properties of the inflammasome substrates IL-1β and IL-18. As discussed in the next section, IL-18 also owns the surprising ability to elicit IFN-γ secretion by memory T cells in the absence of antigenic-triggering, questioning – in some experimental settings – its factual contribution to bona fide Th1 polarization.

Inflammasome and non-cognate lymphocyte activation

Recent findings highlight inflammasome importance in mediating non-cognate IFN-γ release, thereby "adjuvating" immune responses (illustrated in Figure 3). *Salmonella* Typhimurium infection or injection of heat-inactivated lysates stimulated the release of IFN-γ by splenic memory cytotoxic T cells of unrelated specificity [51].

This effect, as shown by the use of knockout mice, was mediated by IL-18 released upon NLRC4 inflammasome activation in DCs as early as two hours after the insult. Importantly, non-cognate $CD8^+$ T lymphocyte-derived IFN-γ contributed to the management of the infection [51]. Similarly, splenic natural killer (NK) and memory $CD8^+$ T cells produced innate IFN-γ secretion starting from eight hours after *Listeria monocytogenes* infection [52]. Inflammatory monocytes were the key cells eliciting, in a caspase 1-dependent manner, lymphocyte-derived IFN-γ release, suggesting that different cell subsets could contribute to IL-18 secretion either sequentially or depending on the infectious agent. In addition, an analogous mechanism takes place in draining lymph nodes where, upon *Pseudomonas aeruginosa* infection, the major source of IL-18 are subcapsular sinus macrophages, which are strategically positioned to capture invading pathogens and particles [53]. Innate IFN-γ secretion by $CD8^+$ T cells and other lymphocyte subsets was observed upon additional bacterial, viral, and protozoan infections, underlining how broadly this phenomenon might contribute to immune responses [51-53].

Recent studies attributed not only to IL-18, but also to IL-1β, in combination with IL-23 the ability to stimulate IFN-γ as well as IL-17 secretion without need for TCR triggering [30,54]. These results further suggest that inflammasome-driven innate lymphocyte functions could be relevant to antifungal and autoimmune responses.

An environment rich in IFN-γ coinciding with antigen presentation to naïve T lymphocytes favors the priming of robust Th1 responses. The advantage of evoking IFN-γ production by lymphocytes could, therefore, be twofold: it helps to activate innate immune cells to control pathogen spread during primary encounter and the development of a Th1-polarized memory response for future challenges.

Concluding Remarks

While emerging evidence highlights the importance of inflammasome-derived IL-18 to elicit innate IFN-γ secretion by lymphocytes, its impact on the concomitant priming of antigen-specific T cells has not been explicitly addressed. Furthermore, to carefully evaluate inflammasome relevance in the priming and polarization of adaptive immune responses, the contribution of the different inflammasomes, their substrates, and IL-1α should be individually addressed. The current understanding is in fact strongly hindered by the lack of such complete information. Hopefully, future work will enable us to better define the role of each of these players.

Nonetheless, the key role of IL-1 in supporting Th17 polarization and the importance of IL-18 in promoting Th1-tailored responses as well as non-cognate IFN-γ release are supported by multiple lines of evidence. The divergent functions of IL-1β and IL-18 in shaping adaptive immunity render the possibility of controlling these two substrates appealing, particularly for vaccination purposes. Favoring IL-18 production represents a promising way to achieve protective Th1 responses. Type I IFNs are known to inhibit pro-IL-1 synthesis and activity of the canonical NLRP3 inflammasome, while they might promote pro-IL-18 [11,13,32,55]. Thus, an attractive adjuvant could combine an inducer of type I IFN to an activator of an alternative inflammasome, such as the AIM2 inflammasome [2], maybe in the form of nucleic acids or safe viral agents.

The last decade witnessed the discovery of inflammasomes as key players of the innate immune response and led to improved clinical treatments for autoinflammatory disorders. The role of inflammasomes in the adaptive immune response has only recently emerged and anticipates a better control of adaptive immunity over the coming years.

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Tables and Figure Legends

Table 1. Implications of inflammasomes in the development of adaptive immune responses in autoinflammatory, autoimmune, and infectious diseases. (**n.a.**, not assessed; arrows in brackets indicate a mild effect)

disease/infection model	IFN-γ (Th1)	IL-17 (Th17)	disease/experimental model	refs
CAPS	→,(↗)	↗	CAPS patients, NLRP3-R258W KI	40,38
EAE (inact. *M. tuberculosis/* pertussis toxin)	↘ ↘	↘ ↘	*caspase-1*$^{-/-}$, *Asc*$^{-/-}$, *Nlrp3*$^{-/-}$, *IL-18*$^{-/-}$ *IL-1RI*$^{-/-}$	30, 33-36
M. tuberculosis	↘	n.a.	*AIM2*$^{-/-}$	46
B. pertussis (adenylate cyclase toxin)	(↘),n.a.	↘	*IL-1RI*$^{-/-}$, caspase-1 inhibitor	43
C. albicans	↘	↘	*Asc*$^{-/-}$, *caspase-1*$^{-/-}$	42
L. pneumophila	n.a. n.a.	↘ ↗	*caspase-1*$^{-/-}$, *IL-1RI*$^{-/-}$, *Nlrc4*$^{-/-}$ *IL-18*$^{-/-}$	45
S. mansoni	↘	↘	*Nlrp3*$^{-/-}$, *Asc*$^{-/-}$	44
H. pylori	→ →	(↗) →	*caspase-1*$^{-/-}$, *IL-18*$^{-/-}$ *IL-1RI*$^{-/-}$	41

Figure 1. Schematic overview of the best-characterized inflammasomes and their main activators.

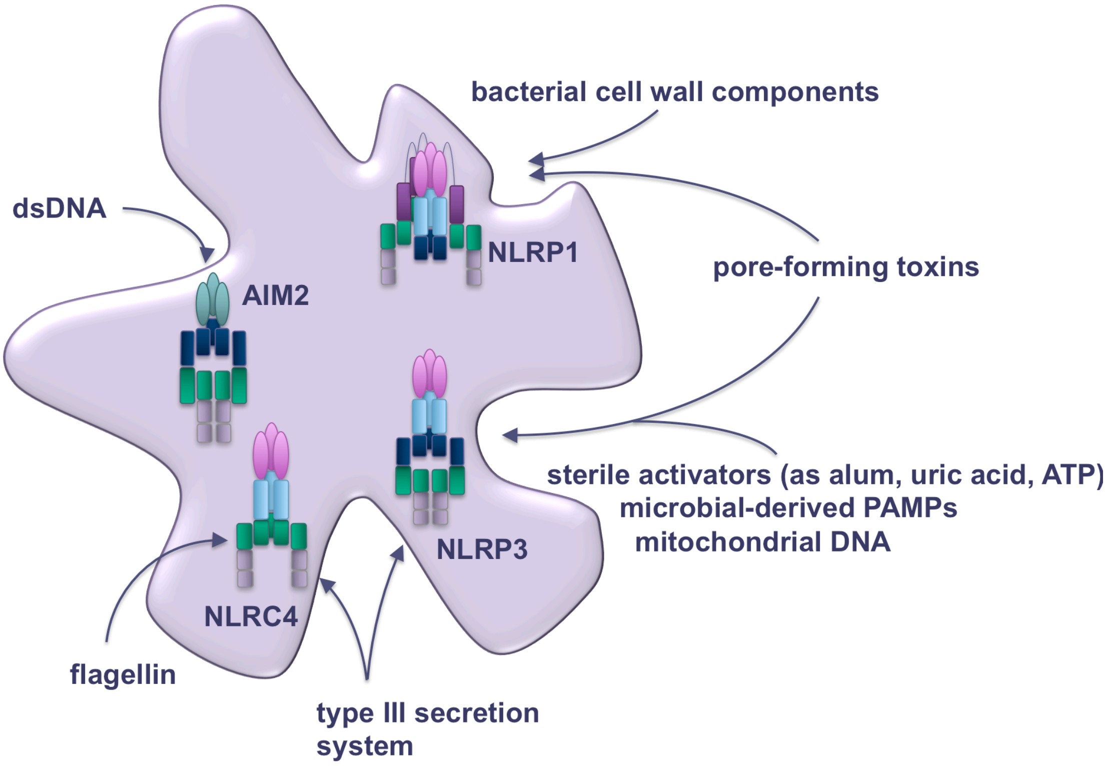


Figure 2. Effects of IL-1 and IL-18 in the polarization of T cell responses.

IL-1β and IL-18 are processed into their active form by the inflammasome and can differentially influence the polarization of T cells. Whereas IL-18 supports Th1 differentiation in synergy with IL-12, IL-1β promotes Th17 differentiation. IL-1α shares with IL-1β this ability, but its secretion can be independent of the inflammasome.

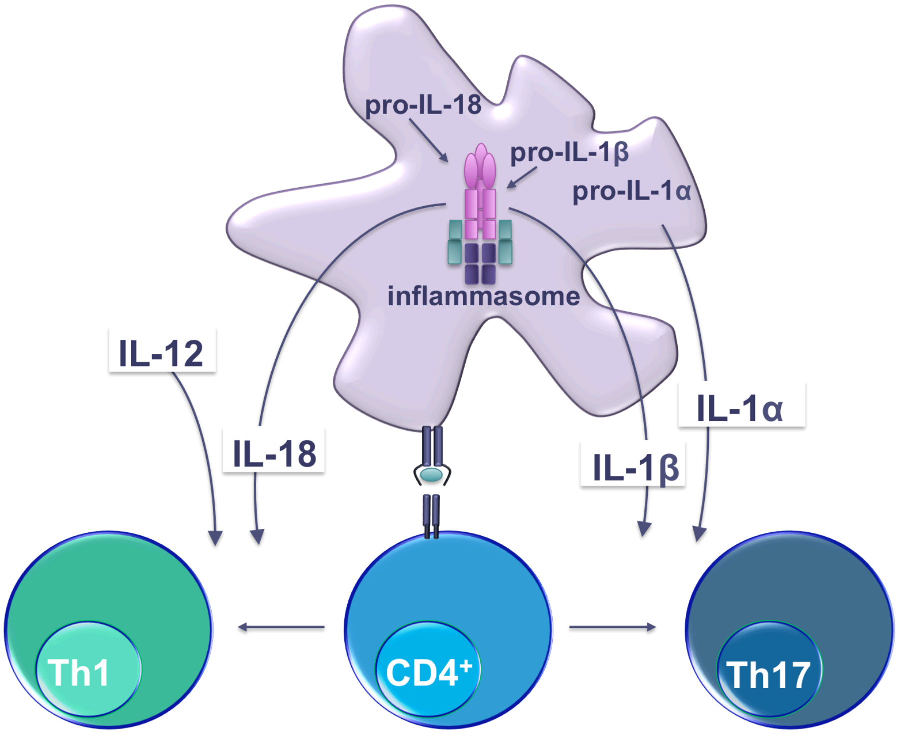
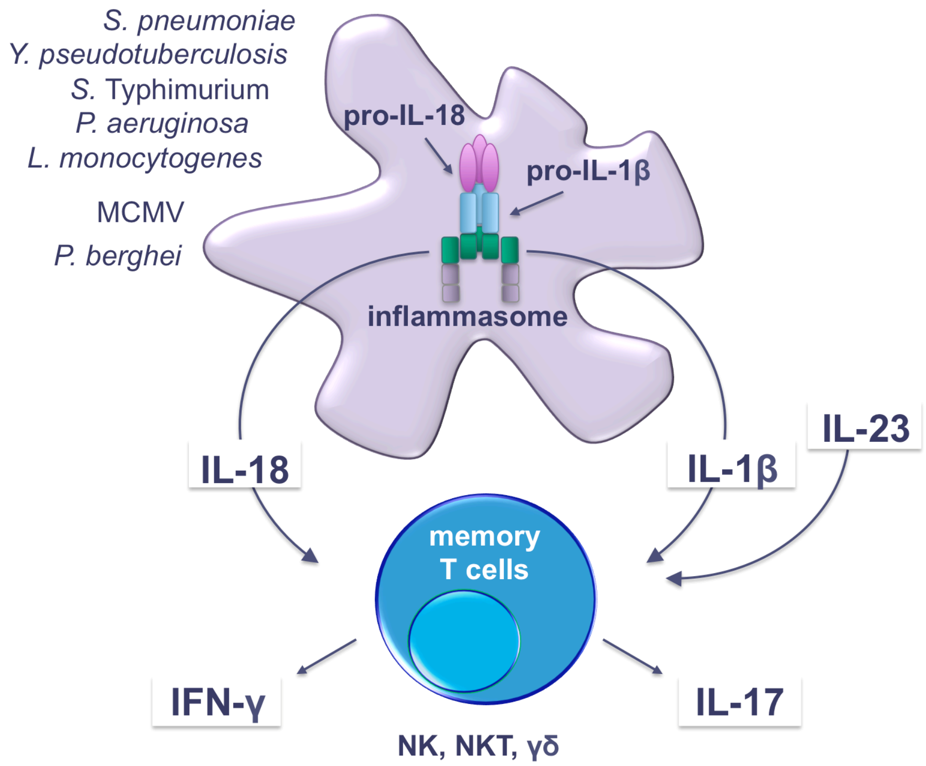


Figure 3. Inflammasome-derived cytokines elicit non-cognate memory T cell effector functions.

In the above-depicted infectious models, it was shown that inflammasome-derived IL-18 drives IFN-γ production by memory CD8$^+$ T cells, even in the absence of TCR stimulation. Similarly, IL-1 together with IL-23 can elicit IL-17 secretion by activated CD4$^+$ and CD8$^+$ T cells in an antigen-independent manner. Furthermore, other lymphocyte subsets such as NK, NKT, or γδ T cells can respond to IL-18 and IL-1 contributing to the innate production of IFN-γ and IL-17.



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