How Inflammasomes Inform Adaptive Immunity

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Abstract

An immune response consists of a finely orchestrated interplay between initial recognition of potential microbial threats by the innate immune system and subsequent licensed adaptive immune neutralization. The initial recognition integrates environmental cues derived from pathogen-associated molecular patterns and cell-intrinsic damage-associated molecular patterns to contextualize the insult and inform a tailored adaptive response *via* T and B lymphocytes. While there are much data to support the role of transcriptional responses downstream of pattern recognition receptors in informing the adaptive immune response, markedly less attention has been paid to the role of post-translational responses to pathogen-associated molecular pattern and damage-associated molecular pattern recognition by the innate immune system, and how this may influence adaptive immunity. A well-characterized post-translational consequence of pattern recognition receptor signaling is the assembly of a multimeric signaling platform, termed the inflammasome, by members of the nucleotide-binding oligomerization domain (Nod), leucine-rich repeat-containing receptors (NLRs), and pyrin and HIN domain (PYHIN) families. Inflammasomes assemble in response to cytosolic perturbations, such as mitochondrial dysfunction and aberrant ion fluxes in the case of the canonical NLRP3 inflammasome or the presence of bacterial lipopolysaccharides in the case of the non-canonical inflammasome. Assembly of the inflammasome allows for the cleavage and activation of inflammatory caspases. These activated inflammatory caspases in turn cleave pro-form inflammatory cytokines into their mature bioactive species and lead to unconventional protein secretion and lytic cell death. In this review, we discuss evidence for inflammasome-mediated instruction and contextualization of infectious and sterile agents to the adaptive immune system.

Introduction

An immune response to an infectious insult begins with sensing of conserved molecular patterns derived from pathogens and host tissue damage. Pathogen-associated molecular patterns (PAMPs) consist of conserved microbial ligands, such as cell wall components and nucleic acids, which imbue the host with the ability to detect diverse microbes using a subset of germline-encoded pattern recognition receptors (PRRs) [1,2]. In addition to recognition of microbial products, PRRs can detect structurally related chemical moieties from stressed and damaged host cells. These endogenous PRR ligands are known as damage-associated molecular patterns (DAMPs). DAMPs serve as a contextual signal for cellular death and tissue damage [2]. Recognition of PAMPs and DAMPs leads to the induction of pro-inflammatory and anti-microbial programs that activate additional innate immune cells, as well as contextualize the adaptive immune response depending on cytokine milieu [3]. In addition to cytokine and chemokine production, professional antigen-presenting cells (APCs), such as dendritic cells (DCs), mature in response to recognition of microbial products [4]. Hallmarks of DC maturation include the upregulation of several activities important for the initiation of T cell-mediated adaptive immune responses [4]. These activities can be grouped into three categories. The first category is upregulation of lysosomal activity, which results in the

efficient degradation and loading of microbe-derived peptides onto major histocompatibility complex (MHC) molecules for presentation of antigen to T cells [5,6]. The second category is the increase in cell surface expression of co-stimulatory molecules, such as CD80 and CD86 (originally known as B7-1 and B7-2 respectively), which are required for appropriate T-cell activation [7]. The third category is the upregulation and release of cytokines, such as interleukin (IL)-12, that can directly act on adaptive immune cells to inform an immune response [8]. These collective activities are necessary to differentiate naïve T cells into their effector and memory cell counterparts [4].

The mechanisms by which PRRs induce cytokine and co-stimulatory molecule expression are best defined from studies of Toll-like receptors (TLRs), whose signaling functions have been reviewed expertly in recent years [1,2]. In brief, activation of TLRs upon microbial detection leads to the formation of a large cytoplasmic supramolecular organizing center (SMOC) called the myddosome, whose principal effector function is to promote the activation of pro-inflammatory transcription factors of the NF-κB and AP-1 family [1,9]. These transcription factors function to induce numerous genes important for inflammation and adaptive immunity. Most cytokines that are important for T-cell activation are regulated by TLRs, and the expression of these genes is coupled tightly to the secretion of the bioactive cytokine that they encode [2]. However, one family of cytokines differs from this paradigm of coupled cytokine expression and secretion. The IL-1 family is unique in its decoupling of expression and release of bioactive molecules, as many members are transcribed and translated in response to TLR signaling but require additional signals to be effectively released from cells [10,11]. The IL-1 family consists of several cytokines that influence adaptive immunity, with the most commonly discussed being IL-1α, IL-1β, IL-18, and IL-33 [10,11]. These cytokines differ from most others in that they do not contain an N-terminal secretion signal. Whereas most TLR-dependent chemokines and cytokines are secreted *via* the biosynthetic pathway immediately upon synthesis, IL-1 family cytokines are produced as latent factors in the intracellular environment of the cell. These latent cytokines are only released after the cell experiences a second stimulus [10,12–14]. Work in recent years has revealed that several families of PRRs induce this second signal that releases IL-1 family cytokines [15–21]. These PRRs include the nucleotide-binding leucine-rich repeat containing (NLR) proteins, the AIM2-like receptors (ALRs) and the protein Pyrin [15–21]. NLRs, ALRs, and Pyrin survey the cytosolic (or nuclear) compartments for microbial products or indications of cellular dysfunction, and upon detection induce the formation of a SMOC called the inflammasome. Inflammasomes, like myddosomes, are not present in resting cells; instead, they assemble downstream of PRR engagement to elicit the activation of specific enzymes that are present within these complexes [1,9]. Whereas myddosomes induce the activation of kinases that promote inflammatory transcription factor activation, inflammasomes induce the activation of the enzyme caspase-1. Caspase-1 plays a critical role in the release of IL-1 family cytokines, as this enzyme cleaves the cytosolic protein gasdermin D (GSDMD) [22–24]. Upon cleavage, the N-terminus of GSDMD oligomerizes into a ring-shaped pore that inserts into the plasma membrane *via* interactions with acidic phosphoinositides such as a phosphatidylinositol 4,5-bisphosphate and phosphatidylserine [25–28]. The GSDMD pore creates ionic imbalances in the cell that ultimately leads to osmotic lysis and the release of IL-1 family cytokines into the extracellular space [25–29]. This form of cell death has been termed pyroptosis [29,30]. Caspase-1 can also cleave members of the IL-1 cytokine family, but the consequences of these cleavage events differ between each family member [10]. IL-1β and IL-18 must be cleaved in order to achieve inflammatory bioactivity [31–34]. IL-1α need not be cleaved to induce bioactivity, and IL-33 cleavage by caspase-1 leads to its inactivation [14,35–38]. The model described above presents an interesting conundrum, as IL-1 family cytokines play important roles in the initiation of adaptive immunity, yet producer cells die in the process of releasing these cytokines. As DCs require hours (and perhaps days) of viability *in vivo* to effectively stimulate antigen specific T cells [39–42], it is possible that the source of IL-1 important for these events is provided in trans (by cells other than the APCs). An alternative possibility is that mechanisms exist that allow for IL-1 family cytokines to be released from living cells. In this review, we will discuss both of these possibilities. We discuss examples where inflammasomes and IL-1 family cytokines have been implicated in the generation of adaptive immunity during infection, vaccination, autoimmunity, and cancer. We further highlight recent studies that have uncovered a mechanism by which cells may induce the inflammasome-dependent release of IL-1 while retaining viability, and discuss the potential implications of these findings for host defense.

Primer on adaptive immunity

As was alluded to in the prior section, the innate immune system activates the adaptive immune system primarily through the actions of APCs. Professional APCs such as DCs process antigens, thereby degrading proteins into immunostimulatory peptides that are presented on MHCI or MHCII based on the route of antigen acquisition and processing [43]. T cells that detect peptide antigens in the context of MHC are largely grouped into T conventional cells and T regulatory cells (Tregs), based on their roles in propagating or regulating immune responses.

Antigens that are processed by the proteasome (or immunoproteasome) in the cytosol of nucleated cells can be loaded on MHCI for presentation to a subset of adaptive immune cells known as CD8 T cells [43]. Mature T cells exist in a naïve state prior to antigen exposure [44]. Antigen-specific CD8 T cells have major roles in the direct recognition and killing of any infected or transformed cells that present cognate antigen in the context of MHCI [45]. In addition to cytotoxic responses, CD8 T cells can also release instructive cytokines such as interferon-γ (IFN-γ) [45]. Another subset of T cells that utilize alpha beta T-cell receptor (TCR) chains that are known to mediate target cell killing and instructive cytokine release are the natural killer (NK) T cells [46]. These cells have semi-invariant TCRs and primarily detect lipid antigens as opposed to peptide antigens [46]. Antigens that are processed by lysosomal degradation can be loaded on MHC2 for presentation to another major class of adaptive immune cells known as CD4 T cells [43,44]. Naïve CD4 T cells can be influenced by antigen recognition, cytokine milieu, and contextual costimulation by APCs to differentiate naïve T cells into effector T cells of various subtypes including T helper cell 1, T helper cell 2, and T helper cell 17 (Th1, Th2, and Th17, respectively) [44]. These subtypes have defined roles in certain pathogenic contexts, as they are able to release instructive cytokines that shape the subsequent immune response. Th1 cells require the cytokines IL-12 and IFN-γ in addition to TCR engagement and costimulation for efficient differentiation from naïve CD4 T cells [44,47]. These helper cells are important in enhancing the action of innate immune cells such as macrophages through production IFN-γ [44]. This activation of cells such as macrophages is particularly useful in combating immune evasive intracellular bacteria and extracellular bacteria. Th2 cells require the cytokine IL-4 in addition to TCR engagement and costimulation for efficient differentiation from naïve CD4 T cells [44,47]. These helper cells are important in the response to parasites including helminths and are implicated in pathological responses such as allergy. Th2 cells produce the instructive cytokines IL-4, IL-5, and IL-13 to skew an immune response toward a type 2 response [44]. Th17 cells require TGF-β and IL-6 with TCR engagement and costimulation for initial differentiation [48]. They also require IL-1 to form stable Th17 cells under certain conditions. These helper cells are associated with the immune response to fungal infections and pathology associated with many autoimmune disorders. Th17 cells produce the instructive cytokine IL-17 [48]. Effector T cells can form long-lived memory T cells that are primed for antigen specific re-activation in the event of reinfection [49]. In addition to these effector T-cell subsets, CD4 T cells can also form Tregs. These cells repress immune responses in order to maintain tolerance or encourage tissue repair after an immune reaction [50]. These cells require TGF-β and IL-2 for differentiation, in addition to TCR

engagement [50]. Gamma delta T cells utilize the gamma and delta chains of the TCR during rearrangement, as opposed to the alpha beta for all the aforementioned T cells. These T cells are present at barrier sites and can produce instructive cytokines such as IL-17 and IFN-γ [51]. Beyond T cells, the adaptive immune system also comprises other lymphocytes known as B cells. These cells are responsible for the recognition of virtually limitless three-dimensional epitopes, usually of intact proteins [52]. B cells can undergo selection after somatic hypermutation and class switch recombination to then increase B-cell receptor affinity for specific antigens and alter antibody effector function [52]. These highly specific B-cell receptors can then be secreted as antibodies when B cells differentiate into plasma cells [52,53]. These antibodies provide humoral immunity to a host through various effector functions such as neutralization or opsonization of antigen [53]. The adaptive immune system comprises many specialized arms that can unleash subsequent immune programs for specific classes of antigenic insults. All of these responses fundamentally depend on contextualization from innate immune cells.

Instruction of adaptive immunity *via* inflammasome-dependent cytokines

As described above, a major effector function of the inflammasome is the activation of the cysteine protease caspase-1 [15]. Active caspase-1 has clear links to adaptive immunity through the release of IL-1 family cytokines that are important for T-cell activation and memory cell formation. In addition to cleavage of IL-1β and IL-18 into their bioactive forms, inflammasomes also facilitate the secretion of the inflammatory proteins HMGB-1 and IL-1α that do not require processing for biological activity [13,54]. Although IL-1α is often secreted in addition to IL-1β after inflammasome-dependent pyroptosis, some stimulations allow for IL-1α secretion independent of the inflammasome [14,35,36]. IL-1α and cleaved IL-1β signal through the heterodimeric IL-1R, which consists of the IL-1R1 and IL-1R accessory protein (IL-1RAcP) [55–57].

IL-1 signaling has numerous activities that are important for adaptive immune responses [11]. IL-1R signaling *via* IL-1α or cleaved IL-1β can provide a survival signal to naïve T cells, as IL-1 causes a transient release of the survival cytokine IL-2 from T cells [58]. IL-1R signaling also upregulates IL-2R surface expression, potentially providing pro-survival and proliferation signals to stimulated naïve T cells [58]. Furthermore, IL-1R signaling expands naïve and memory T cells and prolongs T cell help to B cells for antibody production [59]. IL-1β signaling allows for a breach in tolerance through expansion of conventional T cells even in the presence of Tregs cells, confirming

that IL-1 provides a strong pro-survival and proliferation signal to T cells [60]. IL-1β is also required for the stable differentiation of the T helper cell subset that produces IL-17 (Th17 cells) from naïve T cells [61–64]. As IL-1α also signals through IL-1R, it is likely that IL-1α could substitute for IL-1β in this role. Indeed, in *ex vivo* cultures naïve T cells treated with IL-1α were able to stably differentiate into Th17 cells [65,66]. Th17 cells are associated with defense against extracellular bacteria and fungal pathogens [67,68]. These cells are also associated with progression of sterile autoimmunity such as multiple sclerosis (MS) [69–71]. IL-1β in conjunction with IL-23 stimulates IL-17 production from a group of γδ T cells that can exacerbate autoimmunity [72].

Not all IL-1 family members signal *via* the same receptor. IL-33 (first named nuclear factor from high endothelial venules [73]), for example, signals *via* the receptor ST2, which can be expressed on type-II immunity T helper cell subset (Th2) and Tregs [74–77]. IL-33 also makes use of IL-1RAcP similar to the IL-1R complex [78,79]. A recent study suggests that receptor proximal signaling strategies differ between IL-1R and ST2, despite both using IL-1RAcP to propagate intracellular signaling [80]. IL-33 signaling induces proliferation of Th2 cells and production of allergy-associated cytokines IL-4, IL-5, and IL-13 [74,75,77,81]. In regulatory T cells, IL-33 signaling *via* ST2 promotes a tissue repair response through upregulation and release of the anti-inflammatory mediator amphiregulin [82,83]. IL-33 and IL-1α reside in the nucleus of some cells and can be released in a biologically active form after necrotic cell death [73,84–87]. IL-33 was originally assumed to be cleaved by active caspase-1 to release a bioactive fragment similar to the role of caspase-1 in maturation of pro-IL-1β. Instead, it is now appreciated that caspase-1-mediated cleavage inactivates IL-33 [37,38]. Intriguingly, some studies have shown that active caspase-1 and inflammasome components can be released from cells and reside in the extracellular matrix [88,89]. This potentially broadens the scope of influence a pyroptotic cell could have over the local cytokine milieu if extracellular caspase-1 was capable of inactivating IL-33 released from surrounding necrotic cells.

IL-18 is another IL-1 family member that is translated in a pro-form and matured by active caspase-1 after inflammasome activation [34,90]. This cytokine signals through a heterodimeric receptor complex consisting of IL-18Rα, which bears significant homology to IL-1R, and IL-18Rβ [91]. Like IL-1α, pro-IL-18 does not need to be upregulated in many cell types as it is expressed constitutively in macrophages, Kupffer cells, osteoblasts, chondrocytes, and synovial fibroblasts [92–95]. IL-18 was first known as IFN-γ-inducing factor for its described role in the induction of IFN-γ from T cells after infection with *Propionibacterium acnes* and subsequent lipopolysaccharide (LPS)

challenge [92]. IL-18 in conjunction with other cytokines such as IL-12 serves to increase IFN-γ production from type-I immunity T helper subset (Th1) cells and NK cells [96–98]. This synergy likely occurs through IL-12-mediated upregulation of the IL-18R complex on naïve T cells [97,99,100]. IL-18 signaling then results in upregulation of IL-12R on these polarized Th1 cells leading to a feed forward differentiation loop [101].

Figure 1 provides a summary of the activities of these IL-1 family members on T-cell functions. In subsequent sections, we delve into the roles of inflammasomes and IL-1 family cytokines in driving adaptive immunity to pathogenic insults and sterile inflammation.

Role of inflammasomes in adaptive immune responses to infectious agents

Inflammasomes are well suited to contextualize pathogen invasion as many of the nucleating receptors are situated within the sterile cytosol compartment of cells. The NLRP3 inflammasome is best characterized, with many disparate molecular triggers, such as potassium efflux, lysosomal rupture, reactive oxygen species (ROS) production, and mitochondrial disruption, that initiate assembly of this SMOC [102–107]. Many of these perturbations to homeostasis could indicate pathogenic bacterial invasion. In the case of infections with *Streptococcus pneumoniae,* the pore-forming toxin pneumolysin (PLY) is a major virulence factor that activates the NLRP3 inflammasome [108]. Membrane disruption by PLY causes NLRP3-dependent inflammasome assembly and the consequent caspase-1-dependent cleavage of IL-1β and IL-18 [108–111]. The NLRP3 inflammasome is crucial for the release of IL-1α and mature IL-1β from DCs and macrophages after pneumococcal infection and PLY treatment [108,111]. Treatment of splenocytes with PLY resulted in induction of IL-17A and IFN-γ secretion [108]. PLY is also necessary for IL-17A and IFN-γ secretion in the lungs of mice infected with *S. pneumoniae* [108]. NLRP3 is also important for host survival as NLRP3 knock-out (KO) mice show reduced body weight, increased bacterial burden, and decreased survival compared with wild-type mice [111]. The pore-forming adenylate cyclase toxin (CyaA) from *Bordetella pertussis* also activates the assembly of NLRP3 inflammasomes, and cleaved IL-1β is produced in an NLRP3 and caspase-1-dependent manner following challenge with CyaA [112]. IL-1R KO mice infected with *B. pertussis* have less Th17 cells and increased bacterial loads [112]. Inflammasomes may also be important for host defense against *Mycobacterium tuberculosis* as IL-1β KO and IL-1R KO mice have increased susceptibility to *M. tuberculosis* infections [113–115]. Macrophages infected with *M. tuberculosis* release IL-1β and IL-18 by an NLRP3-dependent process *in vitro*, although
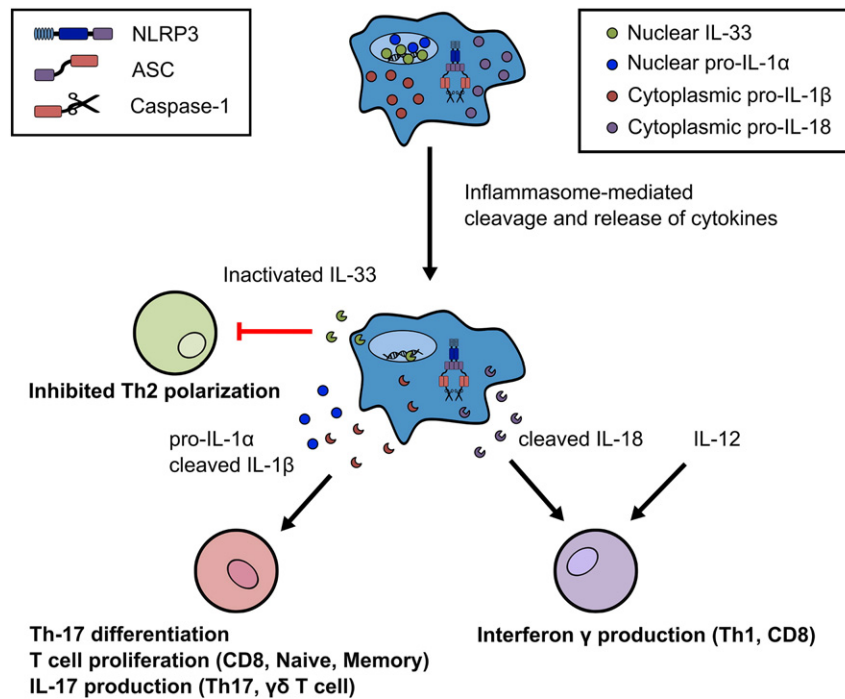
Fig. 1. Inflammasome-dependent cleavage and release of IL-1 family member cytokines that influence T-cell immunity. Inflammasome activation leads to the cleavage of some IL-1 family members including IL-1β, IL-18, and IL-33. Cleavage of IL-33 by active caspase-1 leads to inactivation of this Th2 skewing cytokine, thus providing a mechanism that inflammasome activity may impinge on Th2 adaptive immune responses. In contrast, cleavage of IL-1β and IL-18 by active caspase-1 results in bioactive cytokines. IL-1β, in addition to pro-IL-1α, can enforce Th17 stable differentiation and induce T-cell proliferation. IL-1β can also cause IL-17 production and secretion from human Th17 cells and murine γδ T cells that may exacerbate autoimmune inflammation. Cleaved IL-18 in conjunction with the cytokine IL-12 enhances IFN-γ from Th1 and CD8 T cells.

this dependency on NLRP3 is less clear *in vivo* [113,115,116]. In experiments using heat-killed *M. tuberculosis* in conjunction with complete Freund's adjuvant (CFA), caspase-1 and IL-1β are required for generation of Th17 cells [117]. In the context of a live infection with *M. tuberculosis*, inflammasome-independent IL-1R signaling, likely from release of IL-1α from necrotic cells, can provide differentiation signals to generate Th17 adaptive immunity [113,115,118]. Thus, the role of the inflammasome in generating immunity to *M. tuberculosis* may depend on whether the microbial products are used as an adjuvant or live infection, and this distinction highlights the sufficiency but not necessity of inflammasome signaling to this intracellular pathogen.

The NLRC4 (IPAF) inflammasome is also important in controlling intracellular bacterial infections [16,17,119–122]. This inflammasome is assembled by members of the NAIP family of NLRs, which are direct sensors of bacterial flagellin or subunits of bacterial type III secretion systems [123–126]. Once these bacterial products are detected in the cytosol by their respective receptors, an NLRC4-containing inflammasome is assembled that promotes caspase-1 activation. NLRC4-dependent pyroptosis restricts bacterial infections likely through destruction of a

requisite intracellular replication niche [119]. In addition, flagellin derived from *Salmonella enterica* serovar Typhimurium, *Yersinia pseudotuberculosis*, and *Pseudomonas aeruginosa* can promote NLRC4 inflammasome assembly in splenic CD8α DCs resulting in the release of cleaved IL-1β and IL-18 [127]. This pool of IL-18 is capable of stimulating IFN-γ secretion from memory CD8 T cells in the spleen [127]. Immune control of *Legionella pneumophila* infections depends on the flagellin sensing PRR NAIP5 (also known as Birc1e) and NLRC4 [16,120,121]. Using an airway infection model of *L. pneumophila*, flagellin and NLRC4 were determined to be required for the generation of IL-17-producing T cells [128]. Further characterization illustrated that Th17 differentiation is dependent on caspase-1 and IL-1R after *L. pneumophila* challenge [128]. Infection with the intracellular pathogen *Anaplasma phagocytophilum* elicits IL-18 production that is in part due to the NLRC4 inflammasome and is independent of the NLRP3 inflammasome, thereby stimulating the production of IFN-γ assayed from serum samples [129]. Moreover, caspase-1 KO and ASC KO mice have reduced Th1 responses that lead to increased susceptibility to *A. phagocytophilum* infection [129]. Many other bacterial pathogens have been explored for their roles in activating the

inflammasome in innate immune cells as reviewed elsewhere [130], but the relative roles of pyroptosis and IL-1 release in generation of adaptive immune responses to these bacteria remain to be defined.

The role of inflammasomes in antimicrobial defense extends beyond bacterial infections and includes infections by viral and fungal pathogens as well [131–135]. Direct recognition of viral infection byproducts, such as nucleic acids, and indirect recognition of cellular disruption can activate inflammasomes in response to viruses [132,136–139]. The cytosolic sensor of double-stranded DNA (dsDNA), AIM2, has been implicated in the assembly of inflammasomes and the consequent generation of IL-18 after infections with Vaccinia virus and mouse cytomegalovirus [136]. In addition, the nuclear DNA sensor IFI16 forms an inflammasome in response to viral DNA during Kaposi sarcoma-associated herpes virus infection and mediates pyroptosis in response to abortive human immunodeficiency virus (HIV) infection in human CD4 T cells [137,140,141]. Beyond direct recognition of viral nucleic acids, cells can sense infection with influenza virus after incorporation of a proton selective ion channel into the membrane of host cells. Specifically, insertion of the M2 ion channel into membranes of the Golgi apparatus was required for inflammasome activation during influenza virus infection as shown through *in vitro* infection studies in bone marrow-derived macrophages and DCs [132]. Aberrant ion fluxes from this ion channel much like bacterial pore-forming toxins allow for the activation and oligomerization of the NLRP3 inflammasome during influenza infection [132]. Moreover, the inflammasome seems crucial for adaptive responses against influenza as the CD4 and CD8 T-cell response as well as influenza-specific antibody titers are stunted in caspase-1 and ASC KO mice [131]. IL-1R signaling is important for intact antibody response and T-cell recruitment to the lung after influenza infection as seen by impaired IgM production and T-cell counts in infected IL-1R KO mice [142]. CD8 T cells are often thought of as the main antiviral effector cells of the adaptive immune system, and signaling through IL-1R enhances CD8 cytolytic programs by upregulating effector proteins, such as granzyme B, as well as promoting antigen-driven proliferation of CD8 T cells [143]. Interestingly, a potential mechanism relating age to influenza susceptibility was identified by the finding that aged mice contain DCs with decreased inflammasome components such as ASC and caspase-1 but increased pro-IL-1β [144]. These mice also show lower IL-1β secretion in response to influenza infection with concomitant deficits in total leukocyte counts in aged mice as compared with their younger counterparts [144]. The addition of an adjuvant that stimulates NLRP3 inflammasome activation increases influenza vaccine efficacy in aged mice [145]. Defects in NLRP3 activation can also be rescued through treatment with the bacterial potassium ionophore nigericin, with rescue of IL-1β production in aged mice [144]. Of note, the inflammasome may also play a harmful role in responses to subsequent bacterial infections that are often associated with influenza infections in the context of aged humans [146]. Using mouse strains deficient in the innate immune proteins MAVS and TLR7 as a model for suppressed immune function, infection with influenza resulted in subsequent mortality that was independent of viral load yet dependent on neutrophil influx, bacterial burden, and caspase-1/-11 [146]. These findings suggest that while inflammasome signaling may aid in adaptive responses to the primary viral infection, inflammasome signaling may also result in tissue damage, with profound effects on organismal survival in response to subsequent bacterial infection. Like studies on adaptive immune responses to *M. tuberculosis*, the adaptive immune response to influenza infection requires IL-1R signaling in T cells, but the source of the IL-1 can come from cleaved IL-1β or IL-1α release. In addition to direct action on T cells, IL-1R signaling has been implicated in enforcing the maturation and migration of pulmonary DCs to lymphoid tissue to activate influenza-specific CD8 T cells [147]. In the natural response to influenza, many studies support the role of the inflammasome in the release of IL-1 in the lung of influenza-infected animals and activation of Th1 and CD8 adaptive immune responses [131,139,148]. A study investigating DNA based vaccines through plasmids encoding the hemagglutinin influenza antigen noted that antibody responses to hemagglutinin are greatly stunted in AIM2-deficient mice, which do not depend on IL-1β or IL-18 signaling. This study suggests that other consequences of inflammasome signaling, such as pyroptosis and the release of DAMPs, may contribute to formation of adaptive immune responses. In addition to detection of influenza infection, the inflammasome appears to be important in generating an adaptive immune response against the central nervous system (CNS) tropic West Nile virus (WNV). *In vivo* infection studies demonstrate that IL-1β is released during WNV infection [149]. In addition, IL-1R-deficient mice display stunted antiviral responses from CD8 T cells in the CNS. The source of IL-1 in WNV-infected animals likely comes from activation of the inflammasome, as caspase-1 and NLRP3 KO mice are more susceptible to infection with WNV [149].

The adaptive response to fungal infections such as *Candidiasis* depends on Th17 cells [68]. As the role of IL-1β in the differentiation of Th17 cells is well known, one might expect that the inflammasome instructs the adaptive immune system in fungal infections. Consistent with this idea, hyphae from *Candida albicans* activates the NLRP3 inflammasome, and NLRP3 KO mice are highly susceptible to disseminated and mucosal *C. albicans* infection [133–135]. NLRC4 is also involved in the immune response to mucosal *C. albicans* infection, although the mechanism of NLRC4 activation in this infectious context is unknown

[150]. Reduced Th1 and Th17 responses in caspase-1 KO and ASC KO mice provides further evidence for the role of the inflammasome in the adaptive response to *C. albicans* infection [151]. Lack of these adaptive responses leads to fungal outgrowth and increased morbidity after infection with *C. albicans* in caspase-1 KO and ASC KO mice [151]. Inflammasome-dependent cytokines are directly implicated in generating adaptive immune responses to *C. albicans*, as exogenous IL-18 rescues the deficit in Th1 polarization in caspase-1 KO mice [152]. IL-1β treatment of *C. albicans*-specific human Th17 cells elicits both IL-17 and IFN-γ secretion *ex vivo* suggesting that IL-1β enforces a pro-inflammatory cytokine program in these cells beyond its role in Th17 differentiation [153]. *In vitro* studies have shown that stimulation of yeast-derived products such as curdlan and zymosan can activate IL-1β secretion from macrophages and DCs in an NLRP3-dependent manner [154]. Curdlan also induces IgM production and upregulation of CD69 on stimulated B cells that is dependent on NLRP3 but independent of the myddosome forming adaptor protein MyD88 suggesting a role of NLRP3 in formation of humoral immune responses [154]. Additional studies have implicated a signaling pathway mediated by the PRR Dectin-1, which senses fungal PAMPs and results in the assembly of NLRP3 inflammasomes in response to hyphae. This observation illustrates that the inflammasome responsiveness to hyphae can contextualize Th17 responses between colonizing yeast and invasive hyphae. From this discussion of bacterial, viral and fungal infections, a theme has emerged whereby the initiation of adaptive immune responses to microbial encounters depends on the activity of inflammasomes and IL-1 family cytokines. In the next section, we expand the discussion on the influence of the inflammasome on adaptive responses to include non-infectious immune activators.

The inflammasome has also been suggested to affect adaptive immune responses to protozoan parasites. Activation of the NLRP3 inflammasome during infection with *Leishmania major* can alter the adaptive immune response [155–159]. BALB/c mice that are susceptible to *L. major* infection lacking the inflammasome components NLRP3, ASC, or caspase-1 had lower IL-1β and IL-18 production at infection sites and proved more resistant to infection [155]. Surprisingly, IL-18 was shown to promote Th2 differentiation. Neutralizing IL-18 led to lower *L. major* titers and signs of infection [155]. C57BL/6 mice infected with the Seidman strain of *L. major* develop non-healing, chronic lesions and reduced parasite clearance [159]. Mice that were deficient for inflammasome components NLRP3, ASC, or caspase-1/caspase-11 were able to resolve infections and did not develop chronic lesions. Moreover, IL-1β- and IL-1R-deficient mice also showed increased parasite clearance [159]. Conversely, another study using C57BL/6 mice also

notes that NLRP3 inflammasome can activate in response to *in vitro* infection of macrophages with different *Leishmania* species, and show a role for inflammasome-dependent IL-1β in promoting nitric oxide synthase (NOS2) production of nitric oxide *in vivo* [157]. This production of nitric oxide was IL-1R and MyD88 dependent and provided resistance to infection with *Leishmania amazonesis, Leishmania braziliensis,* and *Leishmania infantum chagasi* [157]. *L. amazonesis* was recently shown to activate ROS production and NLRP3 activation in infected macrophages downstream of Dectin-1, Syk, and phagocytosis [160]. ROS production and inflammasome activation restricted parasite replication inside macrophages and provided organismal resistance to infection *in vivo* [157,160]. Moreover, *Leishmania* can modulate pro-inflammatory cytokine release through cleavage of NLRP3 in infected macrophage through the action of the virulence factor metalloprotease GP63 that is common to all infectious *Leishmania* species [158]. The role of inflammasome dependent IL-1 family members in modulating the immune response to *Leishmania* species members may be species and mouse strain specific. Mice deficient for IL-1β and IL-1α are more resistant to infection on the BALB/c background due increased beneficial IFN-γ producing Th1 cells and reduced detrimental IL-4 Th2 cells [161]. Injection of exogenous IL-1β can also increase lesion progression and infection with *L. amazonesis* on the C57BL/6 background [162]. BALB/c mice deficient in IL-18 and infected with *Leishmania mexicana* or *L. major* have delayed lesion growth and lower parasite burden [156,163]. These studies suggest that IL-1 family members can somehow skew the immune response toward a Th2 response that makes BALB/c mice susceptible to *Leishmania* infection. More intuitively, IL-18-deficient mice on the C57BL/6 background prove more susceptible to *Leishmania* infection as they have decreased IFN-γ producing T cells [164,165], although another study suggests that IL-18 may only be involved in early lesion control [166]. More studies are needed to unify conclusions on the role of IL-1 family members and inflammasome signaling in adaptive responses to *Leishmania*.

Genetic analysis of symptomatic patients from the Amazon infected with *Plasmodium vivax* revealed associated single nucleotide polymorphisms in the inflammasome receptor NLRP1 [167]. The NLRP3 inflammasome can also activate in response to *Plasmodium* infection through release of crystalline heme known as hemozoin during the blood growth stage. Hemozoin causes the activation of the NLRP3 inflammasome and release of IL-1 family members *in vitro* and *in vivo* [168–170]. In addition to NLPR3 activation, cytosolic DNA can activate the AIM2 inflammasome after *Plasmodium* infection [171]. The inflammasome might be detrimental to immune response against *Plasmodium* as mice deficient in inflammasome components NLPR3, ASC, and

caspase-1 or IL-1β are resistant to *Plasmodium* infection [168,169], although other studies suggest that inflammasome components and inflammasome-dependent cytokines do not play a significant role in the pathology of *Plasmodium* infection *in vivo* [172,173]. Models of parasite and bacterial co-infection demonstrate that infection with *Plasmodium falciparum* or *P. vivax* results in NLRP3- and NLRP12-dependent IL-1β release [174]. Co-infection studies also reveal that inflammasome activation contributes to mortality as mice deficient for NLRP3, NLRP12, ASC, and caspase-1 had higher rates of survival compared to wild-type mice [174]. Primary infection with *P. vivax* sensitized mice to mortality following either bacterial infection or LPS injection [174].

Genetic analyses of a North American patient cohort revealed NLRP1 SNPs associated with congenital toxoplasmosis [175]. Human monocytes infected with *Toxoplasma gondii* release IL-1β [175,176]. Knock down of caspase-1 and ASC inflammasome components in human monocytes demonstrates that inflammasomes form after infection with *T. gondii* [175]. *T. gondii* infection can also activate the NLRP3 inflammasome [177]. Mice deficient in NLRP1, NLRP3, ASC, or caspase-1 are more susceptible to *T. gondii* suggesting that inflammasome signaling *in vivo* is protective for the host [177,178]. IL-18 is detectable in the serum of mice infected with *T. gondii*, although both IL-1 and IL-18 are protective as mice deficient for either IL-18 or IL-1R are more susceptible to *T. gondii* infection [177,178]. Although there is evidence that inflammasome signaling and inflammasome-dependent cytokines are important for host defense to *T. gondii*, further studies are needed to establish how the inflammasome affects adaptive immune responses in the context of protozoan parasitic infections with *T. gondii*.

Additional studies suggest that the NLPR3 inflammasome can form in response to infection with other protozoan parasites such as *Trypanosoma cruzi* and *Entamoeba histolytica* [179–182], although these studies have not established a role for the inflammasome signaling in informing the adaptive immune response. Further studies are required to determine how inflammasome activation *in vivo* can affect immune responses against *T. cruzi* and *E. histolytica*. A recent study also suggests that host–protozoan interactions with *Tritrichomonas musculis* can activate the inflammasome with the consequence of providing adaptive immune protection from bacterial infections [183].

Role of the inflammasome in autoimmunity

As we have discussed for infectious diseases, IL-1β and IL-18 likely contribute to differentiation of naïve and primed T cells into effector Th1 and Th17 cells that mediate autoimmune disease. A major candidate autoimmune disease that is potentially instructed by inflammasome activities is MS. Evidence supporting this statement is ample and includes patient samples that display increased expression of IL-1β and IL-18 as well as caspase-1 [184–186]. In addition, serum levels of IL-18 are increased in MS patients [187,188]. The mouse model for MS known as experimental autoimmune encephalomyelitis (EAE) utilizes CFA to cause an immune response against major CNS antigens, such as myelin oligodendrocyte glycoprotein. *In vivo* studies that immunize against myelin oligodendrocyte glycoprotein have shown dependency on caspase-1 for disease progression [189]. As these studies utilize CFA, which contains heat killed *M. tuberculosis*, the adjuvant may be the inflammasome-stimulating component in EAE. *M. tuberculosis* is not unique in its ability to promote inflammasome activity in EAE, as studies using pertussis toxin to prompt EAE have identified the pyrin inflammasome as the inducer of cleaved IL-1β release [190]. Interestingly, in contrast to caspase-1, which is often implicated in inflammasome activities during infections, a recent study implicates IL-1β processing in T cells by a caspase-8-dependent mechanism in propagating a Th17 response in EAE, although the canonical inflammasome adaptor protein ASC is still required [191]. The cytokines IL-1β and IL-18 derived from DCs have been shown to be important for generation of Th17 and γδ T-cell responses in EAE [65,72,192].

Beyond MS, genomic studies have implicated polymorphisms in the inflammasome-associated receptors NLRP1 and NLRP3 with susceptibility to rheumatoid arthritis [193,194]. Mechanistic insights into this association are lacking, although one study suggests that inflammasome signaling and basal priming in mice lacking A20, a negative regulator of TLR signaling, can exacerbate arthritis in mouse models [195]. Systemic lupus erythematous (SLE) is another autoimmune disease that has potential involvement of inflammasome activation in perpetuating systemic inflammation. Immune complexes containing dsDNA activate the NLRP3 and AIM2 inflammasomes [196,197]. The generation of anti-nuclear antibodies by auto-reactive B cells depends on IL-1β, potentially offering a feed-forward loop of inflammation [198]. Unsurprisingly, supernatants from cells stimulated with dsDNA immune complexes that activate the NLRP3 inflammasome are able to stimulate IL-17 secretion from memory CD4 T cells [196]. Like with rheumatoid arthritis, NLRP1 has been genetically associated with SLE in patients [199]. Caspase-1 activation is associated with vascular damage in a mouse model of SLE [200]. Consistent with these results, macrophages from SLE patients contain active NLRP3 inflammasomes [201]. Furthermore, expression of the cryopyrin-associated periodic syndromes-associated mutant NLRP3 R258W leads to severe

organ damage in a mouse model of lupus [202]. Like with MS, inflammasome-dependent cytokines IL-1β and IL-18 show elevated levels in the serum of lupus patients [203–205]. Studies suggest that increased IL-18 and localization of plasmacytoid DCs to the kidneys might activate tissue-resident T cells and mediate kidney damage in SLE, which is a major consequence of lupus in patients [204,205]. More studies are required to determine if inflammasome activation is a requisite step in the progression of autoimmunity. Of particular interest would be parsing out the relative roles of pyroptosis from the release of T cell stimulating cytokines such as IL-1β and IL-18 after inflammasome activation as has been investigated in auto-inflammatory disorders [206].

Inflammasomes and vaccines

As has been discussed above, ample and diverse evidence supports the role of IL-1 family cytokines in T cell-mediated immunity. As IL-1 release is classically associated with inflammasome-mediated cell death, a conundrum emerges. How can a T-cell response depend on IL-1 (released from dead cells) and also depend on antigen presentation by a living cell? While it is possible that the IL-1 necessary for T-cell activation and differentiation is provided in trans, from dying cells, another possibility is that mechanisms of IL-1 release from living APCs exist. Recent work from our group suggests that DCs can indeed be induced to release inflammasome-dependent IL-1 while retaining viability [207]. When murine DCs are treated with TLR ligands, such as bacterial LPS, these cells will upregulate MHC and costimulatory molecule expression and release of inflammatory cytokines that contain N-terminal signal sequences [3,4]. However, they will not release IL-1 family cytokines that are present in their intracellular compartment as previously discussed. When DCs are exposed to TLR ligands and a DAMP, such as oxidized phosphorylcholine derivatives, these cells assemble inflammasomes and induce the release of IL-1 family cytokines while retaining viability [207]. The addition of IL-1 release coupled with the repertoire of TLR-dependent cytokines that normally occur during TLR activation renders these cells highly immunostimulatory and have therefore been described as hyperactive DCs [207]. Interestingly, the ability of living DCs to release IL-1 and TLR-dependent cytokines allows these hyperactive cells to induce more robust antigen-specific T-cell responses than are normally elicited by traditionally activated DCs [207]. At least two other studies have also recently reported stimulations that cause inflammasome-dependent IL-1β release in the absence of pyroptosis. These stimulations include responses to LPS in human and porcine monocytes and peptidoglycan in mouse macrophages [208,209]. In fact, much like our

group has demonstrated that using oxidized phospholipids as an adjuvant can induce stronger antigen-specific T-cell responses *in vivo*, a recent study revealed that peptidoglycan from a mutant strain of *Staphylococcus aureus* that is highly sensitive to degradation by the enzyme lysozyme can cause protective immunity against subsequent *S. aureus* infection through the generation of a memory T-cell response [210]. These studies raise an important question regarding the potential role of the inflammasome in licensing adaptive immunity and the potential applications of inflammasome activation toward next-generation vaccine development. In addition to stimulation-specific resistance to pyroptosis, several studies also note cell type-specific responses downstream of inflammasome activation. Neutrophils treated with ATP activate the NLRP3 inflammasome or infected with *Salmonella* activate the NLRC4 inflammasome resulting in release IL-1 family members without signs of lysis such as lactate dehydrogenase release [211,212]. In a majority of papers that link inflammasome activation to adaptive immunity, the link stems from release of IL-1β and IL-18. The role of cell lysis in secretion of these cytokines is intimately connected to inflammasome activation where secretion of these cytokines occurs secondary to cell lysis [12,29,213]. It is interesting to note that while membrane permeability seems to be a requisite step for IL-1 release, pyroptosis can be prevented by preventing osmotic lysis with glycine buffering with marginal effect on IL-1 release [29,214–216]. With the knowledge that membrane permeability seems to be required for IL-1β release and cleavage of GSDMD by inflammatory caspases-1/-11 causes large pore formation in the plasma membrane, one could speculate that GSDMD pores may facilitate IL-1 release from living cells [25–28,215]. GSDMD-independent mechanisms of IL-1 release likely exist, as strongly pyroptotic stimuli do not cause IL-1 release at acute time points in GSDMD KO macrophages, although these macrophages can undergo secondary necrosis after longer stimulations [23]. These recent studies change the paradigm of cell lysis concomitant with IL-1β and IL-18 secretion, and may reveal the relative roles cellular lysis and pro-inflammatory cytokines play in informing a subsequent immune response.

While the role of hyperactive APCs in adaptive immunity needs further exploration, it is worth considering whether the activities of current adjuvants may depend on this novel cell activation state. For example, a major adjuvant in human vaccines is aluminum hydroxide (alum), a particulate that activates the NLRP3 inflammasome in phagocytes through rupture of lysosomal compartments [103,217–219]. Consequently, alum causes the release of cleaved IL-1β and IL-18 from macrophages by a caspase-1-dependent process [220]. During alum-dependent responses *in vivo*, DAMPs, such as oxidized lipids described above, are likely released from dying cells. Indeed,

DAMPs have already been implicated in alum adjuvanticity, as alum-dependent responses depend on more than just release of pro-inflammatory cytokines. Alum-mediated release of DNA during cell death and permeabilization of lysosomes that release cathepsins within cells influence protective immunity [221,222]. These released DAMPs may act with any available PAMPs that might also be present to hyperactivate DCs and influence the development of T cell-mediated immunity. Alternatively, it is possible that adjuvants can be engineered to specifically introduce oxidized lipids that supplement the adjuvants already present in these vaccines, as a means of promoting more effective T-cell responses.

Further studies are needed to characterize the relative roles of lytic cell death and release of cellular antigens and DAMPs from the release of pro-inflammatory cytokines in the context of adjuvants.

Inflammasomes and cancer

Inflammasome signaling may also contribute to immune responses in the context of cancer. A clear role of inflammasome protection from cancer has been observed in the gut, as inflammasomes are necessary components for maintenance of an intact barrier [223–226]. Mice deficient for components of the inflammasome such as ASC, NLRP3, and NLRP6 are more susceptible to dextran sulfate sodium-induced colitis, highlighting that inflammasomes can limit chronic inflammation in the gut through production of IL-18 [223,227]. NLRP6 in hematopoietic cells prevents increased susceptibility to dextran sulfate sodium-induced colitis and tumorigenesis [225]. NLRP3 has also been confirmed to play a role in preventing colitis-induced tumorigenesis [226]. An additional study links the NLRC4 inflammasome to control of tumorigenesis through prevention of chronic inflammation in the colon [228]. The link of inflammasomes to adaptive immune control of tumorigenesis could stem from the production of IL-18 in response to invading gut bacteria. One study has shown that reduction of IL-18 through loss of NLRP3 leads to a reduction of IFN-γ production in the gut [224]. IL-1β may serve to be pro-tumoral depending on the context as IL-1β has been shown to promote tumor invasiveness [229,230]. In addition, the release of angiogenic factors downstream of IL-1R signaling may serve to promote early tumor formation [230,231]. In a mouse model of breast cancer, blocking IL-1R signaling through administration of the IL-1Ra prevents tumor-associated macrophage and myeloid-derived suppressor cell accumulation in tumors as well as preventing metastases. Adding to the context-specific efficacy of inflammasome signaling on adaptive immune responses to tumors, studies have implicated NLRP3 activation in tumors with accumulation of myeloid-derived suppressor cells that can suppress adaptive

immune responses to tumors [232,233]. Anti-tumor effects of inflammasome signaling may be important for the adaptive immune response to late stage tumors after cancer treatment. After chemotherapy, DCs activate the NLRP3 inflammasome and prime tumor-specific CD8 T cells leading to an anti-tumor adaptive immune response [234]. Engineered tumor cells that express bacterial flagellin cause a robust CD8 T-cell response against the tumors that depends on synergistic activation of TLR5 signaling and the NLRC4 inflammasome [235]. The role of inflammasome signaling in generating an adaptive immune response against tumors deserves additional studies, as the current literature would suggest that inflammation downstream of the inflammasome could be anti-tumoral or pro-tumoral depending on the particular tumor and intervening therapy.

Adaptive immune control of inflammasome signaling

A majority of the inflammasome biology literature centers around inflammasome activation in traditional innate phagocytes, such as macrophages and DCs. Recent studies have sought to identify if inflammasomes can be active in other cell types. In response to radiation, one study has found inflammasome assembly to occur in adaptive immune cells, such as T and B cells. Inflammasome assembly in these cells proceeds independently of NLRP3 [236]. A recent study also using radiation identifies AIM2 to be the responding receptor to DNA damage in the gut of irradiated mice in epithelial and bone marrow-derived cells [237]. This study also highlights the role of cell death in tissue inflammation, in contrast to the role of inflammasome-mediated cytokines such as IL-1β and IL-18 [237]. One group has identified that HIV infection can result in inflammasome assembly and pyroptosis in CD4 T cells [140,141]. This group determined that abortive infections with HIV causes assembly of inflammasomes in lymphoid, but not blood, CD4 T cells that leads to eventual cell lysis [140,141,238]. These studies suggest that T cells are able to form functional inflammasomes in response to viral infections, and that pyroptosis may contribute to CD4 T-cell decline in the context of HIV infection [140,141]. It is interesting to note that CD4 T cells from humans seem to constitutively express pro-IL-1β, whereas many myeloid cells require a NF-κB-activating stimulus to express this caspase-1 substrate [141]. Another recent study has also identified T cell-intrinsic inflammasome assembly downstream of TCR engagement in coordination with complement receptor signaling [239]. T cell-intrinsic ASC is required for Th17-mediated pathology in EAE. This study suggests that T cells with active inflammasomes can release active IL-1β downstream of caspase-8. This IL-1β may serve as an autocrine survival signal to these pathogenic T
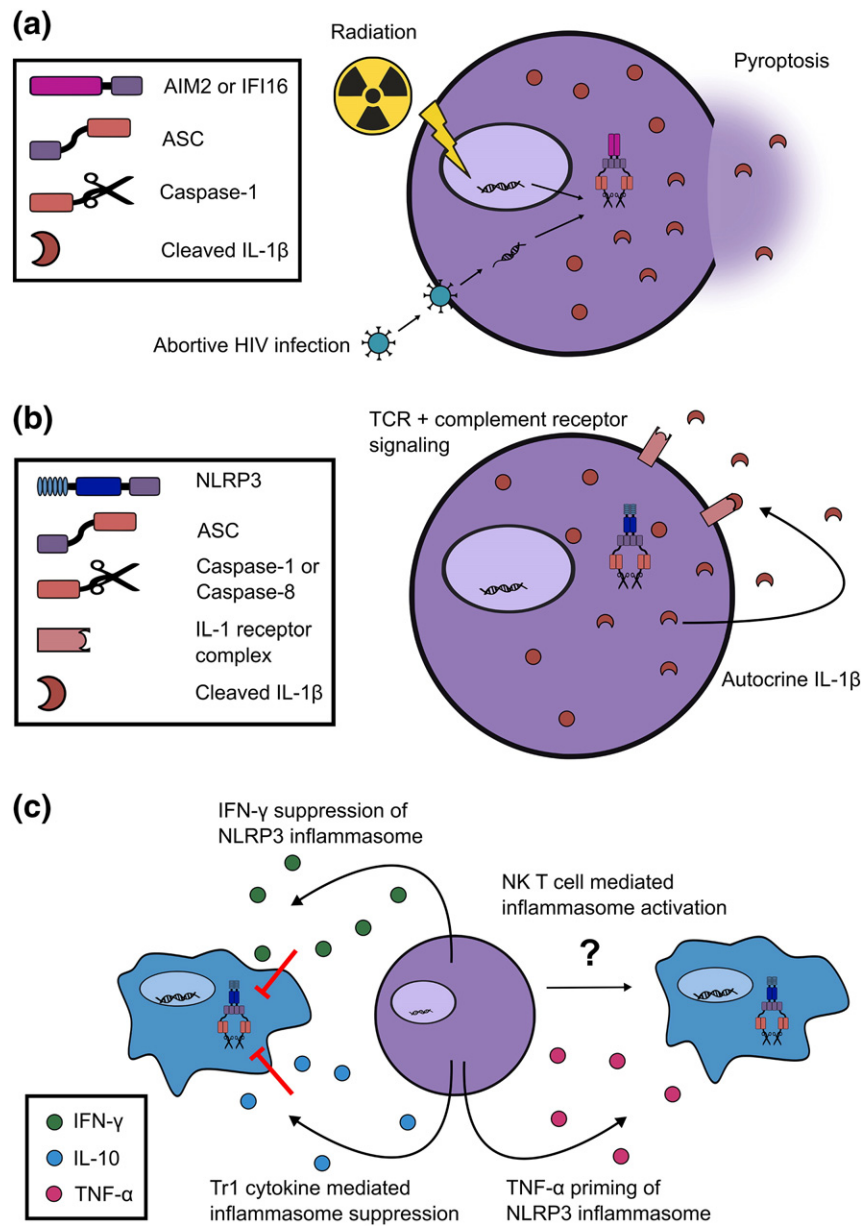
Fig. 2. T-cell regulation of cell-intrinsic and -extrinsic inflammasomes. (a) DNA sensing pathways activate after abortive HIV infection and radiation therapy, which causes assembly of the IFI16 and AIM2 inflammasomes, respectively in T cells. Abortive HIV infection proceeds to pyroptosis in human lymphoid-derived CD4 T cells, but not in blood CD4 T cells. These cells have high levels of pro-IL-1β prior to infection and thus are able to release cleaved IL-1β after inflammasome assembly. Radiation therapy induces DNA damage that results in AIM2 inflammasome assembly and pyroptotic cell death in many cell types including T cells in mice. (b) TCR signaling likely upregulates pro-IL-1β and NLRP3, and intracellular complement receptor signaling results in ROS production and inflammasome assembly. T cell-intrinsic ASC is required for Th17-mediated pathology in EAE. These T cells might release cleaved IL-1β downstream of ATP sensing from other necrotic cells, and this IL-1β may provide autocrine signaling promoting pathogenic Th17 cell survival. (c) T cells capable of secreting IFN-γ may inhibit NLRP3 inflammasome signaling. Tr1 cells secrete IL-10 and other suppressive cytokines. These cytokines have been shown to inhibit the assembly of the NLRP3 inflammasome. NK T cells can induce IL-1β release from monocytes by an ill-defined mechanism. NK T cells can also release TNF-α that can serve as a priming signal for the NLRP3 inflammasome.

cells [191]. NLRP3 is also required for the production of Th2 cytokines, although this appears to be inflammasome independent [240]. These recent findings suggest that inflammasomes and their components can operate within adaptive immune cells such as T cells.

Adaptive immune cells also can influence inflammasome assembly in other cell types. Innate-like NK T cells also coordinate inflammasome activation in traditional phagocytes. Activated human NK T cells trigger IL-1β processing and secretion from monocytes in the absence of significant lysis in a caspase-8-dependent mechanism [241]. Co-culture of iNK T cells with monocytes was sufficient to prompt release of IL-1β, and this phenotype was not recapitulated with transwell experiments suggesting that NK T cell and monocytes must contact each other [241]. Moreover, NK T cells positively regulate priming of the NLRP3 inflammasome through release of TNF-α that acts to upregulate IL-1β and NLRP3 in macrophages in response to α-galactosylceramide treatment [242]. As IL-1β can activate proliferation and effector functions from different T-cell subsets, the concept of adaptive immune induction of IL-1β secretion from either T cells or innate immune cells is intriguing. Further studies are required to determine the molecular events that determine T cell-initiated inflammasomes in cell-intrinsic and -extrinsic situations. The adaptive immune compartment has also been implicated in negative regulation of inflammasome signaling. IFN-γ can negatively regulate NLRP3 inflammasome activation [243], although IFN-γ has also been reported to increase caspase-11 expression leading to non-canonical inflammasome signaling in the context of bacterial infection [244]. In addition, adaptive immune cells such Tr1 cells can produce suppressive cytokines, such as IL-10, that can negatively regulate NLRP3 inflammasome signaling [245]. Interestingly, another study shows that direct contact from effector and memory CD4 T cells can abolish NLRP1 and NLRP3 inflammasome activation in macrophages [246]. These negative regulatory mechanisms downstream of adaptive immune activation could serve as a way to diminish innate immune responses after the adaptive immune system has started responding to a threat. Figure 2 summarizes how T cells can regulate the assembly of inflammasomes in cell-intrinsic contexts as well as in other cell types. Further studies should investigate whether T cells can survive inflammasome activation like has been recently described for traditional phagocytes as this could serve as an autocrine survival factor particularly for CD8, Th17, and certain γδ T cells.

Concluding remarks

The role of inflammasome-associated IL-1 family cytokines in shaping adaptive immune responses is now well established in regard to differentiation of Th17 cells and promoting effector functions of Th1 cells and CD8 T cells. The additional role that cell lysis may play after inflammasome activation through the release of additional DAMPs and self-antigens deserves further study, especially in the context of

driving autoimmunity. The separation of pyroptosis and unconventional protein secretion downstream of inflammasome activation also remains to be elucidated in terms of molecular determinants that contribute to this cell fate decision. The role of the adaptive immune system in regulation of inflammasome activation requires further study to determine the extent to which adaptive immune cells contribute to inflammasome signaling in infectious and sterile contexts.

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