Molecular Immunology 107 (2019) 142–164

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Inflammasome activation and Th17 responses

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ARTICLE INFO

Keywords:
Inflammasomes
IL-1β
IL-1R
T-helper cells
Th17
IL-17

ABSTRACT

Immune sensing of exogenous molecules from microbes (e.g., pathogen-associated molecular patterns) and nonmicrobial molecules (e.g., asbestos, alum, and silica), as well as endogenous damage-associated molecular patterns (e.g., ATP, uric acid crystals, and amyloid A) activates innate immunity by inducing immune-related genes, including proinflammatory cytokines, which further facilitate the development of adaptive immunity. The roles of transcriptional responses downstream of immune sensing have been widely characterized in informing adaptive immunity; however, few studies focus on the effect of post-translational responses on the modulation of adaptive immune responses. Inflammasomes activated by the previously described endo- and exogenous stimuli autocatalytically induce intracellular pro-caspase-1, which cleaves the inactive precursors of interleukin-1β (IL-1β) and IL-18 into bioactive proinflammatory cytokines. IL-1β and IL-18 not only contribute to the host defense against infections by activating phagocytes, such as monocytes, macrophages, dendritic cells, and neutrophils, but also induce T-helper 17 (Th17)- and Th1-mediated adaptive immune responses. In synergy with IL-6 and IL-23, IL-1β activates IL-1 receptor (IL-1R) signaling to drive the differentiation of IL-17-producing Th17 cells, which not only play critical roles in host protective immunity to infections of bacteria, fungi, and certain viruses but also participate in the pathology of inflammatory disorders and tumorigenesis. Consequently, targeting inflammasomes and IL-1/IL-1R signaling may effectively improve the treatment of Th17-associated disorders, such as autoinflammatory diseases and cancers, thereby providing novel insights into drug development.

1. Introduction

Primed $CD4^+$ T cells can be differentiated into distinct subsets of effector T cells, such as T-helper 1 (Th1), Th2, and Th17 cells, which are defined by their functional capabilities and secretion patterns of specific cytokines (Sandquist and Kolls, 2018; Wacleche et al., 2017). Th1 cells restrict intracellular pathogen infection by enhancing the phagocytosis process, while Th2 cells mainly control extracellular pathogens and activate plasma B cells. Th1 cells are amplified by interferon (IFN)-γ and interleukin-12 (IL-12). In contrast, Th2 cells are developed via IL-4. The source of differentiating cytokines originates from the host reaction towards microbial antigens, parasitic antigens, or allergens (Sandquist and Kolls, 2018; Wacleche et al., 2017). In the past decade, Th17 cells have been identified as another $CD4^+$ T helper subset acting on the host immune system that Th1 or Th2 subsets are not well applicable to (Korn et al., 2009). Cytokines and the relevant pathways responsible for Th17 cell differentiation have been elucidated. Th1 and Th2 cells exert their function via interferon (IFN)-γ and IL-4, respectively. In contrast, Th17 cells are characterized by the secretion of cytokines, such as IL-17 A, IL-17 F, IL-21, and IL-22. IL-17 A and IL-17 F form a homodimer or heterodimer to activate their receptor IL-17R, which is widely distributed across the host body (Korn et al., 2009). Thus, Th17 cells are closely associated with the systematic immune reactions, which activate a broad range of host defense against various microbial infections and are involved in autoimmune and autoinflammatory diseases. IL-1β, IL-6, and IL-23 play critical roles in Th17 cell differentiation and expansion. IL-1β binds to the IL-1 receptor (IL-1R, also known as IL-1R1) to activate IL-IR signaling, which is critical for the early differentiation of Th17 cells (Chung et al., 2009). Accordingly, a proinflammatory environment with IL-1β plus other initiating cytokines orchestrates Th17 responses, which lead to pathogen clearance, autoimmunity, and anti-tumor immunity (Korn et al., 2009; Sandquist and Kolls, 2018).

IL-1β exhibits a strong proinflammatory characteristic and is involved in certain autoimmune diseases. In contrast to other proinflammatory cytokines, such as IL-6, IFNs, and TNF-α that have a signal peptide for secretion, pro-IL-1β does not have a signal peptide (Monteleone et al., 2015). Prior to secretion, pro-IL-1β must be

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https://doi.org/10.1016/j.molimm.2018.12.024
Received 18 November 2018; Received in revised form 20 December 2018; Accepted 21 December 2018
Available online 08 February 2019
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processed into mature IL-1β, which is released under the strict control of inflammasomes, a large complex assembled from several proteins (Monteleone et al., 2015). Inflammasome pathways are involved in the detection of invading pathogens and other danger signals to initiate both innate and adaptive immunity. Inflammasome activation-induced secretion of IL-1β can drive the early differentiation of Th17 cells (Chung et al., 2009; Mills et al., 2013). Numerous studies have indicated that inflammasome activation is closely related to Th17 differentiation. Stimuli of inflammasome pathways such as pathogenic toxins and endogenous danger signals that activate inflammasome pathways and induce IL-1β secretion, also robustly favor Th17 cell differentiation via IL-1/IL-1R signaling, which establishes a direct link between inflammasome activators and Th17 responses (Mills et al., 2013). Thus, there is an inflammasome–IL-1/IL-1R–Th17 axis in the host immune response. This review updates the knowledge regarding inflammasome activation and its related Th17 responses.

2. Inflammasomes and IL-1β secretion

2.1. Inflammasome activation

Th17 differentiation is driven by IL-1β, which is regulated by NF-κB, activator protein 1 (AP1), or the MAPK signaling pathway at the mRNA level, while its maturation and secretion at the protein level are controlled by inflammasome activation.

As a multifunctional proinflammatory cytokine, IL-1β is tightly regulated by various pathways, as well as endogenous and environmental conditions. Normally, priming signals that induce *pro-IL-1β* mRNA transcription are required for the activation of some inflammasome pathways. Most mammalian cells do not have a ready pool of pro-IL-1β. In contrast, pro-IL-18, which is processed similarly by inflammasome activation, is constitutively expressed; therefore, the priming signals may not be the same requirements (Patel et al., 2017). Pathogen-associated molecular patterns (PAMPs), such as LPS, can activate TLRs-MyD88/TRIF signaling, which leads to the activation and translocation of NF-κB family proteins into the nucleus to promote *pro-IL-1β* transcription. During bacterial infections, the nucleotide-binding domain and leucine-rich repeat containing protein (NLR) family members NOD1 and NOD2 respond to intracellular γ-D-Glu-mDAP and Muramyl dipeptide (MDP), respectively, through RIP-like-interacting CLARP kinase (RICK) and CARD9 for the upregulation of NF-κB and MAPK controlled proinflammatory genes, particularly *pro-IL-1β*. The C-type lectin receptors, such as Dectin-1, Dectin-2, and macrophage-inducible C-type lectin (Mincle), also function as pattern recognition receptors (PRRs) by recognizing carbohydrate ligands from microbial pathogens to activate NF-κB family proteins through Syk-/CARD9-dependent pathways, which leads to the upregulation of inflammatory cytokines including *pro-IL-1β* (Kingeter and Lin, 2012). In addition to PAMPs, endogenous danger-associated molecular patterns (DAMPs), such as reactive oxygen species (ROS), oxidized low-density lipoprotein (oxLDL), saturated fatty acids (SFAs), amyloids, advanced glycation end-products (AGEs), and cholesterol crystals also prime *pro-IL-1β* transcription (Patel et al., 2017).

Inflammasomes are large intracellular multiprotein complexes activated by certain physiological and pathogenic stimuli including infectious agents and changes in cell homeostasis, which play an essential role in protective immunity against pathogens and the pathogenesis of autoimmune and autoinflammatory disorders (Sharma and Kanneganti, 2016). Inflammasome activation is typically organized and complicated by four parts: the inflammasome sensors including some PRRs; an adaptor protein referred to as apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC); the cysteine-dependent aspartate-directed protease named caspase-1 (formerly known as IL-1 converting enzyme); and the downstream substrates, including pro-IL-1β and pro-IL-18. The inflammasome sensors can be directly or indirectly activated by exogenous or endogenous danger signals, which lead to ASC activation. ASC forms a large multimeric complex referred to as 'ASC speck' in the cytoplasm. Oligomerized or nucleated ASC, in turn, recruits pro-caspase-1 into the complex, which is then converted into active p10/p20 subunits by autocatalytic cleavage (Sharma and Kanneganti, 2016). The active caspase-1 subunits induce the proteolytical process of the substrates pro-IL-1β/pro-IL-18, as well as the cleavage of pore-forming protein gasdermin D (GSDMD), which contributes to IL-1β/IL-18 secretion and pyroptosis, a particular inflammatory form of rapid cell death (Evavold and Kagan, 2018; Sharma and Kanneganti, 2016). To date, three types of inflammasome sensors have been identified, including NLRs, absent in melanoma 2 (AIM2)-like receptors (ALRs), and Pyrin, which are featured by inducing caspase-1 activation referred to as the canonical inflammasomes. Apart from the canonical pathways, noncanonical inflammasomes have recently been identified, which require the direct sensing of intracellular LPS by mouse caspase-11 or its human orthologues caspase-4/5 during inflammatory responses.

2.2. NLR inflammasomes

2.2.1. NLRs

NLRs are characterized as containing a central nucleotide-binding and oligomerization domain (NOD) that mediates self-oligomerization. Most NLRs have a variable N-terminal domain (NTD) that mediates downstream protein-protein interaction, and a C-terminal leucine-rich repeat (LRR) domain involved in stimuli sensing (Fig. 1) (Malik and Kanneganti, 2017). According to the NODs, they are further subdivided into NLRPs or NLRCs which possess a pyrin domain (PYD) or caspase activation and recruitment domain (CARD), respectively. Although there are 22 NLRs in humans and at least 34 members in mice, only NLRP1, NLRP3, and NLRC4 are well characterized as inflammasome sensors that can form a platform for recruiting and activating ASC and/or pro-caspase-1. Other NLRs, such as NLRP6, NLRP9b, and NLRP12, are also proposed to form inflammasomes, whereas their roles as inflammasome sensors have not been well clarified (Malik and Kanneganti, 2017). It is of substantial interests to determine whether the last NLRs participate in inflammasome activation and the corresponding stimuli. The inflammasome sensors without CARD, such as NLRP3, AIM2, and Pyrin, require the CARD containing protein ASC as an adaptor to recruit pro-caspase-1, while NLRP1 and NLRC4, which possess a CARD, can directly form an inflammasome complex with pro-caspase-1 (Fig. 1) (Malik and Kanneganti, 2017).

2.2.2. NLRP1 inflammasome

NLRP1 is the first NLR identified to form inflammasome complexes as a cytoplasmic sensor that induces IL-1β/IL-18 secretion (Martinon et al., 2002). Humans only have one NLRP1 that contains a PYD, NOD, LRR domain, a function-to-find domain (FIIND), and a C-terminal CARD. In contrast, mice have three NLRP1 orthologs, including NLRP1A, NLRP1B, and NLRP1C, which share a similar domain organization of human NLRP1. Notably, mouse NLRP1 lacks the N-terminal PYD found in human NLPR1 and instead harbors a region referred to as NR100 (Fig. 1). *Bacillus anthrax* derived anthrax lethal toxin, which consists of a protective antigen (PA) for host cell binding and a lethal factor (LF) translocated into the cytoplasm through a PA-formed channel, can cleave NLRP1B by LF within the N-terminal NR100 domain to activate NLRP1B (Broz and Dixit, 2016). After cleavage, NLRP1B induces inflammasome assembly by recruiting pro-caspase-1 directly through its CARD domain, which leads to inflammasome activation, subsequent IL-1β/IL-18 secretion, and pyroptosis (Fig. 2) (Moayeri et al., 2012; Muehlbauer et al., 2007). N-terminal proteolytic cleavage by (LF) is also observed in rat NLRP1, mouse NLRP1A, and human NLRP1, which suggests that proteolysis is a conserved mechanism of NLRP1 inflammasome activation (Chavarria-Smith et al., 2016). However, lethal toxin does not induce the cleavage of human NLRP1 or lead to NLRP1 inflammasome activation (Moayeri et al.,

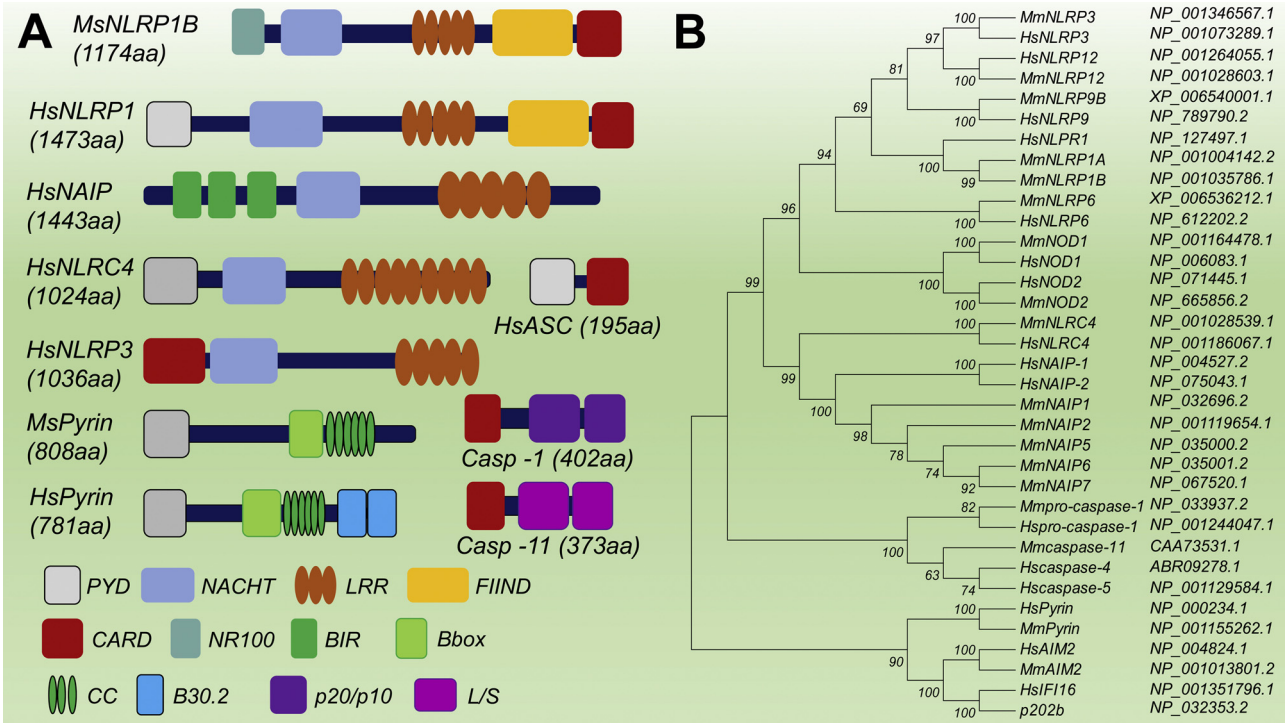

Fig. 1. Domain organization (A) and phylogenetic tree analysis (B) of inflammasome-related proteins. The phylogenetic tree was constructed with MEGA7 using the neighbor-joining method with 1000 bootstrap tests. The numbers at nodes indicate bootstrap values. Ms, Mus musculus; Hs, Homo sapiens; Casp, caspase; L/S, large/small subunits.

2012; Muehlbauer et al., 2007). MDP was suggested to be an agonist of human NLRP1 (Faustin et al., 2007); however, it was later shown to be a mistake. Thus the ligand for human NLRP1 remains unclear (Yu et al., 2018). Notably, NLRP1 that contains a CARD can directly interact with the CARD of pro-caspase-1 without the requirement of ASC to assemble the inflammasome complex. Although NLRP1 inflammasome assembly is generally ASC-independent, some groups have demonstrated that ASC was necessary for NLRP1 inflammasome formation and pro-caspase-1 autoproteolysis. Moreover, ASC can promote NLRP1 inflammasome activation-induced IL-1β secretion when the lethal toxin is not sufficiently high (Fig. 2) (Man and Kanneganti, 2015).

The cleavage of NLRP1B within the N-terminal NR100 domain is essential and sufficient to induce NLRP1B activation. In addition, the proteolytic cleavage within the FIIND domain is required for inflammasome assembly (Sharma and Kanneganti, 2016). NLRP1 is the most prominent inflammasome sensor in the human skin. The PYD and LRR domains of human NLRP1 exert autoinhibitory functions, which are essential in maintaining NLRP1 as an inactive monomer. Gain-of-function mutations in these domains increase self-oligomerization by disrupting the PYD and LRR domains, leading to spontaneous activation of NLRP1 inflammasome and IL-1R signaling, which causes skin inflammatory and cancer susceptibility syndromes (Place and Kanneganti, 2018; Zhong et al., 2016). Mouse NLRP1B serves as a substrate of lethal toxin. The lethal toxin can induce NLRP1B cleavage to relieve the self-autoinhibition conferred by the NR100/LRR domain and induce conformational changes, which lead to NLRP1B oligomerization and inflammasome activation. *Toxoplasma gondii* infection induces NLRP1 inflammasome activation in both rat and mouse models; however, there are no detectable products of NLRP1 processing and cleavage (Cirelli et al., 2014; Gorfu et al., 2014), which suggests that the mechanism of NLRP1 activation in this context might be different from previously posited. Thus, the proteolysis or cleavage of NLRP1 may not be a prerequisite for inflammasome assembly. Moreover, it cannot exclude that NLRP1 cleavage is still important in this context as the potential cleavage products of NLRP1 are too low or unstable to be detected. Thus, to reconcile this discrepancy, a thorough analysis of the potential NLRP1 cleavage products is required (Ewald et al., 2014). The proteasome is essential for NLRP1B activation, and its degradation activity is specific to NLRP1B instead of other inflammasome sensors (Muehlbauer et al., 2007; Wickliffe et al., 2008). Thus, another potential mechanism for NLRP1B inflammasome activation is that lethal toxin or other microbial pathogens, such as *T. gondii*, cause the cleavage or degradation of other substrates, which serve as negative regulators of the NLRP1B inflammasome. Furthermore, NLRP1B auto-processing within the FIIND might also contribute to NLRP1B maturation, thus acting as a licensing event of NLRP1B inflammasome activation (Broz and Dixit, 2016). Among all NLRs, NLRP1 is characterized by a FIIND that displays an auto-proteolytic ability (Fig. 1). Autoproteolytic cleavage generates a C-terminal fragment of NLRP1 that contains the CARD, which subsequently results in pro-caspase-1 recruitment and inflammasome activation (Yu et al., 2018). FIIND domains of both human and mice NLRP1 show similar auto-proteolysis, and genetic disruption of this domain leads to impaired NLRP1 self-oligomerization of and reduced pro-caspase-1 activation, which demonstrates that FIIND auto-proteolytic cleavage contributes to NLRP1 inflammasome activation. Moreover, the auto-proteolytic cleavage site in the FIIND domain of zebrafish NLRP1 is evolutionarily conserved, and the lack of the FIIND domain will abolish its capability of activating zebrafish inflammatory caspases and classical NLRP1 inflammasome activation (Li et al., 2018).

NLRP1 plays a critical role in defending against infections of bacteria, such as *B. anthracis*, and protozoans, such as *T. gondii*. Genetic variants of NLRP1 are susceptible to infections of microbial pathogens, including leprosy, bacterial meningitis, human papillomavirus, and *Toxoplasma* (Yu et al., 2018). NLRP1 variants are also associated with various autoinflammatory diseases, such as vitiligo, Addison's disease, type 1 diabetes, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), celiac disease, giant cell arteritis, systemic sclerosis-related fibrosing alveolitis, rheumatoid arthritis (RA), psoriasis, preeclampsia, partial seizures, and Alzheimer's disease (AD), as well as cancers, such as asbestos-associated mesothelioma and

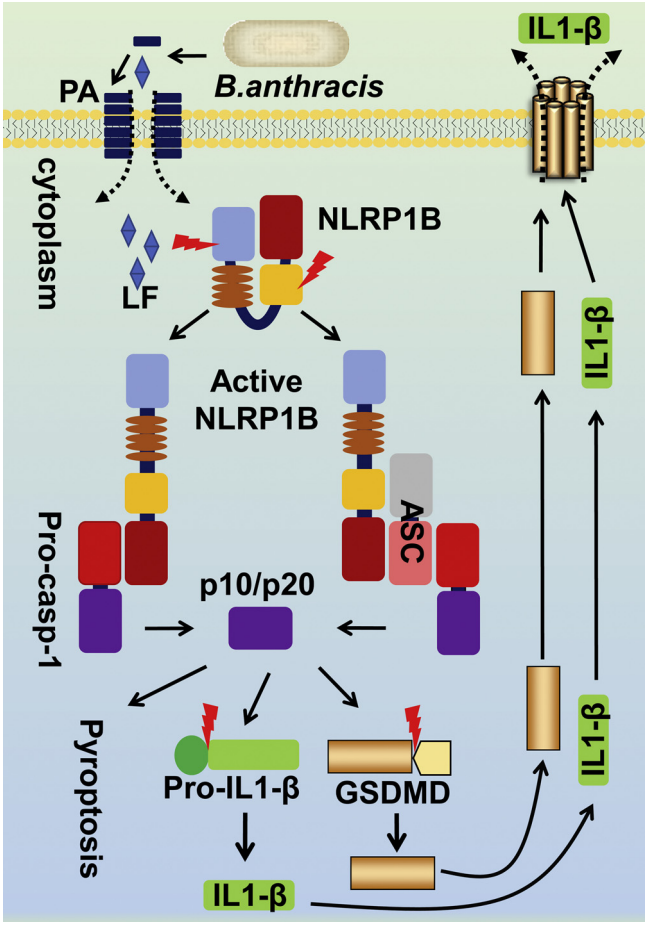

Fig. 2. NLRP1B inflammasome. Anthrax lethal toxin released from *B. anthracis* is a well-characterized NLRP1B inflammasome stimulator. Lethal toxin is a bipartite toxin containing one protective antigen (PA) and one lethal factor (LF). LF is translocated into the cytoplasm through PA-formed channel. NLRP1B inflammasome is activated upon the cleavage of N-terminal NR100 domain by LF, leading to IL-1β/IL-18 secretion and pyroptosis. Autoproteolytic processing within the FIIND domain also contributes to NLRP1B activation. There are two pathways driving IL-1β/IL-18 secretion and pyroptosis. When activated by a high dose of LF, NLRP1B directly binds to pro-caspase-1 via its CARD domain, which is sufficient to induce caspase-1 activation and inflammasome activation without the requirement of ASC. In response to the low dose of LF, NLRP1B recruits ASC and forms intracellular 'ASC speck' via homotypic CARD interactions. Then, active caspase-1 subunits p10/p20 process pro-IL-1β/1L-18 into maturation form, leading to IL-1β/IL-18 release and pyroptosis.

malignant melanoma (Yu et al., 2018). NLRP1-associated SNPs contribute to aberrant IL-1β/IL-18 secretion in host tissues. Notably, NLRP1-associated diseases in humans and mice mainly affect keratinocyte-adjacent tissues in the skin and eyes, where NLRP1 is significantly higher expressed in keratinocytes than other inflammasome sensors. Furthermore, keratinocyte cell lines that express the mutant NLRP1 have increased IL-1β production and pyroptosis. Aside from skin, NLRP1 is also expressed in the brain and mucosal surfaces (Yu et al., 2018). A gain-of-function mutation of mouse NLRP1A, Q593 P, results in a caspase-1–/IL-1β–mediated systemic inflammatory disease and a spontaneous inflammasome activation with sustained IL-1β/IL-18 secretion and pyroptosis. These mice exhibit a significant loss of hematopoietic progenitors because of cell-intrinsic pyroptosis that further affects their capacity to differentiate into mature myeloid cells (Masters et al., 2012). However, the specific activator and mechanisms that regulate the NLRP1A inflammasome remain unclear.

2.2.3. NLRP3 inflammasome

2.2.3.1. Canonical pathway for NLRP3 inflammasome activation. NLRP3, one of the most studied inflammasome sensors, is also referred to as cryopyrin for its genetic association with a hereditary autoinflammatory disease called cryopyrin-associated periodic syndromes (CAPS) featured by local inflammatory symptoms such as skin rashes and episodes of fever (Hoffman et al., 2001). NLRP3 is also implicated in the pathogenesis of other autoinflammatory diseases, such as arthritis, gout, diabetes, obesity, and AD (Guo et al., 2015). NLRP3 consists of an N-terminal PYD, a central NOD, and a C-terminal LRR domain (Fig. 1). In contrast to other NLRs, such as NLRP1, NLR family apoptosis inhibitory proteins (NAIPs), and NLRC4, NLRP3 is not constitutively expressed, and its protein amounts are not sufficient for inflammasome activation in most cell types (Aubert et al., 2016). Thus, NLRP3 inflammasome activation is a two-step process through two signals: signal 1 is the priming step that upregulates the expression of *NLPR3*, *pro-IL-1β*, and other inflammasome components through NF-κB or activator protein 1 (AP1) pathways; signal 2 is the triggering step that initiates NLRP3 inflammasome assembly by various stimuli, which leads to caspase-1-mediated IL-1β/IL-18 secretion and pyroptosis (Fig. 3).

Among NLRs, NLRP3 is featured by being activated via a set of diverse stimuli, which can be divided into three classes. Class one includes certain PAMPs, such as microbial nucleic acids and bacterial pore-forming toxins that derive from viruses, bacteria, fungus, or protozoan pathogens; class two contains various DAMPs, such as ATP, uric acid (UA) crystals, and amyloid A; class three comprises particulate matters from the outside environment, such as silica, asbestos, and alum (Man and Kanneganti, 2015). Some of these stimuli have previously been demonstrated to be sources that induce severe autoimmunity, e.g., allergic asthma is closely related to serum amyloid A (SAA); certain autoinflammatory diseases are associated with DAMPs, such as ATP (Ather et al., 2011). Stimuli of signal 2 that act as agonists of NLRP3 inflammasome have not yet been shown to directly interact with NLRP3. Accordingly, it is proposed that another secondary trigger upstream of NLRP3 may mediate the interaction with NLRP3 (Fig. 3), e.g., DHX33, an RNA helicase, can bind cytoplasmic viral dsRNA and then directly interacts with NLRP3 to promote the inflammasome assembly and activation (Mitoma et al., 2013). To now, there is no unified mechanism and common model established for NLRP3 inflammasome activation. Several potential mechanisms by these stimuli are proposed as follows (Mangan et al., 2018).

Four mechanisms have been proposed to explain how NLRP3 are assembled into inflammasome complex (Fig. 3). The 'pore formation and ion perturbation model' is featured by pore-forming on the plasma membrane and dysregulation of opening channels or ionophores, which stimulates an efflux of potassium ions (K^+), leading to NLRP3 oligomerization and activation (Munoz-Planillo et al., 2013). Perturbations of other ions, such as chloride (Cl^-) and calcium (Ca^{2+}), also have an influence on NLRP3 activation (Tang et al., 2017; Yifei Zhang et al., 2018). Furthermore, the high level of extracellular potassium inhibits NLRP3 inflammasome activation via disruption of the membrane potential (Yifei Zhang et al., 2018). NLRP3 inflammasome was also activated via the destabilization of lysosome caused by phagocytosis of particulate crystals and aggregates, which is referred to as the 'lysosomal disruption model' featured by the release of cathepsins after lysosomal disruption (Orlowski et al., 2015). Released cathepsins further interact with and activate NLRP3. These NLRP3 activators can be divided into three categories: (1) endogenous particles formed under pathological conditions, such as uric acid (Martinon et al., 2006) and cholesterol crystals (Duewell et al., 2010); (2) crystals from the outside environment, such as silica and asbestos crystals (Dostert et al., 2008); (3) amyloid polypeptides (Halle et al., 2008), some of which are relevant to a series of autoinflammatory diseases. The third model proposes that intracellular metabolic perturbation activates NLRP3 inflammasome. GB111-NH2 and CL097, which interfere with the TCA

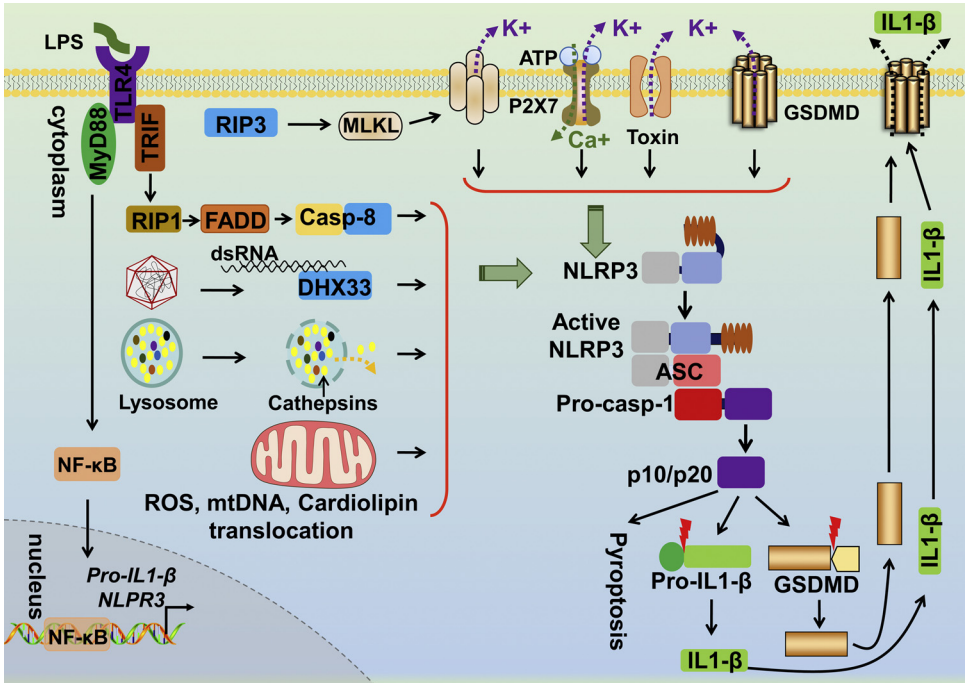

Fig. 3. NLRP3 inflammasome. Priming signal is a requisite step for NLRP3 inflammasome activation. TLR ligands such as LPS improve the expression of pro-IL-1β and NLRP3 via MyD88/TRIF–NF-κB signaling. In signal 2, several mechanisms have been proposed to trigger NLRP3 inflammasome activation. In pore formation and ion perturbation model, NLRP3 inflammasome is activated by K^+ efflux and $Ca2^+$ influx caused by pore-forming channels of P2X7, GSDMD, MLKL, or bacterial toxins. Crystals and aggregates such as uric acid, cholesterol crystals, silica, asbestos crystals, etc. activate NLRP3 through lysosomal disruption model which induces the release of cathepsins. Other stimuli including ROS, mtDNA, cardiolipin, and viral dsRNA also trigger NLRP3 inflammasome assembly, leading to the IL-1β/IL-18 release and pyroptosis. Necroptosis mediated MLKL pores and caspase-8 activation also results in NLRP3 inflammasome activation.

cycle and mitochondrial complex I, respectively, induce NLRP3 assembly (Sanman et al., 2016). N-acetylglucosamine generated after bacterial peptidoglycan degradation in phagosomes is sensed through the inhibition of glycolytic enzyme hexokinase, which subsequently leads to the dissociation of hexokinase from mitochondrial voltage-dependent anion channels, resulting in NLRP3 inflammasome activation via the disruption of the glycolytic pathway and mitochondrial function. Glycolytic inhibitors and specific metabolic perturbations that affect hexokinase function and localization also activate NLRP3 inflammasome. Potassium efflux and the loss of mitochondrial integrity may not participate in peptidoglycan-induced NLRP3 inflammasome activation, whereas mitochondrial DNA (mtDNA) release, ROS, and cardiolipin may contribute to these effects (Wolf et al., 2016). Furthermore, the dysregulation of mitochondria also causes NLRP3 inflammasome activation. The byproducts generated from dysregulated mitochondria, including ROS, oxidized mtDNA, and mitochondrial lipid cardiolipin, induce NLRP3 assembly, monitoring intracellular homeostasis. Moreover, irregular activities of mitochondria including mitophagy, mitochondrial fission, and fusion are also sensed by NLRP3 and induce inflammasome activation (Mangan et al., 2018).

One recent study identified common cellular signaling downstream of the stimuli sensing by NLRP3 and clarified how diverse stimuli lead to NLRP3 inflammasome activation (Chen and Chen, 2018). The trans-Golgi network (TGN) is disassembled into the dispersed TGN (dTGN) by different NLRP3 stimuli, which leads to the recruitment of NLRP3 to the dTGN through ionic bonding between the polybasic region of NLRP3 and negatively charged phosphatidylinositol-4-phosphate (PtdIns4P). Consequently, the dTGN serves as a scaffold for NLRP3 aggregation into multiple puncta. NLRP3 then interacts with ASC and induces ASC polymerization, which thereby leads to inflammasome activation. When the NLRP3-PtdIns4P interaction on the dTGN was interrupted, NLRP3 aggregation induced by different stimuli and downstream signaling were blocked. This NLRP3 activation mechanism indicates that the recruitment of NLRP3 to dTGN is an early and common cellular event for NLRP3 aggregation and activation, thereby explaining why NLRP3 can indirectly sense diverse stimuli and initiate inflammasome activation. This finding further supports that host cells can respond to various 'danger signals' by sensing the homeostasis of the cellular environment (Chen and Chen, 2018).

2.2.3.2. Noncanonical pathway for NLRP3 inflammasome activation. In addition to the previously discussed canonical model (refer to 2.2.3.1), there are other pathways that lead to NLRP3 inflammasome activation. The activation of caspase-11/4/5–dependent noncanonical inflammasomes can indirectly activate NLRP3 inflammasome (Yi, 2017). Noncanonical inflammasome activation results in the cleavage of GSDMD, which forms pores in the plasma membrane and further induces potassium efflux, as well as the cleavage of the cytoplasmic region of pannexin-1, causing the extracellular release of ATP and P2 X 7-pore forming, both of which ultimately lead to NLRP3 activation (Yi, 2017).

2.2.3.3. Alternative pathway for NLRP3 inflammasome activation. Two signals are required for NLRP3 inflammasome activation. Signal 1 is a priming signal that elevates the transcription of *pro-IL-1β* and *NLRP3*. In signal 2, stimuli such as a high concentration of ATP induce NLRP3 inflammasome assembly. However, freshly obtained human peripheral blood monocytic cells (PBMCs) can secret IL-1β induced by stimuli in signal 1, such as TLR4 agonists, including LPS, lipopeptides, and lipoteichoic acid, without the requirement of signal 2 (Netea et al., 2009; Piccini et al., 2008). The release of IL-1β is limited to monocytes instead of primary macrophages, dendritic cells (DCs), or THP-1 cells, which require signal 2 for inflammasome activation and IL-1β secretion. Mechanistically, freshly obtained PBMCs possess constitutively activated caspase-1 (Netea et al., 2009). TLR4 agonists, such as LPS, cause the release of a high concentration of ATP into the extracellular milieu, which successively activates NLRP3 inflammasome via P2X7 pore forming-mediated potassium release. While macrophages or DCs are unable to release ATP into the extracellular environment, signal 2 is required for NLRP3 inflammasome activation and IL-1β processing. Genetic screening indicated that TLR4–TRIF–RIP1–FADD–caspase-8 signaling is required for the activation of the alternative NLRP3 inflammasome pathway following stimulation of TLR4 agonist (Gaidt et al., 2016). Notably, this alternative pathway for NLRP3 inflammasome activation is species-specific and only exists in human and porcine monocytes.

2.2.3.4. Necroptotic pathway for NLRP3 inflammasome activation. Another nonclassical pathway for NLRP3 activation is

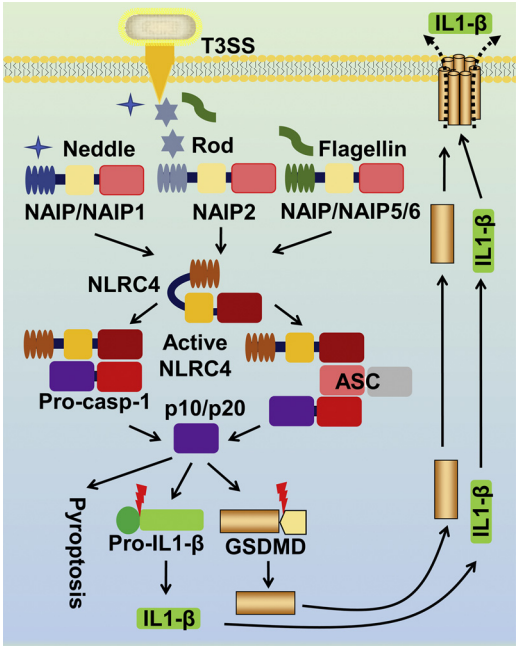

Fig. 4. NAIP-NLR4C inflammasome. Certain bacteria, mostly gram-negative bacteria, inject virulence factors into the cytoplasm of host cells via type III secretion system. Besides virulence factors, bacteria conserved proteins including flagellin as well as needle and inner rod of T3SS are also injected into the cytoplasm. NLRC4 inflammasome responds to these bacterial proteins via NAIPs such as NAIP1, NAIP2, and NAIP5/6, resulting in IL-1β/IL-18 release and pyroptosis. NLRC4 activates caspase-1 and induce inflammasome assembly via both ASC-dependent and -independent manners.

mediated by RIP3/mixed-lineage kinase domain-like protein (MLKL)-dependent necroptosis. Similar to pyroptosis, necroptosis is also a proinflammatory form of cell death characterized by RIP3 activation and MLKL phosphorylation. Phosphorylated MLKL forms pores on the plasma membrane, which causes necroptosis and potassium efflux, thus leading to NLRP3 inflammasome activation (Humphries et al., 2015). However, RIP3 also promotes NLRP3 inflammasome and IL-1β secretion independent of RIP3 kinase activity, MLKL, and necroptosis, which is closely related to the activation of TRIF and caspase-8 (Lawlor et al., 2015).

2.2.4. NAIP-NLRC4 inflammasome

In contrast to other inflammasome sensors, such as NLRP3, Pyrin, and AIM2 that recruit pro-caspase-1 via ASC, NLRC4 is characterized by an N-terminal CARD, which can directly interact with the CARD of pro-caspase-1 and activate this protease, thereby enabling inflammasome activation, IL-1β/IL-18 secretion, and pyroptosis (Fig. 4). Nevertheless, the presence of ASC enhances NLRC4-induced pro-caspase-1 activation. Activated NLRC4 also associates and colocalizes with ASC after bacterial infection. Although the expression of NLRC4 is upregulated by stimuli such as TNF-α and genotoxic stress-induced P53 activation, the basal expression level of NLRC4 in epithelial and immune cells is sufficient for inflammasome activation.

NLRC4 inflammasome is mainly activated by intracellular bacteria, such as *Pseudomonas aeruginosa*, *Vibrio cholera*, *Salmonella enterica serovar* Typhimurium, and *Yersinia pseudotuberculosis*. Specifically, NLRC4 inflammasome is activated by two bacterial conserved elements: flagellin and type III secretion system (T3SS) apparatus, which both contribute to bacterial pathogenesis. Thus, NLRC4 is closely related to bacterial clearance. Flagellin from bacteria, such as *P. aeruginosa* and *V. cholera*, are used as a mobility force to colonization or invade the host immune system. Due to its widespread presence in various bacterial species and the abundant expression on the cell surface, the detection of flagellin as a bacterial invasion signal is beneficial for host cells. T3SS of gram-negative bacteria by which virulence factors are injected into host cytoplasm is another common target of the NLRC4 inflammasome. T3SS basically consists of three components, including a base, a needle, and a translocon located at the tip of the needle (Galan et al., 2014). The rod, an α-helix protein, connects the base part of the cell membrane and the needle structure that extends beyond the outer membrane of the bacteria. The needle serves as a hollow channel for the injection of bacteria virulent factors into the cytoplasm of host cells. T3SS shows significant sequence homology with the flagellin system; thus, it was hypothesized that T3SS evolved from flagellum. Interestingly, NLRC4 cannot directly interact with these inflammasome activators; instead, NAIPs serve as the direct sensor of flagellin and T3SS to induce NLRC4 inflammasome assembly and activation (Fig. 4) (Kofoed and Vance, 2011; Zhao et al., 2011). There are seven NAIP orthologs (NAIP1-7) in mice, while only a single NAIP in humans. Needle and inner rod subunits of T3SS are recognized by NAIP1 and NAIP2, respectively, whereas NAIP5 and NAIP6 sense cytoplasmic flagellin (Kofoed and Vance, 2011; Rayamajhi et al., 2013; Yang et al., 2013; Zhao et al., 2011). Human NAIP recognizes needle and flagellin via two different alternative-splicing forms; however, it cannot detect rod (Yang et al., 2018).

Similar to other NLRs, NLRC4 maintains inactive in normal conditions by a winged-helix domain together with an NOD that stabilizes NLRC4 in a closed conformation, which results in an autoinhibitory structure (Tenthorey et al., 2014). The LRR domain also contributes to maintaining this inactive form by sterically contacting with the NOD which inhibits NLRC4 oligomerization (Diebolder et al., 2015). Thus, both inhibition mechanisms make NLRC4 inactive in the absence of ligands. The cryo-EM structure shows that the LRR domain must be rotated to make NLRC4 suitable for the active oligomer form (Sharma and Kanneganti, 2016). Upon binding with bacterial ligands, NAIPs are activated by forming the different NAIP-ligand complex, which interacts with the auto-inhibited NLRC4 and provides a platform for self-oligomerization and inflammasome assembly (Yang et al., 2018).

NLRC4 inflammasome is well-known to induce IL-1β/IL-18 secretion and pyroptosis. In addition, NLRC4 activation induces the change of actin polymerization and eicosanoid storm characterized by prostaglandins and leukotrienes (Man et al., 2014) (von Moltke et al., 2012). Gain-of-function mutations of NLRC4 are closely related to autoinflammation and enterocolitis (Canna et al., 2014; Kitamura et al., 2014; Romberg et al., 2014). The role of NLRC4 in the defense against pathogen infection has been thoroughly investigated in mouse models, while its role in human autoinflammatory diseases requires further investigation.

2.3. ALR inflammasome

2.3.1. ALRs

AIM2 is a member of AIM2-like receptors (ALRs), which typically consist of an N-terminal PYD and a C-terminal hematopoietic interferon-inducible nuclear protein with 200-amino acid repeat (HIN200) domain (Fig. 1) (Lugrin and Martinon, 2018). There are four members of ALRs in humans including AIM2, IFI16, IFIX, and MNDA, whereas at least 13 members exist in mice, such as Aim2/p210, p204, and p202 (Wang et al., 2018).

2.3.2. AIM2 inflammasome

The basal expression of AIM2 is predominately observed in the spleen, small intestine, and peripheral blood. Similar to NLRP3 inflammasome components, the AIM2 expression is upregulated after immune stimulations. Most ALRs, including AIM2, can be upregulated by the NF-κB and IFN pathways, which defined the early studies of ALR associated with inflammation and immunity (Lugrin and Martinon, 2018). Intracellular detection of invading bacteria and viruses activates type I IFNs, which subsequently induce AIM2 expression. Microbial or synthesized dsDNA is recognized by the cytoplasmic cGAS sensor and

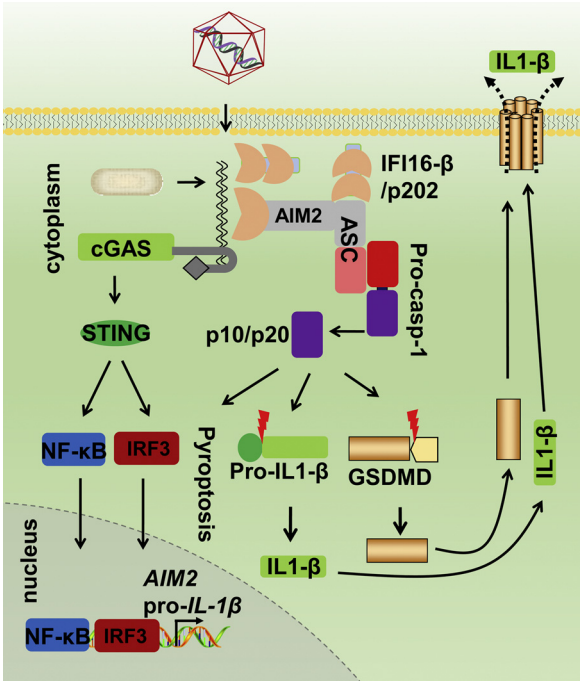

Fig. 5. AIM2 inflammasome. Activation of AIM2 inflammasome requires a priming step via the recognition of intracellular dsDNA derived from bacteria or viruses by cGAS-STING pathway, leading to the transcription of *pro-IL-1β* and *AIM2*. AIM2 specifically recognizes intracellular DNA and induces inflammasome assembly, leading to IL-1β/IL-18 secretion and pyroptosis in an ASC-dependent manner. Moreover, IFI16-β, an isoform of IFI16 can interact with AIM2 and sequester cytoplasmic DNA from AIM2-mediated DNA sensing, leading to the prevention of AIM2 oligomerization, ASC clustering, and subsequent inflammasome activation.

activates the NF-κB and IFN pathways via the adaptor protein STING, which acts as a priming signal by elevating the expression level of AIM2 and other inflammasome components. In contrast to the stimuli in signal 1 of NLRP3 inflammasome, such as LPS, dsDNA not only activates the priming signal for AIM2 upregulation through the cGAS-STING pathway but also directly induces simultaneous post-translational assembly of AIM2 inflammasome (Lugrin and Martinon, 2018).

AIM2 contains a PYD that mediates protein-protein interactions and an HIN200 domain responsible for dsDNA binding. AIM2 recognizes cytoplasmic DNA derived from bacteria and virus via the HIN200 domain. Upon DNA sensing, AIM2 interacts with ASC via a homotypic PYD interaction; ASC, in turn, recruits pro-caspase-1 through CARD-CARD interactions, which leads to AIM2 inflammasome assembly, IL-1β/IL-18 secretion, and pyroptosis (Fig. 5) (Wang et al., 2018). AIM2 plays an essential role in the defense against numerous viruses, such as vaccinia virus, mouse cytomegalovirus, and herpes simplex virus 1 (HSV-1), bacteria, such as *Francisella tularensis* and *Listeria monocytogenes* (Kim et al., 2010; Rathinam et al., 2010), and fungi, such as *Aspergillus fumigatus* (Hayward et al., 2018). To fight back, the HSV-1 tegument protein VP22 inhibits AIM2 inflammasome activation by directly interacting with AIM2 to prevent its oligomerization, a critical initial step in inflammasome assembly. A mutant virus HSV-1ΔVP22 that lacks VP22 strongly activates AIM2 inflammasome and induces IL-1β secretion. In AIM2 knockout cells, HSV-1ΔVP22 does not activate inflammasome or induce IL-1β secretion. VP22 also blocks AIM2 inflammasome activated by cytoplasmic dsDNA, such as poly(dA-dT). The viral yields of HSV-1ΔVP22 are largely diminished in wild-type (WT) mice, which clearly restored in AIM2-deficient animals (Maruzuru et al., 2018).

In addition to playing a critical role in sensing microbial DNA and defending against invading pathogens, AIM2 also activates the immune system by detecting aberrant self-DNA, such as damaged DNA, genomic DNA released into the cytoplasm following the loss of nuclear envelope integrity, self-DNA secreted by exosomes, DNA from apoptotic or necrotic bodies, and DNA generated during disease development, such as SLE and tumor (Lugrin and Martinon, 2018). For example, AIM2 senses radiation-induced DNA damage in the nucleus, where the inflammasome complex is formed and pyroptosis is triggered (Hu et al., 2016). The side effects caused by some chemotherapies, such as irinotecan (CPT-11) and gastrointestinal tract toxicity, are mediated by AIM2-dependent pyroptosis and excessive inflammation (Lugrin and Martinon, 2018). The detection of self-DNA may play a positive role in the defense against diseases, such as cancer, as well as lead to uncontrolled immune responses that contribute to autoimmune and autoinflammatory diseases (Wang et al., 2018).

2.3.3. *IFI16 inflammasome*

In contrast to AIM2 that localizes in the cytoplasm, the other three human ALRs, including IFI16, IFIX, and MNDA, are primarily localized in the nucleus. During viral infection, IFI16 shuttles between the cytoplasm and nucleus, enabling IFI16 to function as both a nuclear and cytoplasmic DNA sensor. IFI16, which contains one N-terminal PYD and two C-terminal HIN200 domains, is also involved in inflammasome activation as a nuclear DNA sensor by interacting with ASC and inducing inflammasome assembly following herpes virus infection (Wang et al., 2018). In addition, IFI16 plays a vital role in the pathogenesis of acquired immunodeficiency syndrome (AIDs) by detecting the truncated fragments of DNA derived from HIV-1 in the cytoplasm of $CD4^+$ T cells, which causes cell depletion through inflammasome activation-induced pyroptosis (Doitsh et al., 2014; Monroe et al., 2014).

In mice, the activity of AIM2 inflammasome is negatively regulated by another ALR member referred to as p202 that only has two HIN200 domains but lacks PYD. A novel human IFI16 isoform named IFI16-β has a similar domain structure of mouse p202 and performs as a functional equivalent to p202 by exerting an inhibitory effect on AIM2 inflammasome (Fig. 5). IFI16-β interacts with the HIN domain of AIM2 to prevent AIM2 oligomerization and ASC clustering. IFI16-β has a higher dsDNA affinity than AIM2; thus, it sequesters cytoplasmic DNA and prevents AIM2-mediated DNA sensing, leading to inflammasome inhibition. Interestingly, AIM2 and different IFI16 isoforms are upregulated in the PBMCs of SLE patients, which suggests a role of ALRs in SLE pathogenesis (Wang et al., 2018).

2.4. *Pyrin inflammasome*

Pyrin is a recently identified inflammasome sensor, which is associated with an autoinflammatory disease referred to as familial Mediterranean fever (FMF) with the syndrome of episodic fever and joint inflammation. In addition to FMF, Pyrin also associates with other autoinflammatory diseases, such as Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND), mevalonate kinase deficiency (MKD) also called hyper IgD syndrome (HIDS), mevalonate aciduria (MA), and the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) (Heilig and Broz, 2018). Pyrin is predominately restricted in immune cells, including neutrophils, monocytes, and DCs; its expression is induced by PAMPs, such as LPS, and cytokines, including IFN-γ, TNF-α, IL-4, and IL-10 (Heilig and Broz, 2018). Human Pyrin consists of the N-terminal PYD, a B-box zinc finger domain, a coiled-coil (CC) domain, and the C-terminal B30.2/SPRY domain. In contrast, mouse Pyrin lacks the B30.2/SPRY domain (Fig. 1).

Because the PYD of Pyrin interacts with NLRP3 and NLRC4, it was originally thought to be a regulator of NLR inflammasome (Chae et al., 2011), while a later study demonstrated that Pyrin alone is sufficient to act as an inflammasome sensor (Xu et al., 2014). Pyrin cannot directly sense PAMPs; however, it is activated by microbial infection caused-perturbation of cellular homeostasis defined as 'homeostasis-altering

molecular processes' that lead to the inactivation of RhoA GTPase. Pyrin inflammasome is activated after sensing the modified RhoA GTPase by bacteria toxins, including TcdB from *Clostridium difficile*, VopS from *Vibrio parahemolyticus*, IbpA from *Histophilus somni*, PT from *Bordetella pertussis*, and C3 from *Clostridium botulinum* (Xu et al., 2014). The bacteria toxin-mediated RhoA GTPase modification includes adenylation, glucosylation, deamination, and ADP ribosylation, which lead to RhoA GTPase inactivation and Pyrin inflammasome activation, representing a universal signature of Pyrin sensing and the activation mechanism (Aubert et al., 2016; Just et al., 1995; Yarbrough et al., 2009). Although the modification is essential for Pyrin inflammasome activation, the direct interaction between RhoA GTPase and Pyrin has not been detected, and the consequences of the modification and the intermediary steps involved in this process remain elusive. Subsequent studies have indicated the mechanism of how inactivation of RhoA GTPase leads to Pyrin inflammasome activation (Gao et al., 2016; Park et al., 2016; Van Gorp et al., 2016). Under resting conditions, Pyrin is phosphorylated at S242 to maintain an inactive form by RhoA serine-threonine kinases protein kinase N1 and 2 (PKN1/2). The phosphorylated Pyrin binds to 14-3-3ε, a member of phosphoserine-binding proteins, which maintains Pyrin as an inactive state (Fig. 6). Following the inactivation of RhoA GTPase by bacteria toxin-mediated modification, the activities of the RhoA serine-threonine kinases PKN1/2 are inhibited, which leads to decreased phosphorylation of Pyrin and its dissociation from 14-3-3ε. For example, TcdB induces Pyrin dephosphorylation at S242. Thus, the inactive Pyrin associated with 14-3-3ε is relieved, and the released Pyrin subsequently binds to ASC and induces inflammasome assembly, leading to IL-1β/IL-18 secretion and pyroptosis. Mutation at the phosphorylation site S242 of Pyrin attenuates 14-3-3ε binding, which causes Pyrin-related autoinflammation associated with neutrophilic dermatosis (Masters et al., 2016). As a countermeasure, *Yersinia* spp. evolves the strategy to evade Pyrin inflammasome by secreting the virulence factor YopM to recruit and activate PKN1/2 kinase, which leads to increased Pyrin phosphorylation and decreased Pyrin activation (Fig. 6) (Chung et al., 2016; Ratner et al., 2016). To date, the detailed mechanisms that control Pyrin phosphorylation, dephosphorylation, and subsequent nucleation events remain unclear. Furthermore, cytoskeleton dynamics are also an important regulator of Pyrin activation. For example, Colchicine, which maintains microtubule integrity, reduces the symptoms of FMF patients (Goldfinger, 1972). However, whether microtubule dynamics serve as a direct trigger of Pyrin or only a regulator downstream of Pyrin activation remains elusive.

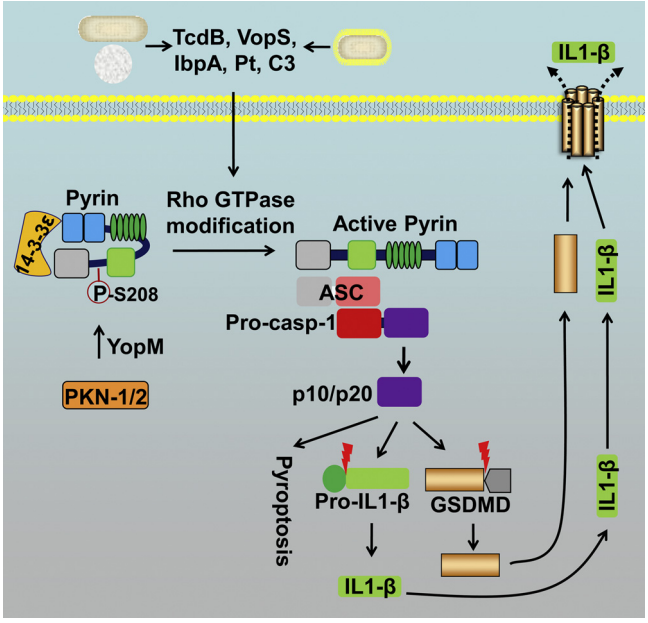

Fig. 6. Pyrin inflammasome. In normal condition, Pyrin is phosphorylated and associated with 14-3-3ε to maintain an autoinhibition state. The phosphorylation of Pyrin is kept by RhoA serine-threonine kinase PKN-1/2 which is furtherly controlled by RhoA GTPase. Bacterial toxins such as TcdB, IbpA, VopS, Pt, and C3 cause the inactivation of RhoA GTPase by a series of modification. Thus, the activities of PKN1/2 are suppressed, leading to decreased phosphorylation of Pyrin and its dissociation from autoinhibition complex with 14-3-3ε. Released Pyrin interacts with ASC and pro-caspase-1 to form inflammasome complex, resulting in IL-1β/IL-18 secretion and pyroptosis. Antagonistically, bacterial toxin YopM recruits and activates PKN-1/2 for inhibition of Pyrin inflammasome to benefit its infection.

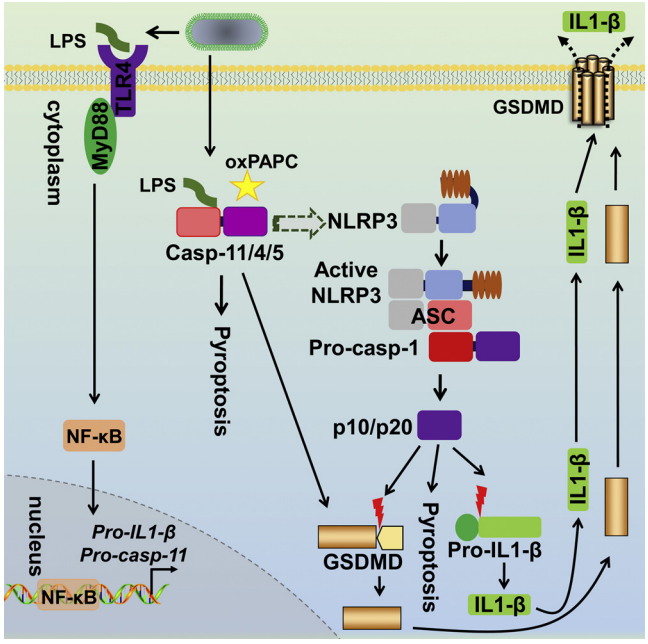

Fig. 7. Noncanonical inflammasome. Activation of noncanonical inflammasome requires a priming step. Extracellular TLR ligands such as LPS induces the transcription of *pro-IL-1β* and *pro-caspase-11* through TLR4–MyD88–NF-κB pathway. Intracellular LPS released by gram-negative bacteria or intracellular oxPAPC can be directly detected by caspase-11/4/5, leading to cleavage of GSDMD and pyroptosis. Active caspase-11/4/5 also induces the activation of noncanonical NLRP3 inflammasome and IL-1β/IL-18 secretion.

2.5. Noncanonical inflammasomes

The noncanonical inflammasomes are activated after the sensing of intracellular LPS by mouse caspase-11 or its human counterpart caspase-4/5, which subsequently induces oligomerization of LPS–pro-caspase-11/4/5 complexes, resulting in IL-1β/IL-18 secretion and pyroptosis in macrophages and monocytes (Fig. 7) (Yi, 2017). The scaffolds of caspase-11/4/5–mediated noncanonical inflammasomes have different and unique characteristics compared with those of caspase-1–dependent canonical inflammasomes. The noncanonical inflammasomes are assembled independent of ASC; however, they rely on the direct interaction between pro-caspase-11/4/5 and LPS, which is accomplished by the binding of pro-caspase-11/4/5 CARD to the lipid A tail of LPS (Fig. 7). LPS specifically interacts with pro-caspase-11/4/5 and not with other caspases (Shi et al., 2014). This pro-caspase-11/4/5–LPS complex, in turn, is oligomerized by homotypic CARD interactions. The activation of noncanonical inflammasomes cleaves GSDMD to generate N- and C-terminal fragments, which play an essential role in noncanonical inflammasome-dependent pyroptosis and IL-1β/IL-18 secretion (Fig. 7). Although activated caspase-11/4/5 does not directly cleave pro-IL-1β/pro-IL-18, the secretion of IL-1β/IL-18 is observed,

which may be explained by the positive effect of activated caspase-11/4/5 on NLRP3 inflammasome (Fig. 7). In response to intracellular LPS, caspase-11–mediated secretion of IL-1β/IL-18 requires the activation of NLRP3 inflammasome through an unknown mechanism to cleave pro-caspase-1 into an active form, which, in turn, induces the subsequent processing of pro-IL-1β/pro-IL-18. Caspase-1 knockout macrophages that express caspase-11 fail to secret IL-1β after intracellular LPS stimulation, which confirms an essential role for caspase-1 in IL-1β secretion (Kayagaki et al., 2011). In contrast, caspase-1 is not required for noncanonical inflammasome-induced pyroptosis.

Similar to canonical NLRP3 inflammasome, the activation of caspase-11-mediated noncanonical inflammasomes also requires two processing steps referred to as the priming signal and triggering signal in macrophages (Yi, 2017). In the priming signal, PAMPs, microbial pathogens, and other immune stimulators activate the NF-κB and IFN pathways to induce the transcription of *pro-caspase-11*, *pro-caspase-1*, *pro-IL-1β*, and other components required for noncanonical inflammasome activation. Only the priming signal cannot induce IL-1β secretion and pyroptosis in macrophages, which requires the triggering signal involved in the detection of intracellular LPS, oligomerization of the pro-caspase-11–LPS complex, and inflammasome assembly.

Prior to the identification of caspase-11/4/5 as cytoplasmic LPS sensors, the membrane-localized TLR4 had been recognized to sense extracellular LPS and activate the NF-κB and IFN pathways. The interaction between TLR4 and LPS is facilitated by the LPS-binding proteins CD14 and MD2, while whether other factors can cooperate with caspase-11/4/5 in the recognition of cytoplasmic LPS is unknown. The activation of the TLR4 pathway by LPS not only contributes to the priming signal of caspase-11 noncanonical inflammasome but also induces IL-1β release in human monocytes without the further requirement of a triggering signal.

Pro-caspase-11/4/5 also directly sense intracellular oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphatidylcholine (oxPAPC) to activate noncanonical inflammasome, triggering IL-1β/IL-18 secretion and/or pyroptosis via GSDMD cleavage (Fig. 7) (Zanoni et al., 2016). OxPAPC is one class of DAMPs released from dying cells and acts as an LPS mimic, which functions as newly identified ligands of caspase-11/4/5 to activate noncanonical inflammasome. oxPAPC triggers IL-1β secretion without pyroptosis in DCs and macrophages because GSDMD pores allow the release of IL-1β without cell death (Evavold et al., 2018; Zanoni et al., 2017). Following the activation of caspase-11, DCs display a hyperactive state with enhanced IL-1β secretion without pyroptosis. Interestingly, oxPAPC binds directly to the catalytic domain of caspase-11, which is distinct from LPS that binds to the CARD region. LPS and oxPAPC may initiate different function modes of DCs. When LPS binds with the CARD region of caspase-11, an antimicrobial mode of noncanonical inflammasome is activated, which exposes intracellular bacteria to neutrophils via pyroptosis. In contrast, when oxPAPC binds with the catalytic domain of caspase-11, an immunoregulatory mode is initiated, which aims to enhance T cell activation. oxPAPC also suppresses noncanonical inflammasome in macrophages by competing with LPS for caspase-11 binding, which leads to the suspension of LPS-induced pyroptosis, IL-1β secretion, and septic shock (Chu et al., 2018).

Caspase-11–dependent non-canonical inflammasomes also positively affect NLRP3–ASC–caspase-1 inflammasome, which is defined as a noncanonical NLRP3 inflammasome to distinguish from the canonical NLRP3 inflammasome (refer to 2.2.3.1). The activation mechanism of non-canonical NLRP3 inflammasome affected by caspase-11 has been proposed, in which caspase-11 might affect NLRP3 activators, such as potassium efflux. The non-canonical NLRP3 inflammasome is activated through the cleavage of GSDMD by active caspase-11 and subsequent GSDMD pore formation in the plasma membrane, which leads to potassium efflux that acts as an activator of NLRP3 inflammasome. Thus, cleaved GSDMD, as well as certain bacterial toxins, can induce pore formation to activate the NLRP3 inflammasome through the disruption of the cellular ion homeostasis. In addition, activated caspase-11 by cytoplasmic LPS cleaves pannexin-1 which forms an ion channel for potassium efflux (Yang et al., 2015). However, whether the potassium efflux acts as a bridge between caspase-11 activation and NLRP3 inflammasome remains elusive.

2.6. Other NLR inflammasomes

NLRP6, NLRP12, and NLRP9b also participate in inflammasome activation. NLRP6 and NLRP12 play an important role in intestinal homeostasis. NLRP6 may influence microbiota homeostasis, which is related to chemically-induced colitis and colitis-associated tumorigenesis. *NLRP6*$^{-/-}$ mice display an inflammatory sign of colitis, intestinal hyperplasia, and inflammatory cell recruitment, which may be explained by the sensing of signals from microbiota by NLRP6 in intestinal epithelial cells. Moreover, microbiota-derived metabolites modulate the intestine microenvironment via stimulating NLRP6 inflammasome activation (Wlodarska et al., 2014). NLRP6-mediated secretion of IL-18 plays an important role in the pathogenesis of dysbiotic microbiota accompanied by the fluctuation of taurine, spermine, and histamine (Levy et al., 2015). However, how NLRP6 controls IL-18 secretion is unclear. NLRP6 also recognizes viral RNA, regulates the MAPK proinflammatory pathway, (Anand et al., 2012) and activates type I/III IFNs (Wang et al., 2015). Whether these actions of NLRP6 are involved in inflammasome activation is of great interest. One recent study shows that gram-positive bacteria produced lipoteichoic acid (LTA), a molecule regarded as the counterpart biomolecule of lipopolysaccharide (LPS) of gram-negative bacteria because of their structural and immunological similarities, which acts as the activator of NLRP6. Stimulated by cytoplasmic LTA or gram-positive bacterium *L. monocytogenes*, NLRP6 recruits caspase-11 and caspase-1 via ASC to form the inflammasome complex, leading to the processing of caspase-11, which then promotes caspase-1 activation and IL-1β/IL-18 maturation in macrophages. NLRP6$^{-/-}$ and Casp11$^{-/-}$ mice show decreased bacterial loads, impaired IL-18 secretion, and reduced susceptibility to *L. monocytogenes* infection, while the administration of recombinant IL-18 to these mutant animals restored their susceptibility to bacterial infection. Therefore, NLRP6 can sense cytoplasmic LTA and induce inflammasome activation and IL1-8 secretion, which may exacerbate systemic gram-positive pathogen infection (Hara et al., 2018).

Similar to NLRP6, NLRP12 also participates in inflammasome activation and plays a role in the resistance to *Yersinia pestis* and *Plasmodium* infection (Ataide et al., 2014; Grenier et al., 2002; Vladimer et al., 2012). NLRP12 was originally identified to maintain intestinal homeostasis via the suppression of noncanonical NF-κB pathway–mediated proinflammatory signaling. *NLRP12*$^{-/-}$ mice are susceptible to colitis and colorectal tumorigenesis due to excessive NF-κB and ERK activation (Zaki et al., 2011). Moreover, NLRP12 dampens the proinflammatory pathway and antimicrobial peptides during *S. typhimurium* infection, which is a leading cause of food poisoning (Zaki et al., 2014). NLRP12 not only inhibits inflammation by itself but also promotes specific commensals that can prohibit gut inflammation. *NLRP12*$^{-/-}$ mice exhibit perturbation of microbiota, which induces decreased diversity of the microbiome, resulting in the lack of protective gut commensal strains and the enrichment of colitogenic strains. NLRP12 may also reduce high-fat diet (HFD)-induced obesity by maintaining beneficial microbiota (Chen et al., 2017; Truax et al., 2018). NLRP12 has an influence on experimental autoimmune encephalomyelitis (EAE) in mouse models by acting as a negative regulator during T-cell receptor (TCR) activation (Gharagozloo et al., 2018; Lukens et al., 2015). Overall, NLRP6 and NLRP12 are responsible for intestinal homeostasis via modulating both NF-κB signaling and inflammasome activation, whereas, the specific ligands and detailed mechanism for their activation remain elusive.

NLRP9b maintains intestinal homeostasis in defense against rotavirus infection in intestinal epithelial cells (Zhu et al., 2017). Rotavirus

is a dominant cause of severe gastroenteritis and diarrhea in children. It specifically infects the intestinal epithelial cells and evolves strategies to evade the IFN and NF-κB pathways (Graff et al., 2009; Sen et al., 2014). DHX9, an RNA helicase, acts as a viral dsRNA sensor and interacts with NLRP9b to activate ASC-dependent inflammasome activation, which results in caspase-1 activation, IL-1β/IL-18 secretion, and GSDMD-mediated pyroptosis. Similar to NAIPs-NLRC4 inflammasomes, the proximal sensor DHX9 directly senses rotavirus dsRNA and then interacts with and activates the inflammasome activator NLRP9b. DHX9 can unwind dsDNA, dsRNA, and DNA/RNA hybrids, and other forms of nucleic acids that may activate NLRP9b inflammasome. The genuine role of DHX9-NLRP9b inflammasome must be confirmed, and whether other members of RNA helicase contribute to inflammasome activation should be explored.

2.7. Effect of inflammasome activation

2.7.1. Pyroptosis and IL-1β/IL-18 secretion

Inflammasome activation results in two apparent downstream effects: pyroptosis and IL-1β/IL-18 secretion. Pyroptosis is executed by GSDMD, which is cleaved by active caspase-1 or caspase-11/4/5. Cleaved GSDMD subsequently forms membrane pores downstream of inflammasome activation. GSDMD has been detected in the esophagus, stomach, and skin, which is the potential site for pathogen entry into hosts, indicating a putative role in immune defense (Feng et al., 2018). The GSDMD C terminal domain interferes with the N-terminal domain (GSDMD-N), making GSDMD inactive under resting conditions (Kuang et al., 2017). Upon inflammasome activation, GSDMD is cleaved by active caspase-1 or caspase-11/4/5, which leads to the release of GSDMD-N (Shi et al., 2015). After release, GSDMD-N preferentially binds to the inner part of the plasma membrane and oligomerizes to form a 10–16-nm diameter of GSDMD pore, which causes pyroptosis and the passage of IL-1β with a diameter of 4.5 nm and IL-18 with a diameter of 5.0 nm (Feng et al., 2018; Kovacs and Miao, 2017; Shi et al., 2017). Moreover, GSDMD pore-mediated Ca^{2+} influx induces membrane repair by recruiting the endosomal sorting complexes required for transport (ESCRT) machinery to the damaged plasma membrane areas, thereby suppressing pyroptosis and IL-1β secretion. The inhibition of ESCRT machinery augments pyroptosis and GSDMD-dependent cytokine release. Thus, ESCRT machinery eliminates GSDMD pores by membrane repair, thereby restricting pyroptosis and limiting IL-1β secretion (Ruhl et al., 2018).

The secretion mechanisms of IL-1 family cytokines, including IL-1β/IL-18, are unique because they lack the signal peptide that commonly exists in other types of cytokines, such as TNF-α, and directs the secretion via an endoplasmic reticulum (ER)/Golgi-dependent mechanism. Prior to the finding of the GSDMD-mediated pore-forming mechanism for IL-1β/IL-18 secretion, vesicular and nonvesicular models had been proposed to mediate their secretion (Monteleone et al., 2015). Vesicular models include secretory lysosomes, multivesicular bodies and exosomes, microvesicle shedding, and secretory autophagy; and non-vesicular models contain direct translocation with or without membrane transporter and passive release during cell death (Monteleone et al., 2015). As previously discussed, IL-1β/IL-18 secretion accompanies inflammasome activation-induced GSDMD pore-forming and subsequent pyroptosis. *GSDMD*$^{-/-}$ macrophages are resistant to pyroptosis and fail to induce IL-1β release (He et al., 2015; Shi et al., 2015). However, IL-1β can be normally secreted from other cell types, such as neutrophils and monocytes, without a requirement of pyroptosis (Chen et al., 2014). In these conditions, GSDMD forms pores to induce IL-1β release without further undergoing pyroptosis because immune cells should maintain survival to accomplish their immune functions (Evavold et al., 2018).

2.7.2. Pyroptosis in immune response

Pyroptosis represents a general innate immune effector mechanism downstream of inflammasome activation triggered by microbial infection from teleost fish to mammals (Vincent et al., 2016; Fink and Cookson, 2005). Pyroptosis is a form of programmed inflammatory cell death induced by GSDMD-mediated pore formation on the plasma membrane, characterized by cell swelling, lysis, and the release of cellular contents, including DAMPs. Pyroptosis occurs in various cell types, including macrophages (Fink et al., 2008), DCs (Edgeworth et al., 2002), enterocytes (Sellin et al., 2014), and hematopoietic progenitors (Masters et al., 2012). However, monocytes and neutrophils are exempt from pyroptosis following inflammasome activation (Chen et al., 2014; Gaidt et al., 2016; Miao et al., 2010). Pyroptosis removes pathogen-infected cells, disrupts the pathogen replication niche, directly kills intracellular bacteria through pore-induced intracellular traps, acts as an alarm signal that recruits immune cells to the site of infection, and promotes the release of important proinflammatory cytokines (Jorgensen et al., 2016; Miao et al., 2010; Shi et al., 2017).

2.7.3. IL-1β/IL-18 secretion in immune response

IL-1β/IL-18 secreted after inflammasome activation induce neutrophils and macrophages to engulf pathogens, promote inflammatory cell recruitment, and further amplify inflammatory responses (He et al., 2016; van de Veerdonk et al., 2011b). Apart from its impact on innate immunity, inflammasome activation also initiates adaptive immunity through the modulation of T helper cell subsets, skewing development in favor of Th1 and Th7 cells (Evavold and Kagan, 2018; Mills et al., 2013). IL-1β secreted after inflammasome activation activates IL-1R signaling, which has a substantial influence on Th17 cell differentiation and related immune responses (Chung et al., 2009).

3. Inflammasome-derived Th17 responses

3.1. T helper cells

T cells, which belong to a group of leukocytes as an important part of adaptive immunity, originate from hematopoietic stem cells in the bone marrow and migrate to the thymus for maturation. Mature T cells exist as the naïve state prior to antigen exposure, which are precursors of effector and memory T cell subsets. Naïve T cells leave the thymus and navigate to circulate in the blood, secondary lymphatic organs, or peripheral tissues where they constantly survey for antigens. Antigen-presenting cells (APCs), such as DCs, process antigens into immunostimulatory peptides, present them on major histocompatibility complex (MHC) and display them at the cell surface. When encountering the peptide-MHC complexes, some naïve T cells are activated, multiplied clonally, and differentiated into effector T cells, such as cytotoxic T cells ($CD8^+$) and helper T cells ($CD4^+$) (Evavold and Kagan, 2018). Once pathogens are eliminated, most effector T cells die; however, a small pool of them form long-lived memory T cells, which can rapidly respond for antigen-specific reactivation when reinfection occurs (Omilusik and Goldrath, 2017).

Antigens processed by immunoproteasome are loaded on MHC I and presented to naïve cytotoxic T cells. Antigens processed by lysosomal degradation are loaded on MHC II and presented to naïve helper T cells (Evavold and Kagan, 2018). Cytotoxic T cells (also referred to as $CD8^+$ T cells) have a major role in direct recognition and killing of infected cells and tumor cells that present cognate antigen in the context of MHC I. $CD8^+$ T cells also secret instructive cytokines, such as IFN-γ, and are implicated in transplant rejection. Helper T cells (also known as $CD4^+$ T cells) help to regulate the activity of other immune cell types by secreting numerous cytokines, promoting B cell maturation into antibody-producing plasma cells, activating cytotoxic T cells, and maximizing the bactericidal activity of phagocytes, such as macrophages (Evavold and Kagan, 2018). Thus, they participate in infectious diseases, immune disorders, and tumorigenesis. The importance of helper T cells can be assessed from its infection by HIV, which may cause the loss of functional $CD4^+$ T cells and lead to AIDS.

Helper T cells exert an instrumental role in orchestrating adaptive immune responses through differentiating into specialized effector subsets. During the initial encounter with APCs, the activation and differentiation of naïve $CD4^+$ T cells are regulated by antigen recognition, contextual co-stimulation of APCs, and the specific cytokines secreted by DCs and macrophages in response to antigenic stimulation. Certain cytokines, some of which arise from inflammasome activation, stimulate the differentiation of naïve $CD4^+$ T cells into helper T subsets, such as Th1, Th2, Th17, regulatory T cells (Tregs), and follicular helper T cells (Tfh), which are characterized by distinct functions and cytokine profiles (Cannons et al., 2013).

Th1 cells activate innate immune cells, such as macrophages, by producing IFN-γ, which are particularly important for combating immune evasive intracellular viruses and bacteria. Th2 cells produce IL-4 and IL-13, stimulate mast cells, eosinophils, and basophils and invoke antibody production in B cells; thus, they are crucial for barrier protection and neutralizing extracellular toxins and pathogens, such as helminths and other extracellular parasites. Th2 cells are also implicated in pathological responses, such as allergy. Th17 cells are essential for controlling fungal and bacterial infections, which are characterized by the expression of the RAR-related orphan receptor gamma t (RORγt) transcription factor and the production of IL-17 A, IL-17 F, IL-21, and IL-22. Th17 cells stimulate a broad range of cell types to recruit neutrophils to infection sites, thereby playing a pivotal role in immune defense. Th17 cells are also involved in the induction and maintenance of autoimmune and inflammatory diseases. In addition to these effector T-cell subsets, naïve $CD4^+$ T cells form Tregs with the help of TGF-β and IL-2. Tregs characterized by the expression of the transcription factor Foxp3 are typically recognized as a specialized subset of $CD4^+$ T cells. Tregs suppress exacerbated immune responses to antigens to preserve immune tolerance (Evavold and Kagan, 2018). IL-21 and IL-6, as well as transcription factor B-cell lymphoma 6 (Bcl-6), promote Tfh cell development. Tfh cells are distinguished from effector Th cells based on cell-surface markers, such as programmed cell death-1 (PD-1) and inducible T-cell costimulator (ICOS). Tfh cells help B cells to generate germinal centers (GC) and develop long-term protective humoral immunity (Cannons et al., 2013).

3.2. Th17 differentiation

3.2.1. Transcriptional regulation

The differentiation of Th17 cells from naïve $CD4^+$T cells undergoes three stages in transcriptional regulation. In the immediate phase, classic Th17 transcription factors including *STAT3*, *IRF4*, and *BATF*, cytokines *IL-21* and *LIF*, and the cytokine receptors *IL-2Ra* and *IL-23R* are upregulated. In an intermediate phage, the transcript of the *Rorc* gene that encodes RORγt, which is recognized as a Th17 lineage-specific master regulator, is induced (Zhang et al., 2017). In the late phase, the phenotypic cytokines of Th17 cells, such as *IL-17A*, *IL-17 F*, *IL-21*, and *IL-22*, are increased, while other T cell subset cytokines are suppressed (Ramirez et al., 2017; Yosef et al., 2013). Overall, multiple waves of gene transcription occur to coordinate the dynamic regulatory program of Th17 differentiation in sequential developmental stages.

The activation of STAT3 is a critical step in Th17 differentiation. STAT3 directly regulates the transcription of multiple target genes, including various Th17-related inflammatory cytokines and receptors, such as *IL-17A*, *IL-17 F*, *IL-1R*, and *IL-23R*, as well as Th17 lineage-specific transcription factors such as *Rorc*, *BATF*, and *IRF4* (Wacleche et al., 2017). Apart from upregulating Th17 differentiation-specific genes, STAT3 also improves the expression of genes that are crucial for $CD4^+$ T cell survival and proliferation. Furthermore, it also regulates the balance between Th17 cells and Tregs by inhibiting Treg differentiation (Bettelli et al., 2006; Durant et al., 2010). STAT3 not only affects differentiation, proliferation, and maturation of Th17 cells but also influences epigenetic modifications, such as histone modification during differentiation. For example, STAT3 binds to the intergenic regions of IL-17 A and IL-17 F, which contain enhancer elements. STAT3 is required for Th17 differentiation, and its deficiency abolishes Th17 generation, while the overexpression of STAT3 substantially increases the Th17 population (Zhang, 2018). A dominant negative mutation of STAT3 causes hyper-IgE syndrome, which shows a Th17 deficiency and impaired Th17 responses, leading to uncontrolled infections of *Candida albicans* and *Staphylococcus aureus* (Wacleche et al., 2017). BATF and IRF4 remodel the chromatin landscape and enable Th17-associated transcription factors to access chromatin to promote cytokine-stimulated differentiation of Th17 cells (Stockinger and Omenetti, 2017). BATF and IRF4 are fundamental for the combinatorial regulation of STAT3 during Th17 differentiation (Zhang, 2018). IRF4 or BATF ablation does not induce *Rorc* transcription and Th17 differentiation. RORγt upregulates IL-17 expression by binding to its gene locus (Zhang, 2018). T cells with RORγt deficiency or reduced RORγt transcriptional activity caused by antagonist treatment cannot be differentiated to Th17 cells (Zhang, 2018).

3.2.2. Cytokine regulation

In general, the surrounding cytokine milieu determines the specific types of effector subsets that would be generated from naïve $CD4^+$ T cells. The differentiation of mouse Th17 cells is dependent on transforming growth factor beta (TGF-β) and IL-6 or IL-21 (Zhang et al., 2017), whereas a combination of IL-1β and IL-6 or IL-23 is sufficient for the development of human Th17 cells without the requirement of TGF-β (Fig. 8) (Wacleche et al., 2017). IL-6 or IL-23 alone cannot efficiently generate Th17 cells; however, these cytokines in combination with IL-1β effectively induce IL-17 production in naïve precursors independent of TGF-β in both human and mouse models (Abusleme and Moutsopoulos, 2017; Ghoreschi et al., 2010; Korn et al., 2009). To date, the mechanisms of how these Th17 cells are induced by cytokine combinations without requiring TGF-β signaling as well as how the downstream receptor signaling of IL-1β, IL-6, and IL-23 is synergized remain perplexing (Zhang, 2018; Zhang et al., 2017). Th17 differentiation from naïve $CD4^+$ T cells is triggered by TGF-β and IL-6, while TGF-β alone induces $Foxp3^+$ Tregs, and the presence of IL-6 inhibits Tregs and induces Th17 differentiation (Yosef et al., 2013). Intriguingly, IL-23 can enhance its own signaling effect by upregulating the expression of IL-23R in Th17 cells via STAT3 (Ghoreschi et al., 2010). IL-23 acts as a stabilizing cytokine for inducing and maintaining the inflammatory phenotype of Th17 cells. Overall, the differentiation of Th17 cells from naïve $CD4^+$ T cells typically occurs through co-signaling of IL-1β and IL-6 or IL-23 and may be modulated by other cytokines and inflammation products (Sandquist and Kolls, 2018).

3.2.3. Th17 plasticity

The differentiation of Th17 cells comprises several distinct stages which are strictly regulated by a series of cytokines and transcription factors. In responding to distinct stimuli from physiological and pathogenic conditions, Th17 cells can obtain the phenotype of other T helper cells but continue to have the basic Th17 lineage specification, which is referred to as Th17 plasticity (Fig. 8) (Stockinger and Omenetti, 2017). These Th17 lineages exert the physiological functions of Th17 cells more efficiently in pathogen clearance, barrier tissue homeostasis, and tissue repair at different environmental sites. The transition of Th17 precursors towards the Th1 axis generates 'ex-Th17' Th1 cells (also referred to as Th17/Th1 cells) which is detrimental to animals by driving inflammatory pathologies such as in IBD and Crohn's disease. The transition of Th17 precursors towards the Tfh or Tregs axis produces 'ex-Th17' Tfh cells or 'ex-Th17' Tr1 cells, respectively, both of which are beneficial to animals through barrier protection and pathogen clearance. Based on the immunological phenotypes of detrimental and beneficial effects, the Th17 cell lineages generated through Th17 plasticity are classified as pathogenic and nonpathogenic, respectively. Thus, 'ex-Th17' Th1 cells belong to pathogenic Th17 lineages, while 'ex-Th17' Tfh cells and 'ex-Th17' Tr1 cells are

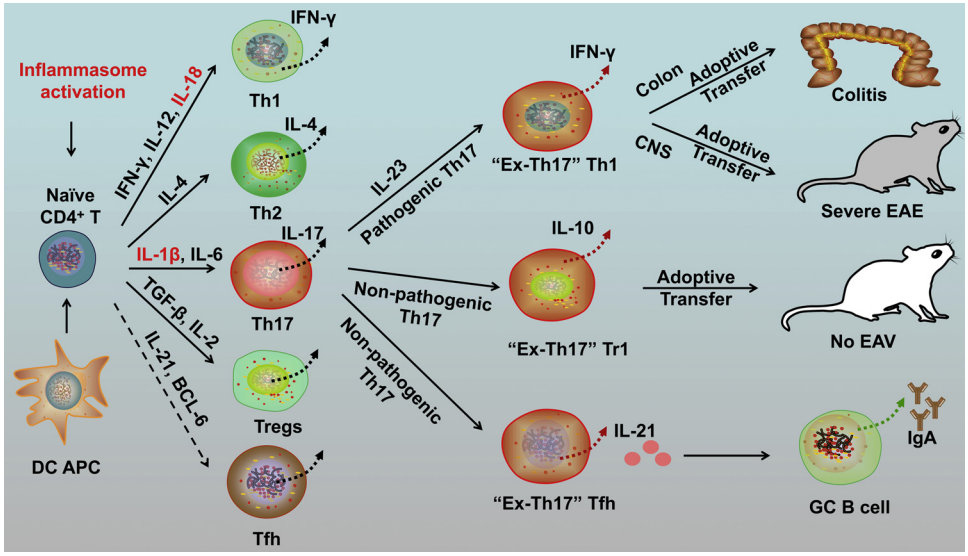

Fig. 8. Th17 differentiation and activation. The differentiation of Th17 undergoes several stages. Initially, naïve CD4$^+$ T cells are primed by dendritic cells activated via pathogen infection or autoinflammation. Then, under distinct cytokine milieu, naïve CD4$^+$ T cells differentiate into different lineages of T helper cells including T helper cell 1 (Th1), Th2, Th17, regulatory T cells (Tregs), and follicular helper T cells (Tfh). Among these initiating cytokines, IL-1β and IL-6 are responsible for inducing Th17 cell differentiation. Further exposure to IL-23 or other cytokines leads to the development of pathogenic Th17 cells. In the colon, pathogenic Th17 cells also termed as 'Ex-Th17' Th1 cells which are featured by secretion of IFN-γ. Adoptive transfer of these cells into wild-type mice induce colitis. In CNS, 'Ex-Th17' Th1 cells generate a series of inflammatory cytokines, including TNF, granulocyte–macrophage colony-stimulating factor, and IFN-γ, contributing to experimental autoimmune encephalomyelitis (EAE). Another type of Th17 cells is nonpathogenic which execute protective role in immune responses. 'Ex-Th17' Tr1 cells serve as regulatory cells and inhibit overactive inflammation by secreting IL-10. 'Ex-Th17' Tfh facilitates IgA production by acquiring phenotype of Tfh cells.

nonpathogenic (Fig. 8). The inducibility to EAE following adoptive transfer is also used as a criterion for the pathogenicity of Th17 cell lineages, whereas a lack of EAE inducibility is interpreted as an indicator of nonpathogenicity (Fig. 8). Cytokine combinations used in Th17 differentiation also determine the pathogenicity of Th17 cell lineages. Combinations of IL-6 and TGF-β appear to drive CD4$^+$ T cells to differentiate into Th17 lineages that could not induce EAE, whereas combinations of IL-1β, IL-6, and IL-23 generate the pathogenic Th17 cell lineages that cause EAE following adoptive transfer (Stockinger and Omenetti, 2017).

Induction towards a more pathogenic proinflammatory state is a prominent feature of Th17 cells. In the spleens of *L. monocytogenes* infected mice, IL-17A– and IFN-γ–producing Th17/Th1 cells are induced through inflammasome-dependent IL-1/IL-1R signaling (Uchiyama et al., 2017). When cocultured with autologous monocytes stimulated with heat-inactivated *C. albicans*, CD4$^+$ T cells can differentiate into IL-17A– and IFN-γ–producing Th17/Th1 cells (Zielinski et al., 2012). During intestinal infection of *Helicobacter hepaticus* or *Citrobacter rodentium*, Th17 cells developed in colon are converted into 'ex-Th17' Th1 cells characterized by the expression of IFN-γ (Stockinger and Omenetti, 2017). Adoptive transfer of 'ex-Th17' Th1 cells into mice induces colitis. In contrast, IL-23–dependent plasticity of Th17 cells induces EAE in the central nervous system (CNS) by the production of TNF, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN-γ. IL-23 plays a leading role in the plasticity of Th17 cells because IL-23–deficient mice fail to produce pathogenic Th17 cells. Pathogenic Th17 cells play a key role in the pathogenesis of autoinflammatory diseases. Under the influence of TGF-β or infections of specific pathogens such as *Nippostrongylus brasiliensis* and *S. aureus* (Stockinger and Omenetti, 2017), Th17 cells trans-differentiate into 'ex-Th17' Tr1 cells characterized by the production of an immunosuppressive cytokine IL-10, which plays a protective role in an animal's body by controlling severe inflammatory reactions (Fig. 8). Th17 cells also trans-differentiate into 'ex-Th17' Tfh cells which promote the production of IgA by GC B cells and contribute to intestinal immune protection (Fig. 8). Thus, therapeutic approaches that target Th17 cells in inflammatory diseases should ensure that the protective functions of Th17 cell lineages are not compromised (Stockinger and Omenetti, 2017).

3.2.4. IL-1/IL-1R signaling and Th17 differentiation

IL-1β plays a crucial role in the development of Th17 via IL-1R signaling. After the binding of IL-1β to IL-1R, the cytokine receptor–coreceptor complexes recruit the adaptor protein MyD88 and subsequently induce NF-κB activation and nuclear translocation, leading to the upregulation of numerous immune related-genes, including proinflammatory cytokines (Mills et al., 2013).

IL-1/IL-1R signaling is indispensable for the early differentiation of Th17. In IL-1R–deficient mice, the differentiation of antigen-specific Th17 cells is abrogated, whereas Th1 and Th2 responses are not substantially affected (Sutton et al., 2006), which results in resistance to organ-specific autoimmune disease such as EAE. IL-1β and IL-23 are sufficient for the development of antigen-specific Th17 cells and EAE (Sutton et al., 2006). IL-1/IL-1R signaling stabilizes Th17 differentiation and the inflammatory effect (Chung et al., 2009). During Th17 differentiation, IL-1β synergizes with IL-6 and stably upregulates the master transcription factors of Th17 cells, including STAT3, IRF4, and RORγt. IL-1β/IL-1R signaling represses SOCS3, a negative regulator of the JAK/STAT signaling pathway, which leads to enhanced STAT3 phosphorylation (Basu et al., 2015). Furthermore, IL-1β induces the expression of IL-23R, IL-1R, and RORγt, which leads to the suppression of IL-2 that has an inhibitory effect on IL-17 production. IL-1/IL-1R signaling enhances the transcription of *IL-17A* and *IL-17F* by facilitating the binding of STAT3 and NF-κB to the *cis*-regulatory elements (Whitley et al., 2018). IL-1β also induces the expression of the NF-κB inhibitor zeta and BATF, the specific transcription factors for Th17 cells (Ikeda et al., 2014).

IL-1β/IL-1R signaling controls the expression of a newly identified transcription factor Bhlhe40, which is required for Th cell-mediated EAE in mouse models (Lin et al., 2016). IL-1β induces Bhlhe40 expression in polarized Th17 cells. Bhlhe40-expressing Th17 cells exhibit an encephalitogenic transcriptional signature, whereas Bhlhe40-deficient Th17 cells are nonencephalitogenic. Bhlhe40-expressing Th cells display a marked production of IL-17 A. IL-1β/IL-1R signaling is required for full Bhlhe40 expression in Th cells after immunization. Pertussis toxin (PTX), a classical co-adjuvant for inducing EAE in mouse models, promotes IL-1β secretion and strongly stimulates Bhlhe40 expression in Th cells, which causes Bhlhe40-dependent EAE. PTX-induced IL-1β secretion in myeloid cells is essential for the development of EAE (Ronchi et al., 2016). PTX-induced Th17 cells are impaired in IL-1β– or ASC–deficient mice. The differentiation of Th17 cells induced by PTX requires IL-1R and MyD88, which suggests that inflammasome activation-mediated IL-1β secretion and intact IL-1R signaling are required in this process (Ronchi et al., 2016). Overall, PTX–IL-1β–Bhlhe40 signaling contributes to the differentiation of pathogenic

Th17 lineages, providing new insights into the IL-1β/IL-1R–Th17 axis (Lin et al., 2016).

The IL-1R-related pathway also affects Th17 differentiation. Single Ig IL-1-related receptor (SIGIRR), an IL-1R pathway inhibitor, suppresses Th17 differentiation via the inhibition of mammalian target of rapamycin (mTOR) kinase. SIGIRR-deficient mice are more susceptible to myelin oligodendrocyte glycoprotein (MOG)-induced EAE; in these animals, the phosphorylation of mTOR kinase induced by IL-1β is enhanced, which results in increased Th17 cell polarization. IL-1β markedly increases the proliferation of SIGIRR-deficient T cells under an *in vitro* Th17 polarization condition, whereas the proliferation is abolished in mTOR-deficient T cells, which indicates the essential role of mTOR activation. In response to IL-1β stimulation, SIGIRR preferentially inhibits mTOR activation through IL-1R–associated kinase 1 (IRAK1) (Gulen et al., 2010). Activation of the mTOR pathway by IL-1β improves Th17 differentiation, while, inhibition of the mTOR pathway by rapamycin suppresses Th17 development. The phosphorylation of mTOR by IL-1β increases the metabolic fitness of the newly dividing Th17 cells under inflammatory conditions, making IL-1β important for Th17 lineage expansion when competing with other lineages in a hostile cytokine environment (Wacleche et al., 2017). Thus, SIGIRR negatively regulates Th17 differentiation through the suppression of IL-1/IL-1R signaling-induced mTOR activation. In addition to suppressing the mTOR pathway, SIGIRR inhibits the expression of Th17-specific transcription factors, such as IRF4 and RORγt (Gulen et al., 2010).

B cell adapter for phosphoinositide 3-kinase (BCAP), an adaptor of IL-1R signaling, contains a novel N-terminal Toll/IL-1R (TIR) homology domain. The TIR domain of BCAP interacts with IL-1R and MyD88 to transmit extracellular signals during priming Th17 responses by IL-1β (Deason et al., 2018). BCAP links IL-1R signaling to the phosphoinositide 3-kinase (PI3K)-mTOR pathway and regulates mTOR-induced glycolysis, providing Th17 cells with a competitive survival ability. BCAP-deficient T cells failed to activate the PI3K pathway in response to IL-1β, and minimal inhibition of mTOR completely abrogated IL-1β–induced differentiation of pathogenic Th17 cells, thereby mimicking BCAP deficiency. The activation of mTOR is crucial for Th17 lineage development. *BCAP*$^{-/-}$ mice are defective in the generation of pathogenic Th17 cells and consequently show reduced susceptibility to MOG-induced EAE. BCAP-deficient T cells are highly defective in IL-17 A production and the development of pathogenic Th17 lineages, which suggests that BCAP is required for Th17 differentiation. In addition, the absence of BCAP cannot alter the development of naturally arising Th17 lineages, and normal Th17 cells are observed in mice with T cell-specific deletions of IL-1R during the steady-state of differentiation, which further supports that IL-1R signaling plays a critical role in the early differentiation of Th17 cells. However, the absence of BCAP leads to defective differentiation of pathogenic Th17 cells. Therefore, BCAP is a critical link between IL-1/IL-1R signaling and the metabolic status of activated T cells that ultimately regulate the differentiation of pathogenic Th17 cells.

IL-1β stimulation forces the induction of a splicing isoform of FOXP3 referred to as FOXP3Δ2Δ7, which not only inhibits Treg function but also strongly favors its differentiation into Th17 cells, linking alternative splicing with the differentiation of T cell subsets in the immune response. Patients with Crohn's disease possess increased levels of FOXP3Δ2Δ7, which correlate with the disease severity and IL-17 production (Mailer et al., 2015). Excessive activation of IL-1R signaling by IL-1β downregulates TGF-β–induced Foxp3 expression, which results in the promotion of Th17 differentiation. The downregulation of Foxp3 depends on IL-1/IL-1R signaling-induced activation of the Akt-mTOR pathway, which suppresses Treg differentiation. Rapamycin, an inhibitor of mTOR, abolishes IL-1β–induced Foxp3 downregulation, which suggests that the Akt-mTOR pathway is involved in IL-1β–induced Foxp3 downregulation. The Akt-mTOR pathway links IL-1/IL-1R signaling with Th17 differentiation through the downregulation of Foxp3, which is involved in the transition of Tregs into Th17 cells (Ikeda et al., 2014).

3.2.5. Inflammasome activation and Th17 differentiation

IL-β plays a significant role in the early differentiation, survival, expansion, and inflammatory effect of Th17 cells as described above. Evidence indicates that IL-1β links numerous stimuli of the inflammasome pathways to Th17 responses via IL-1R signaling. There are direct relationships between inflammasome activation and Th17 cell differentiation; therefore, IL-1β is an important bridge of inflammasomes and Th17 responses (Mills et al., 2013).

UA, which is released from damaged cells and plays a key role in alum adjuvanticity, can drive Th17 differentiation dependent on inflammasome activation-induced IL-1β secretion. Naïve CD4$^+$ T cells cocultured with MDP primed- and UA-treated DCs differentiate towards Th17 lineages. UA crystals alone are poor stimulators of Th17 differentiation, although when coupled with priming stimuli of signal 1, they can potently induce Th17 responses, demonstrating that the priming signal that is required for NLRP3 inflammasome activation is also essential for UA-induced Th17 differentiation. MDP or UA crystals alone cannot induce Th17 differentiation. In this model, Th17 differentiation requires inflammasome-dependent IL-1β secretion; moreover, ASC and caspase-1 are essential in this process. Th17 differentiation driven by MDP/UA-treated DCs depends on NLRP3–IL-1β–IL-1R signaling. Th17 differentiation is abolished when cocultured with NLRP3-deficient DCs, due to impaired secretion of IL-1β. IL-1R–deficient CD4$^+$ T cells have reduced IL-17 A secretion following MDP/UA stimulation. Thus, NLRP3 inflammasome-dependent IL-1β secretion is required for Th17 differentiation driven by MDP/UA stimulation. Th17 differentiation is completely abolished in *ASC*$^{-/-}$ or *caspase-1*$^{-/-}$ mice, which confirms a central role of inflammasome-induced IL-1β secretion in this process. Overall, NLRP3 inflammasome-dependent IL-1β secretion triggered by UA crystals in DCs is crucial for Th17 differentiation.

Complete Freund's Adjuvant (CFA), composed of the heat-killed mycobacteria, such as Mycobacterium tuberculosis is a critical adjuvant of vaccine components. CFA promotes Th17 responses through inflammasome-dependent IL-1β secretion. Both IL-1/IL-1R signaling and MyD88 are required for IL-17 secretion by CD4$^+$ T cells following CFA immunization, which indicates that IL-1/IL-1R signaling rather than TLRs or IL-18R are essential in Th17 responses. Both IL-1α and IL-1β activate IL-1R signaling, whereas the production of IL-17 is only slightly defective in CFA-immunized *IL-1α*$^{-/-}$ mice and substantially reduced in *IL-1β*$^{-/-}$ mice; thus, IL-1β is the primary IL-1 cytokine required for CFA-induced Th17 responses. Mice that lack caspase-1, ASC, or NLRP3 exhibit a deficiency in CFA-induced Th17 differentiation; however, *NLRC4*$^{-/-}$ animals show unimpaired Th17 responses.

The CFA component heat-killed M. tuberculosis induces caspase-1 cleavage and IL-1β secretion via NLRP3 without LPS priming, which is involved in the phagocytosis of M. tuberculosis, potassium efflux, and ROS, indicating that M. tuberculosis itself can activate both signal 1 and signal 2 of NLRP3 inflammasome for pro-IL-1β induction and cleavage. The TLR pathways provide the major stimulation inducing pro–*IL-1β* transcription via NF-κB signaling, whereas pro–*IL-1β* transcripts are normally induced in *MyD88*$^{-/-}$ *TRIF*$^{-/-}$ mice in response to CFA. In contrast, Mincle-CARD9 signaling plays a major role in pro–*IL-1β* transcription in CFA-immunized mice. The mycobacterial glycolipid trehalose dimycolate (TDM, also referred to as cord factor) with a potent adjuvant activity is recognized by Mincle and then upregulates pro–*IL-1β* transcription through CARD9–NF-κB signaling, acting as a priming signal for inflammasome activation. Pro–IL-1β induction is substantially reduced in the skin of *CARD9*$^{-/-}$ but not *NOD1*$^{-/-}$ *NOD2*$^{-/-}$ mice; moreover, Th17 responses are nearly absent in *CARD9*$^{-/-}$ mice following CFA immunization. Thus, CFA component TDM can provide signal 1 for pro-IL-1β upregulation largely via the CARD9- rather than TLR- or NOD1/NOD2-dependent pathway.

In LPS-primed BMDMs, polymeric peptidoglycan isolated from heat-killed M. tuberculosis induces NLRP3 inflammasome activation and IL-

1β secretion independent of NOD1 and NOD2, two cytoplasmic peptidoglycan receptors that activate NF-κB signaling (Shenderov et al., 2013). When administered in mineral oil, peptidoglycan and TDM from M. tuberculosis can synergistically recapitulate the CFA-derived Th17 differentiation, and this response is abolished in *caspase-1*$^{-/-}$ and *CARD9*$^{-/-}$ mice (Shenderov et al., 2013). Therefore, mycobacterial TDM and peptidoglycan, the major components of CFA, activate inflammasome synergistically by providing both priming and triggering signals, respectively. CFA-induced Th17 differentiation provides novel strategies for designing Th17-promoting adjuvants. In addition, NLRP3$^{-/-}$ mice exhibit a mild reduction of Th17 differentiation compared with caspase-1$^{-/-}$ or ASC$^{-/-}$ mice following CFA immunization, which suggests that other inflammasome sensors may participate in CFA-induced inflammasome activation (Shenderov et al., 2013). The deficiency of Th17 differentiation is more severe in IL-1β$^{-/-}$ mice than that in caspase-1$^{-/-}$ mice, which indicates that inflammasome-independent IL-1β secretion also contributes to Th17 differentiation. In addition to caspase-1, other enzymes, such as several neutrophil serine proteases, also cleave pro-IL-1β and induce IL-1β secretion, which may explain the inflammasome-independent secretion of IL-1β that contributes to CFA-induced Th17 differentiation (Shenderov et al., 2013).

3.3. Th17 responses

Th17 cells are typical proinflammatory T cells that promote the expression of inflammatory cytokines, chemokines, and other immune-related mediators. Th17 cells induce an inflammatory effect towards target sites through the production of IL-17 A and IL-17 F, which form homo- or heterodimers and activate IL-17 receptor A (IL-17RA) that is widely expressed in many cell types (Miossec and Kolls, 2012). Thus, IL-17AFs can activate systemic immune responses via their broadly expressed receptors. IL-17R is mostly composed of the combinations of IL-17RA with other IL-17R subunits, including IL-17RB, IL-17RC, IL-17RD, and IL-17RE, to generate different IL-17R co-complexes, which can be activated by distinct IL-17 ligands under different physiological conditions. IL-17RA–IL-17RC heterodimeric receptors respond to IL-17 A and IL-17 F in homodimer or heterodimer (Ely et al., 2009; Toy et al., 2006). In addition to IL-17RC, IL-17RB, IL-17RE, and IL-17RD also interact with IL-17RA and mediate IL-17 signaling (Rong et al., 2009; Song et al., 2011). IL-17RA is widely expressed in hematopoietic cell types and functions as a common component of IL-17R, whereas IL-17RC is restricted to nonhematopoietic cells (Ishigame et al., 2009).

IL-17RA interacts with the adaptor ACT1, which then associates with TNF receptor-associated factor 6 (TRAF6), ultimately leading to NF-κB activation (Chang et al., 2006; Huang et al., 2007). IL-17 A also activates CCAAT/enhancer-binding protein (C/EBP), which results in the binding of C/EBP to the promoter regions of target genes, such as IL-6 (Shen et al., 2006). Both IL-17 A and IL-17 F produced by Th17 cells exert effects on a broad range of cell types for upregulating inflammatory genes, including cytokines, such as IL-1β, IL-6, granulocyte-colony-stimulating factor, and TNF-α, chemokines, such as CXCL1, CXCL8, and CCL10, inflammatory effectors, such as acute-phase proteins and complement, and antimicrobial proteins, such as defensins and mucins. IL-17 A and IL-17 F also act as key cytokines for the recruitment, activation, and migration of neutrophils (Korn et al., 2009).

Inflammation is the major immune effect of Th17 cells by producing IL-17 A and IL-17 F which can act on various cell types of the host body, including epithelial cells, endothelial cells, fibroblasts, and myeloid cells. In endothelial cells, IL-17 induces the production of tissue factors that induce procoagulant activity and proinflammatory cytokines such as IL-6 and IL-8, which lead to local or systemic inflammation. In epithelial cells and fibroblasts, similar effects, such as inflammation and tissue damage induced by IL-17, are observed (Fossiez et al., 1996). IL-17 also induces matrix destruction, which leads to joint damage and inflammation persistence. In osteoblasts and chondrocytes, IL-17 stimulates the production of matrix metalloproteinases, activates receptor activator of NF-κB ligand (RANKL) signaling, and induces proinflammatory cytokines, leading to bone damage and the dysregulation of tissue repair (Koenders et al., 2011). Overall, IL-17 signaling not only initiates acute inflammation but also contributes to chronic tissue inflammation.

Inflammation initiated by Th17 cells is associated with various chronic inflammatory and autoinflammatory diseases, including RA, psoriasis and psoriatic arthritis, ankylosing spondylitis, Crohn's disease, multiple sclerosis, vasculitis and atherosclerosis, asthma, and chronic obstructive pulmonary disease. Intriguingly, some of these diseases have also been associated with dysregulated inflammasome activation (Yang and Chiang, 2015). For example, allergen exposure-induced NLRP3 inflammasome activation promotes IL-1β secretion and drives Th17 responses, which contribute to the pathogenesis of asthma (Besnard et al., 2012).

3.4. Inflammasome-derived Th17 in host immune defense

Inflammasome activation plays an important role in the host defense against microbial pathogens by activating both innate and adaptive immunity. Pyroptosis induced by inflammasome activation exerts its function via the exposure of intracellular bacteria to phagocytes, such as neutrophils, for bacteria clearance. The release of IL-1β and intracellular contents, such as DAMPs, induced by inflammasome activation creates an inflammatory milieu which is suitable for protective Th17 differentiation. Evidence indicates that the function of inflammasomes in defending against bacterial and fungal infection is partially achieved by its promotion of Th17 differentiation and the subsequent IL-17 response (Table 1) (Dunne et al., 2010; Hise et al., 2009).

Th17 cells are crucial in defending against pathogens by secreting Th17-related cytokines, such as IL-17 A, IL-17 F, and IL-22 (Higgins et al., 2006; Ye et al., 2001). IL-17 induces inflammatory cytokines via IL-17R signaling, which contributes to the proliferation of neutrophils and their recruitment to infected sites. IL-17 A facilitates the secretion of antimicrobial peptides, such as lipocalins and calgranulins, from infected epithelial cells. Furthermore, IL-17 A helps to maintain the integrity of the intestinal barrier by inducing claudin (Chen et al., 2003; Fossiez et al., 1996; Huang et al., 2007; Kao et al., 2004; Liang et al., 2006). IL-22 produced by Th17 cells induces antimicrobial peptides and maintains intestinal homeostasis via IL-22 signaling (Sonnenberg et al., 2011). IL-22 is beneficial to mediate anti-bacterial immunity in the gastrointestinal tract (Sonnenberg et al., 2011).

Inflammasome-derived Th17 cells contribute to bacteria clearance and host survival. As an intracellular homeostasis sensor, NLRP3 can be activated by various bacterial products, such as lytic toxins and hemolysin (Munoz-Planillo et al., 2009). Adenylate cyclase toxin from *Bordetella pertussis* induces pore formation and potassium efflux, leading to NLRP3 inflammasome activation (Dunne et al., 2010). Inflammasome activation-induced IL-1β by *B. pertussis* specifically promotes Th17 differentiation and IL-17 A secretion, which is essential for bacterial clearance. *IL-1R*$^{-/-}$ mice show a deficiency in Th17 differentiation and *B. pertussis* clearance. Thus, IL-1/IL-1R signaling is required for the differentiation of antigen-specific Th17 cells, which induce IL-17 A secretion and neutrophil recruitment to enhance bacterial clearance. The pore formation toxin peumolysin from *Streptococcus pneumoniae* activates NLRP3 inflammasome in DCs and macrophages (McNeela et al., 2010; Witzenrath et al., 2011). Both *S. pneumonia* and peumolysin improve the production of IL-17 A and IFN-γ. Thus, the NLRP3–IL-1/IL-1R–IL17 A axis contributes to the host defense against *S. pneumoniae* infection (Table 1) (McNeela et al., 2010; Witzenrath et al., 2011). IL-1/IL-1R signaling is also essential for controlling the infection of *M. tuberculosis*, which induces inflammasome activation (Mayer-Barber et al., 2011, 2010). IL-1β– or IL-1R–deficient mice fail to restrict *M. tuberculosis* infection. *In vitro* infection of *M.*

Table 1
Diseases associated with inflammasome activation-induced Th17 responses.

Diseases	Triggers	Experimental models	T cells	Sensors	References
B. pertussis	CyaA	IL-1R$^{-/-}$ mice	Th17 IL-17^{+} γδ T	NLRP3	(Dunne et al., 2010)
S. pneumoniae	PLY	NLRP3$^{-/-}$, ASC$^{-/-}$, caspase-1$^{-/-}$	IL-17^{+} γδ T	NLRP3	(McNeela et al., 2010; Witzenrath et al., 2011)
M. tuberculosis	unclear	IL-1β$^{-/-}$, IL-1R$^{-/-}$, AIM2$^{-/-}$, NLRP3$^{-/-}$, ASC$^{-/-}$, caspase-1$^{-/-}$	Th17	NLRP3? AIM2?	(Saiga et al., 2012)
Borrelia species	unclear	IL-1β$^{-/-}$, caspase-1$^{-/-}$	Th17	unclear	(Oosting et al., 2011)
L. pneumophila	flagellin	IL-1R$^{-/-}$, caspase-1$^{-/-}$, IPAF$^{-/-}$	Th17	NLRC4	(Lightfield et al., 2008; Zamboni et al., 2006)
K. pneumoniae	flagellin	IL-1R$^{-/-}$, IPAF$^{-/-}$	IL-17^{+} γδ T	NLRC4	(Cai et al., 2012)
Candidiasis	hyphae	ASC$^{-/-}$, caspase-1$^{-/-}$	Th17	NLRP3 NLRC4	(Huang et al., 2004a)
P. brasiliensis	unclear	hMDCs	Th17	NLRP3	(de Castro et al., 2018)
MWS	DAMPs?	NLRP3-R258 W mice, IL-1R$^{-/-}$	Th17	NLRP3	(Meng et al., 2009)
DIRA	DAMPs?	IL-1RN$^{-/-}$	Th17	unclear	(Aksentijevich et al., 2009)
MS	unclear	blood samples	Th17?	unclear	(Huang et al., 2004b; Ming et al., 2002)
EAE	CFA PTX	IL-1β$^{-/-}$, NLRP3$^{-/-}$, ASC$^{-/-}$, caspase-1$^{-/-}$	Th17 IL-17^{+} γδ T	NLRP3	(Martin et al., 2016; Lalor et al., 2011; Sutton et al., 2009)
allergic asthma	SAA ATP UA	IL-1R$^{-/-}$, NLRP3$^{-/-}$, ASC$^{-/-}$, caspase-1$^{-/-}$	Th17 IL-17^{+} γδ T	NLRP3	(Wilson et al., 2009; Besnard et al., 2012; Ather et al., 2011)
RA	unclear	IL-1R$^{-/-}$, NLRP3$^{-/-}$, caspase-1$^{-/-}$	Th17	NLRP3 NLRP1	(Mathews et al., 2014; Vande Walle et al., 2014; Sui et al., 2012)
SLE	dsDNA	blood samples	Th17	NLRP3 AIM2	(Zhang et al., 2013; Zhao et al., 2013; Zhang et al., 2016)
chemotherapy blunting	Gem 5FU	blood samples, NLRP3$^{-/-}$, caspase-1$^{-/-}$	Th17	NLRP3	(Bruchard et al., 2013)

5FU, 5-fluorouracil; CyaA, adenylate cyclase toxin; DIRA, deficiency of IL-1RA; Gem, gemcitabine; hMDCs, human derived dendritic cells; MS, multiple sclerosis; MWS, Muckle-Wells Syndrome; PLY, pneumolysin; RA, rheumatoid arthritis; SAA, serum amyloid A; SLE, systemic lupus erythematous; UA, uric acid.

tuberculosis contributes to NLRP3 activation and IL-1β secretion. As a CFA component, heat-killed *M. tuberculosis* induces Th17 differentiation through NLRP3-dependent IL-1β secretion and IL-1/IL-1R–MyD88 signaling. Therefore, NLRP3 inflammasome activation can develop the protective Th17 response during *M. tuberculosis* infection. *Borrelia burgdorferi spirochetes*, which causes Lyme disease characterized by severe immunopathology such as multiple joint inflammation and neurological disorders, induces inflammasome activation and IL-1β secretion (Oosting et al., 2011). Upon *Borrelia* infection, inflammasome activation-induced IL-1β secretion contributes to Th17 cell differentiation, which contributes to *Borrelia* clearance (Table 1). IL-17 A produced by Th17 cells is also involved in the pathogenesis of chronic Lyme disease; thus, the inflammasome pathway activated in this process could serve as potential immunomodulatory targets for treatment.

NLRC4 also contributes to host clearance of intracellular bacteria. NLRC4 inflammasome activation not only induces pyroptosis but also orchestrates adaptive immunity via IL-1β/IL-18 secretion. NLRC4 inflammasome activation-induced IL-18 secretion in DCs stimulates memory CD8^{+} T cells to produce IFN-γ, which plays an important role in controlling the infections of *Salmonella enterica serovar Typhimurium*, *Yersinia pseudotuberculosis*, and *Pseudomonas aeruginosa* (Kupz et al., 2012). Importantly, *Legionella pneumophila* infection activates NLRC4 inflammasome, which subsequently instructs adaptive immunity towards Th1/Th17 cells in the lung (Table 1). The sensing of *L. pneumophila* flagellin by NAIP5 activates NLRC4 inflammasome, induces caspase-1 cleavage, and IL-1β secretion which activates IL-1R signaling and drives the development of Th17 cells (Lightfield et al., 2008). NLRC4 inflammasome activation also stimulates IL-17 A production from IL-17 producing innate cells when infected by *Klebsiella pneumoniae* (Table 1) (Cai et al., 2012).

Fungal infection also activates inflammasomes to orchestrate adaptive immunity including Th17 responses in the host defense (Table 1) (Huang et al., 2004a). *C. albicans* infection induces NLRP3 inflammasome and IL-1β secretion. *NLRP3*$^{-/-}$ mice exhibit increased susceptibility to disseminated and mucosal infection of *C. albicans* (Gross et al., 2009; Hise et al., 2009; Joly et al., 2009). TLR2 and Dectin-1 serve as the sensors of *C. albicans* to activate the NF-κB pathway and provide the priming signal for NLRP3 inflammasome activation. Upon fungal infection, NLRP3 may be activated via ROS production and potassium efflux. IL-17 A/IL-17RA signaling is important in anti-*C. albicans* immunity. Furthermore, inflammasome-dependent secretion of IL-1β and IL-18 plays an essential role in the development of Th17 and Th1 responses during *C. albicans* infection. ASC- and caspase-1–deficient mice have impaired development of Th1 and Th17 cells, exhibiting more susceptibility to *C. albicans* infection (van de Veerdonk et al., 2011a). Apart from *C. albicans, Talaromyces marneffei* also induces NLRP3 inflammasome activation in human macrophages and DCs, which subsequently contributes to Th1/Th17 responses. *Paracoccidioides brasiliensis* induces NLRP3 inflammasome activation in human DCs, which is necessary for Th1/Th17-mediated anti-fungal immunity (Table 1) (de Castro et al., 2018).

NLRC4 plays a critical role in the host anti-fungal response, particularly in mucosal infection of *candida*. *NLRC4*$^{-/-}$ mice have low levels of proinflammatory cytokines, including IL-1β, and antimicrobial peptides; therefore, they are hypersusceptible to fungal infection (Tomalka et al., 2011). The stimuli that activate NLRC4 inflammasome during fungal infection remain unclear. During disseminated infection of *candidiasis*, *caspase-1*$^{-/-}$ and *ASC*$^{-/-}$ mice show impaired Th1/Th17 responses, the outgrowth of fungus, and a low survival rate (van de Veerdonk et al., 2011a), demonstrating that inflammasome activation contributes to host anti-fungal immunity. Th1/Th17 anti-fungal immunity is instructed by inflammasome activation-induced IL-1β/IL-18 secretion. The addition of IL-18 in *caspase-1*$^{-/-}$ mice restores the development of Th1 responses. IL-1β is essential in *C. albicans*-induced Th17 differentiation and the priming of IL-17/IFN-γ double-producing cells, which suggests that IL-1β is not only important for Th17 cell

differentiation but also boosts cytokine production (Zielinski et al., 2012). Collectively, inflammasome activation-induced secretion of IL-1β/IL-18 after fungal infection promotes Th1/Th17 differentiation, which participates in host anti-fungal immunity.

3.5. Inflammasome-derived Th17 in immune disorders

3.5.1. IL-1/IL-1R signaling-related autoimmune diseases

The role of IL-1β in regulating Th17 responses has been examined in various disease models. The mutation of inflammasome sensors is closely related to numerous autoimmune and autoinflammatory diseases. The dysregulation of inflammasome pathways and IL-1/IL-1R signaling affect the development of Th17 cells. Some gain-of-function mutations in NLRP3 cause increased IL-1β secretion, contributing to the pathogenesis of CAPS, familial cold autoinflammatory syndrome, and Muckle-Wells Syndrome (MWS) which are characterized by hyperinflammation in various tissues and organs (Geddes et al., 2009; Masters et al., 2009). Furthermore, mice that carry a missense mutation in NLRP3 develop similar symptoms as MWS (Meng et al., 2009). Dysregulated activation of NLRP3 inflammasome leads to excessive IL-1β secretion, which augments Th17 cell differentiation, leading to Th17 cell-dominant immunopathology in autoinflammation (Table 1). Furthermore, the mutation of the secreted IL-1R antagonist protein (IL-1RA) that serves as an IL-1 inhibitor via binding to IL-1R also causes autoinflammatory disease featured by serious systemic inflammation, including osteomyelitis, periostitis, and pustulosis (Aksentijevich et al., 2009). IL-1RA mutation makes patients highly responsive to IL-1β stimulation with enhanced Th17 differentiation (Table 1). Collectively, the dysregulation of inflammasome pathways and IL-1/IL-1R signaling is associated with Th17 cell development and related immune disorders.

3.5.2. Inflammasome-derived Th17 and autoinflammatory diseases

The dysregulation of inflammasomes that cause abnormal secretion of IL-1β contributes to several well-known autoinflammatory diseases, including the human inflammatory demyelinating disease multiple sclerosis (MS), allergic asthma, RA, and SLE, by affecting the differentiation of pathogenic Th17 cells.

Patients with MS, characterized by demyelination that occurs in nerve cells from the brain and spinal cord, have increased levels of IL-1β, IL-18, and caspase-1 (Huang et al., 2004b; Ming et al., 2002). Nerve cell damage symptoms are attributed to an excessive autoinflammatory immune response. The serum from MS patients shows an increased level of IL-18, which is only secreted following inflammasome activation, indicating that inflammasome activation is related to MS pathogenesis (Table 1) (Chen et al., 2012; Huang et al., 2004b; Ming et al., 2002; Nicoletti et al., 2001). EAE is the most commonly used experimental model for MS. EAE induced by CFA in a mouse model is characterized by an immune response towards self-antigens, such as myelin oligodendrocyte glycoprotein of the CNS. Furthermore, studies in mice also suggest that IL-1β and IL-18 contribute to the incidence of EAE. *Caspase-1*$^{-/-}$ mice show decreased levels of proinflammatory cytokines, including TNF-α, IL-1β, IFN-γ, and IL-6, as well as a reduced EAE incidence. T cell-intrinsic ASC-dependent inflammasome provides the excessive source of IL-1β, which promotes Th17-mediated EAE (Table 1) (Martin et al., 2016). In this process, TCR activation acts as a priming signal, while the addition of ATP induces ASC-NLRP3–dependent caspase-8 activation and IL-1β secretion. The IL-1R is expressed on Th17 instead of Th1 cells; importantly, ATP treatment enhances the survival of Th17 but not Th1 cells, which suggests IL-1β secretion from Th17-intrinsic inflammasome activation conducted in an autocrine manner contributes to Th17 differentiation and expansion (Martin et al., 2016). IL-1β/IL-18 secreted from DCs after inflammasome activation lead to Th17 and γδ T-cell responses in EAE (Table 1) (Lalor et al., 2011; Sutton et al., 2009). Inflammasome activation in DCs stimulated with *M. tuberculosis* and MOG induces EAE and IL-17 production by T cells. The administration of a caspase-1 inhibitor suppresses IL-17 production and attenuates the clinical signs of EAE, while the injection of IL-1β or IL-18 has the reverse effects, which suggests that both IL-1β and IL-18 are crucial mediators of EAE. *NLRP3*$^{-/-}$ mice show a delayed progression of EAE and reduced IL-17 production, which suggests that NLRP3 activation is necessary for the normal development of Th17 responses and contributes to EAE development (Ciraci et al., 2012). Overall, inflammasome activation-derived cytokines are important for the development of Th17- driven EAE.

In addition to MS, the pathogenesis of allergic asthma, characterized by hyperreaction and chronic inflammation of the airways, is closely associated with inflammasome-derived Th17 responses. Asthma was originally thought to be a Th2 cell-based inflammatory disease, whereas later studies indicated that airway inflammation can be triggered by the excessive production of IL-17 without Th2-related cytokines, such as IL-4 and IL-13, in mouse models (He et al., 2009; Kudo et al., 2012). Allergic sensitization in the airway strongly induces Th17 differentiation by which substantial amounts of neutrophils are recruited to the airway, leading to allergen-induced airway hyperreactivity (AHR) (Table 1) (Wilson et al., 2009). In addition to the recruitment of neutrophils to the airway, IL-17 A also directly acts on airway smooth muscle by inducing hyper-responsiveness and contraction of the tracheal rings. Patients with allergic asthma show increased levels of IL-1β and IL-17, indicating an inflammasome-Th17 differentiation axis in allergic lung inflammation (Table 1) (Besnard et al., 2012). SAA generated by segmented filamentous bacterium facilitates the development of Th17 responses in the gastrointestinal tract and is involved in airway inflammation (Ivanov et al., 2009). As stimuli of signal 2, SAA induces NLRP3 inflammasome activation and IL-1β secretion in DCs, which promotes IL-1-dependent pulmonary inflammation and IL-17–producing Th17 cells (Table 1) (Ather et al., 2011). Overall, an airway exposed to allergens may cause NLRP3 inflammasome activation and proinflammatory cytokine secretion, such as IL-1β and IL-18. IL-1β further promotes Th17 differentiation in the lung through IL-17A-mediated neutrophil recruitment and aggravates lung inflammation.

RA is one of the most common autoinflammatory diseases related to NLRP3 inflammasome. RA is characterized by inflammasome activation and bone destruction in the synovial joints, resulting in irreversible damage to the joints. Both NLRP1 and NLRP3 polymorphisms are sensitive to RA (Table 1) (Mathews et al., 2014; Sui et al., 2012). NLRP3 inflammasome activation affects RA development. *A20*$^{-/-}$ mice show enhanced NLRP3 inflammasome activation and excessive secretion of IL-1β which exacerbates inflammation in the synovial joint, leading to erosive polyarthritis similar to RA in patients (Table 1) (Vande Walle et al., 2014). $CD4^+$ T cells from RA patients have augmented Th17 differentiation, increased NLRP3 activation, and enhanced caspase-1 cleavage. Moreover, the knockdown of NLRP3 in $CD4^+$ T cells suppresses Th17 differentiation. NLRP3 inflammasome is activated in $CD4^+$ T cells from RA patients, which is associated with disease activities and IL-17 A production (Zhao et al., 2018). The concentration of IL-17 A but not IFN-γ in the serum shows a strong correlation with active caspase-1 in $CD4^+$ T cells from RA patients. The knockdown of NLRP3 inhibits Th17 differentiation and IL-17 A production, while it induces a slight expansion of Treg in $CD4^+$ T cells (Zhao et al., 2018). In addition, inhibitors of caspase-1 or IL-1R suppress Th17 differentiation, which indicates that NLRP3 inflammasome is involved in Th17 differentiation in RA. Furthermore, $CD4^+$ T cells from RA patients have increased ROS levels, which lead to NLRP3 inflammasome activation and subsequent promotion of Th17 differentiation in RA patients. The inhibition of ROS reduces NLRP3 inflammasome activation and IL-1β production in $CD4^+$ T cells, leading to the inhibition of Th17 differentiation. Overall, NLRP3 inflammasome activation plays a pathogenic role by promoting Th17 differentiation in RA; thus, targeting NLRP3 inflammasome may be a potential therapy for RA treatment (Zhao et al., 2018).

SLE is a systemic autoinflammatory disease that involves in multiple

organs and is characterized by autoantibodies against the patient's own tissues, particularly anti-nuclear antibodies (Dubois and Tuffanelli, 1964). Inflammasome activation-induced IL-1β secretion plays a central role in the development of Th17 cells, which can accelerate the symptoms of SLE by secreting IL-17 A and other inflammatory cytokines, strongly associating with SLE development (Table 1) (Shin et al., 2013; Zhang et al., 2013). The activation of the P2X7/NLRP3 pathway leads to elevated levels of anti-dsDNA antibodies, an increased Th17/Treg cell ratio, and enhanced pathogenesis of lupus nephritis (Table 1) (Zhao et al., 2013), while the blockade of P2X7 inhibits disease progress and increases the survival of lupus-prone mice. In SLE patients, anti-dsDNA antibodies bind to TLR4 of monocytes and macrophages derived from the blood of SLE patients and activate NLRP3 inflammasome, leading to IL-1β–dependent Th17 amplification (Table 1) (Zhang et al., 2016).

Autoinflammatory disorders are affected by inflammasome activation and the secretion of related cytokines, including IL-1β/IL-18. By promoting the differentiation and proliferation of pathogenic Th17 cells, IL-1β is involved in the pathogenesis of inflammasome-associated autoimmune and autoinflammatory diseases. However, whether inflammasome activation is a prerequisite in the progression of these diseases remains elusive (Evavold and Kagan, 2018).

3.6. Inflammasome-derived Th17 and cancer

The differentiation of Th17 cells driven by inflammasome–IL-1/IL-1R signaling has been identified to play important roles in the host immune defense and autoimmune diseases as described above (refer to 3.4 and 3.5). Interestingly, inflammasome activation also links to anti-cancer immunity through the IL-1/IL-1R–Th17 axis.

Inflammasome activation is involved in the development and progression of cancer. Although the components of the inflammasome pathways are essential for the development of intestinal cancer, the stimuli of inflammasome activation during this process remain unclear. NLRP3, NLRP6, and NLRC4 have been shown to play an important role in maintaining gut homeostasis and microbiota diversity, preventing colitis and colitis-related tumors (Allen et al., 2010; Elinav et al., 2011; Hu et al., 2010). Mice deficient in ASC, NLRP3, or NLPR6 display decreased levels of IL-18, which leads to intestinal hyperplasia, leukocyte infiltration, and increased susceptibility to dextran sodium sulfate-induced colitis (Elinav et al., 2011; Zaki et al., 2010). In addition, mice that lacked NLRC4 or caspase-1 showed a higher tendency for epithelial tumor formation due to enhanced proliferation and reduced apoptosis (Hu et al., 2010).

Inflammasome-dependent IL-1β secretion is also involved in tumorigenesis. IL-1β enhances tumor angiogenesis and invasiveness by the secretion of pro-tumoral factors, such as vascular endothelial cell growth factor and TNF, through IL-1R signaling (Krelin et al., 2007; Voronov et al., 2003). In mouse models, blocking IL-1R signaling reduces the incidence of tumorigenesis with less angiogenic factors (Bunt et al., 2007). IL-1β also induces myeloid-derived suppressor cells (MDSCs), which downregulate anti-tumor immunity. *IL-1R*$^{-/-}$ mice have a delayed MDSC accumulation and reduced primary and metastatic tumor progression. Consistent with these findings, NLRP3 activation facilitates the migration of MDSCs to the tumor site, which diminishes the anti-tumor immunity and vaccine efficacy (van Deventer et al., 2010). Thus, inflammasome-IL-1/IL-1R signaling negatively regulates anti-cancer immunity, making them potential targets for anti-tumor therapies (Bunt et al., 2007). As described above (refer to 3.2.4 and 3.2.5), IL-1β induces the differentiation and proliferation of Th17 cells, which promote tumor growth via IL-17 secretion. IL-17 directly stimulates vascular endothelial cell migration and cord formation, as well as activates the oncogenic IL6-STAT3 pathway, which upregulates pro-survival and pro-angiogenic genes that promote angiogenesis and drive pathological neovascularization in tumors (Wang et al., 2009). IL-17 acts as a pro-angiogenic factor in endothelial, stromal, and cancerous cells, as well as initiates angiogenesis to induce tumor vascularization and promote tumor growth (Iwakura et al., 2011; Shurin, 2013). Th17 responses also exert tumor-promoting effects through IL-17–mediated regulation of MDSCs, which provide tumor-promoting microenvironments at tumor sites (He et al., 2010). Tumor growth is inhibited when IL-17 is neutralized, while systemic administration of IL-17 promotes tumor growth. *IL-17A*$^{-/-}$ mice have increased CD8$^+$ T cell numbers and reduced MDSC tumor infiltration, which inhibits tumor growth (Shurin, 2013). IL-17R deficiency increases the infiltration of CD8$^+$ T cells and reduces the infiltration of MDSCs in tumors, whereas the administration of IL-17 inhibits CD8$^+$ T cell infiltration and increases MDSCs in tumors (He et al., 2010). Therefore, in these conditions, the inflammasome–IL-1β–Th17 axis may show pro-tumoral effects. Notably, in other conditions, such as different tumor environmental contexts and inflammation degrees, IL-17 and Th17 cells exhibit potent anti-tumor cytotoxic T cell responses, leading to tumor regression (Kryczek et al., 2009; Murugaiyan and Saha, 2009).

NLRP3 inflammasome activation in MDSCs attenuates the anti-tumor effect of chemotherapy by inducing IL-17–producing CD4$^+$ T cells. Mechanistically, the administration of chemotherapies, such as gemcitabine (Gem) and 5-fluorouracil (5FU), leads to lysosomal destabilization and cytoplasmic release of cathepsin B. Cathepsin B subsequently binds to NLRP3 and promotes caspase-1 activation and IL-1β secretion in MDSCs, resulting in a reduced anti-tumor immunity. In MDSCs treated with 5FU or Gem, lysosomal permeabilization is induced, and mature cathepsin B is subsequently released into the cytoplasm to specifically interact with endogenous NLRP3, leading to caspase-1 activation and IL-1β secretion. 5FU and Gem induced caspase-1 activation is abolished in *NLRP3*$^{-/-}$ MDSCs and reduced in WT MDSCs with the knockdown of endogenous cathepsin B or treatment with a cathepsin B inhibitor. Thus, 5FU and Gem activate NLRP3 inflammasome by releasing cathepsin B into the cytoplasm via chemotherapy-dependent lysosome permeabilization. Caspase-1 activation and IL-1β secretion in MDSCs are also detected in patients with metastatic colon cancer treated with 5FU. Genetic inactivation of NLRP3, caspase 1, or IL-1R, as well as blocking IL-1R signaling with IL-1RA can markedly improve the anti-tumor efficacy of Gem and 5FU. NLRP3 inflammasome-mediated IL-1β secretion induced by Gem and 5FU in MDSCs enhances the IL-17 producing capacity of CD4$^+$ T cells. IL-17 promotes angiogenesis, which results in tumor progression (He et al., 2010; Wang et al., 2009). In mice, 5FU upregulates the expression of Th17 cell-related genes, such as *IL-17A* and *Rorc*, as well as angiogenesis-related genes, such as *Eng* and *Pecam1*, while IL-1RA treatment blocks these effects. NLRP3 inflammasome-mediated elimination of 5FU-induced anti-tumor effects depends on the induction of Th17 responses through IL-1/IL-1R signaling. When cocultured with Gem- or 5FU-treated MDSCs, naïve T cells differentiate into IL-17–producing CD4$^+$ T cells in an IL-1–dependent manner, whereas when cocultured with *caspase-1*$^{-/-}$, *NLRP3*$^{-/-}$, or *cathepsin B*$^{-/-}$ MDSCs similarly treated with Gem or 5FU, naïve T cells fail to exhibit similar differentiation. In humans, IL-17 production is enhanced in PBMCs after 5FU treatment. In *IL-17A*$^{-/-}$ mice, 5FU exhibits an improved anti-tumor efficacy, whereas the IL-1RA–enhanced anti-tumor efficacy disappears. Therefore, 5FU drives IL-1–dependent CD4$^+$ T cell polarization into IL-17–producing Th17 cells, and IL-17 responses subsequently limit the therapeutic effect of 5FU through promoting angiogenesis. Overall, IL-1β promotes the development of IL-17–producing CD4$^+$ T cells, which can impair the anti-cancer effect of chemotherapeutics via IL-17 responses (Table 1) (Bruchard et al., 2013).

The mushroom Agaricus blazei Murill (AbM), which is well known to promote anti-tumor immunity, can promote *pro-IL-1β* transcription and induce NLRP3 inflammasome-dependent IL-1β secretion in macrophages (Huang et al., 2012). AbM-induced IL-1β secretion is markedly reduced in NLRP3- or ASC-deficient macrophages. AbM-induced inflammasome activation is involved in ATP release, ROS production, and potassium efflux. Similar to 5FU and Gem, AbM also induces the

release of cathepsin B to activate NLRP3 inflammasome, while a cathepsin B inhibitor reduces AbM-induced IL-1β secretion. Similar to Gem and 5FU, AbM activates NLRP3 by inducing the cytoplasmic release of cathepsin B; however, whether Abm-activated NLRP3 inflammasome is responsible for AbM-induced anti-tumor immunity is unclear. It appears that Abm-activated NLRP3 inflammasome can promote tumor growth via the IL-1/IL-1R–IL-17 axis, similar to the action of Gem- or 5FU-activated NLRP3 inflammasome. Further studies are required to establish a bridge between AbM-activated NLRP3 inflammasome and tumorigenesis and tumor progression.

Taken together, inflammasome–IL-1/IL-1R–IL-17 signaling provides a novel mechanism of resistance to chemotherapy- and potentially AbM-mediated anti-tumor activity. Chemotherapy induces MDSC killing to impede tumor-induced immunosuppression; AbM also promotes anti-tumor immunity, while simultaneously activating cathepsin B-dependent NLRP3 inflammasome, which is the dark side of the immune response in these conditions, leading to enhanced IL-17 production and accelerated tumor growth via IL-1/IL-1R signaling. Inhibition of NLRP3 inflammasome or IL-1/IL-1R signaling enhances the anti-tumor efficacy of 5FU and Gem. Thus, the administration of inhibitors of IL-1/IL-1R signaling or NLRP3 inflammasome in combination with chemotherapeutic agents may induce potent anti-tumor effects.

4. Conclusion and future perspectives

Inflammasome activation-driven Th17 cells are essential in controlling pathogen infections. Whether the induction of Th17 responses is a general immune defense strategy downstream of the inflammasome pathways deserves further investigation. Bacteria activate inflammasome pathways and induce IL-1β secretion, which further triggers IL-1R signaling and promotes Th17 cell differentiation, conferring protective immune responses. Adenylate cyclase toxin from *B. pertussis* activates NLRP3 inflammasome and promotes Th17 differentiation via IL-1/IL-1R signaling, which is critical for *B. pertussis* clearance. Exotoxins from numerous bacteria, such as hemolysin from *S. aureus*, have been identified to activate NLRP3 inflammasome (Munoz-Planillo et al., 2009). Patients with loss-of-function-mutations of STAT3 are easily subjected to *S. aureus* abscess due to impaired Th17 differentiation, which suggests that host immunity against *S. aureus* infection is closely related to Th17 responses (Milner et al., 2008). However, whether *S. aureus* hemolysin-induced NLRP3 inflammasome activation plays a role in Th17 differentiation remains unclear. Whether other bacteria producing lytic toxins can induce Th17-dependent anti-bacterial immunity through NLRP3 inflammasome requires further investigation. Infection of *L. pneumophila* or *K. pneumoniae* also activates NLRC4 inflammasome through flagellin, while NLRC4-dependent Th17 responses are important in their clearance (Cai et al., 2012). Other intracellular bacteria, such as *Salmonella enterica serovar* Typhimurium, also induce NLRC4 inflammasome activation; thus, it is of interest to determine whether NLRC4 inflammasome activation also induces Th17 responses and plays a role in bacterial clearance during their infections (Wynosky-Dolfi et al., 2014). AIM2 is crucial in the host defense against bacterial and viral pathogens. AIM2 inflammasome can be activated by cytoplasmic DNA released by *M. tuberculosis*. *AIM2*$^{-/-}$ mice are susceptible to intratracheal infection of *M. tuberculosis* (Saiga et al., 2012). Although Th17 responses play an important role in combating *M. tuberculosis* (Shen and Chen, 2018), whether the Th17-mediated anti-*M. tuberculosis* response is driven by the activation of AIM2 inflammasome deserves further exploration (Table 1). RNA viruses, such as influenza A virus (IAV), HIV-1, Hepatitis C virus, rotavirus, Sendai virus, encephalomyocarditis virus, vesicular stomatitis virus, Zika virus, and West Nile virus as well as DNA viruses, such as Hepatitis B virus, adenovirus, modified vaccinia virus, HSV-1, mouse cytomegalovirus, and varicella-zoster virus, have all been shown to activate inflammasomes (Hayward et al., 2018). Among them, IAV is the best studied. Respiratory infection with IAV results in the activation of the NLRP3 inflammasome in the lung. Mice deficient in NLRP3, ASC, or caspase-1, but not NLRC4, fail to secrete IL-1β/IL-18 in response to IAV. ASC, caspase-1, and IL-1R, but not NLRP3, have modulatory effects on CD4$^+$ and CD8$^+$ immune responses, as well as mucosal IgA secretion and systemic IgG responses (Ichinohe et al., 2009). ASC, caspase-1, and IL-1R, but not NLRP3, are required for protective immunity against an IAV challenge. In IL-1R–deficient mice, IAV-specific CD4$^+$ T cell responses, and IgM levels are reduced, and the recruitment of leukocytes to the lung is also impaired. Furthermore, lung leukocyte infiltration depends on ASC, caspase-1, and IL-1R, which indicates that inflammasome activation and IL-1/IL-1R signaling may mediate this process. Thus, inflammasome activation-induced IL-1β secretion is required for IL-1/IL-1R signaling–dependent adaptive immunity against influenza infection; moreover, whether this immune response relies on IL-1β driven-Th17 differentiation is of interest. For other viruses that activate inflammasome pathways listed above, whether the IL-1/IL-1R–dependent adaptive immunity, particularly IL-1β driven-Th17 responses, is activated during viral infections and plays a role in antiviral immunity is currently unclear; therefore, addressing these questions may have significant impacts on vaccine design and virus management. Parasites, such as *Plasmodium vivax*, are stimulators of NLRP1, NLRP3, and AIM2 inflammasomes (Kalantari et al., 2014; Santos et al., 2016). Most studies have focused on the parasite sensing and activation mechanism of inflammasomes, and there is little knowledge regarding whether and how parasite-induced inflammasome activation establishes adaptive immunity, especially Th17 responses, the unveiling of which may provide novel insights into the protective immunity or immunopathology against these parasites (Shio et al., 2009).

Mutations of the components of the inflammasome pathways are associated with autoimmune and autoinflammatory diseases. Inflammasome activation-induced IL-1β drives the differentiation of Th17 cells through IL-1/IL-1R signaling, which contributes to the pathogenesis of autoinflammatory diseases. As described above, in some cases, Th17 responses clearly contribute to inflammasome-associated autoinflammatory diseases. In contrast, in most cases, it remains unknown whether and how Th17 responses participate in the pathogenesis of inflammasome dysregulation-caused autoimmune disorders. For example, NLRP1 mutations cause susceptibility to a series of autoinflammatory diseases, while whether NLRP1 dysregulation is involved in the development of pathogenic Th17 cells, which are the main cause of inflammatory diseases, remains elusive. Therefore, whether IL-1/IL-1R signaling is the bridge of NLRP1 or other inflammasome sensors and pathogenic Th17 response-associated autoinflammatory disorders is of substantial interest.

Immunogenic tumor cell death induced by chemotherapy activates both innate and adaptive anti-tumor immunity (Shurin, 2013). However, when chemotherapeutics target other cell types, the anti-tumor immunity may be suppressed. In DCs, the NLRP3 inflammasome is activated through P2X7 by ATP released from anthracycline- or oxaliplatin-treated tumor cells. Secreted IL-1β primes IFN-γ–producing CD8$^+$ T cells, which results in enhanced T cell-mediated tumor-cell death (Ghiringhelli et al., 2009). The priming of IFN-γ–producing CD8$^+$ T cells by dying tumor cells is abolished in *IL-1R*$^{-/-}$, *NLRP3*$^{-/-}$, or *caspase-1*$^{-/-}$ mice. Chemotherapy-induced anti-tumor immunity is blunted in *P2X7*$^{-/-}$, *NLRP3*$^{-/-}$, or *caspase-1*$^{-/-}$ animals. Anthracycline-treated breast cancer patients who carry a loss-of-function-mutation of P2X7 develop metastatic disease more rapidly than similarly treated patients who have functional P2X7. Thus, NLRP3 inflammasome activation within DCs is decisive for linking the innate immunity to adaptive immunity in anti-tumor responses. In contrast, chemotherapy via Gem or 5FU induces cathepsin B release from lysosomes into the cytoplasm in MDSCs where cathepsin B activates NLRP3 inflammasome, resulting in the promotion of tumor growth (Bruchard et al., 2013). The activation of the NLRP3 inflammasome by Gem or 5FU in MDSCs can markedly decrease the anti-tumor effects in lymphoma, melanoma, mammary cancer, and lung cancer animal models

(Table 1) (Bruchard et al., 2013). The anti-tumor effect of 5FU is substantially enhanced in *IL-17A*$^{-/-}$ mice, which confirms that IL-1β–dependent Th17 cell polarization limits the chemotherapeutic efficacy. Therefore, inflammasome activation-induced IL-1β secretion in chemotherapy has both pro- and anti-tumor effects, depending on the tumor environment context, the types of IL-1β–producing cells, and potentially the cell types it acts on. Thus, understanding the roles of immunological events (such as CD8$^+$ T cell priming and Th17 responses) in the pro- and anti-tumor responses by chemotherapy is extremely demanding, which may contribute to the development of appropriate combinations for chemotherapy and immunotherapy. Understanding the interplay among chemotherapeutic drugs, tumor cell death, and immune cells will improve the diagnostic, prognostic, and therapeutic management of cancer (Shurin, 2013).

In conclusion, inflammasome activation not only induces innate immunity but also promotes adaptive immunity, particularly Th17 responses through IL-1/IL-1R signaling, thereby playing critical roles in anti-infection and anti-cancer responses. Moreover, the dysregulation of these immune responses also leads to autoinflammatory disorders and cancer. Therefore, targeting the inflammasome–IL-1/IL-1R–Th17 axis may provide novel strategies for therapeutic designs and disease control.

Acknowledgments

We apologize to authors whose studies could not be discussed due to space restrictions. We thank Prof. Jin Dong-Yan for his supports of the manuscript.

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