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Review

The absent in melanoma 2 (AIM2) inflammasome in microbial infection

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ABSTRACT

Inflammasomes play a very important role in the host defense against multiple pathogenic microbes, including bacteria and viruses. Inflammasomes are multiprotein complex platforms that mediate the processing of the two most important inflammatory cytokines, pro-IL-1β and pro-IL-18, to their active forms. The inflammasome is formed by the apoptosis-associated speck-like protein containing a CARD (ASC), procaspase-1 and a sensor protein, either a NOD-like receptor (NLR) or an absent in melanoma 2 (AIM2)-like receptor. The sensor molecule determines inflammasome specificity by detecting specific and conserved microbial products or cell stress signals. Compared with the other inflammasomes, there is much more unknown about the activation or regulation mechanisms of the AIM2 inflammasome. In this review, we will discuss these mechanisms and the specific roles of the AIM2 inflammasome in response to diverse pathogens.

1. Introduction

The host innate immune system has evolved numerous defense mechanisms to quickly sense and recognize microbial infection. Inflammation is an effective and critical process for the host response to infection [1]. The initiation of inflammation begins when host pattern recognition receptors (PRRs) recognize the presence of unique or conserved microbial components, called pathogen-associated molecular patterns (PAMPs) or endogenous damage-associated molecular patterns (DAMPs) generated in the location of tissue injury [2,3]. To date, five classes of PRRs have been identified, including Toll-like receptors (TLRs) [4], C-type lectin receptors (CLRs) [5], retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) [6], NOD-like receptors (NLRs) [7–9], and AIM2-like receptors (ALRs) [10]. NLRs include NLRP1, NLRP3 and NLRC4. ALRs include absent in melanoma 2 (AIM2) and interferon-inducible protein 16 (IFI16) and are composed of an N-terminal pyrin domain (PYD) and a C-terminal hematopoietic, interferon-inducible, nuclear localization (HIN) domain [11,12]. ALRs can sense cytosolic dsDNA directly by their HIN domain. Upon dsDNA binding, ALRs may undergo a conformational change to free the N-terminal PYD to cluster and trigger inflammasome activation.

The inflammasome is a multiprotein signaling platform that activates caspase-1 and processes the maturation of the proinflammatory cytokines, interleukin-1β (IL-1β) and IL-18 to their active forms [13,14]. The canonical inflammasomes are composed of at least three main components: an inflammatory caspase (caspase-1 or caspase-11), an adapter molecule (such as ASC), and a sensor protein (such as NLRP1, NLRP3, NLRP12, NAIP1, NAIP2, NAIP5, or AIM2). The activated inflammasome often induces a type of cell death named pyroptosis and subsequent antimicrobial inflammatory responses. Recently, a novel function of inflammasomes characterized by the induction of caspase-8-dependent apoptosis was also identified [15,16]. AIM2 is a cytosolic double-stranded DNA (dsDNA) receptor. In 1997, AIM2 was first identified by subtractive DNA hybridization in a human malignant melanoma cell line UACC-903(+6) that had received human chromosome 6. However, because of its deletion in the melanoma cell

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Abbreviations: PAMPs, Pathogen-associated molecular patterns; PRRs, Pattern recognition receptors; DAMPs, Damage-associated molecular patterns; TLRs, Toll-like receptors; RIG, Retinoic acid-inducible gene; NLRs, NOD-like receptors; RLRs, Retinoic acid-inducible gene (RIG)-I-like receptors; AIM2, Absent in melanoma 2; ALRs, AIM2-like receptors; IFI16, Interferon-inducible protein 16; PYD, Pyrin domain; HIN, Hematopoietic, interferon-inducible, nuclear localization domain; CLRs, C-type lectin receptors; NLRC4, NLR family CARD domain-containing protein 4; NALP3, NACHT, LRR and PYD domain-containing protein 3; IFNAR, interferon-α/β receptor; *L. monocytogenes*, *Listeria monocytogenes*; *M. tuberculosis* (Mtb), *Mycobacterium tuberculosis*; *M. bovis*, *Mycobacterium bovis*; *F. tularensis*, *Francisella tularensis*; *F. novicida*, *Francisella novicida*; *S. aureus*, *Staphylococcus aureus*; *S. pneumonia*, *Streptococcus pneumonia*; *P. gingivalis*, *Porphyromonas gingivalis*; *Pf*, *Plasmodium falciparum*; mCMV, Murine cytomegalovirus; HSV-I, Herpes simplex virus I; HBV, Hepatitis B virus; AHB, Acute hepatitis B; CHB, Chronic hepatitis B; HPV, *Human papillomavirus*; ATIIs, Alveolar type II cells; AMs, Alveolar macrophages; mtDNA, Mitochondrial DNA; GBPs, Guanylate-binding proteins; LLO, Listeriolysin O pore-forming toxin

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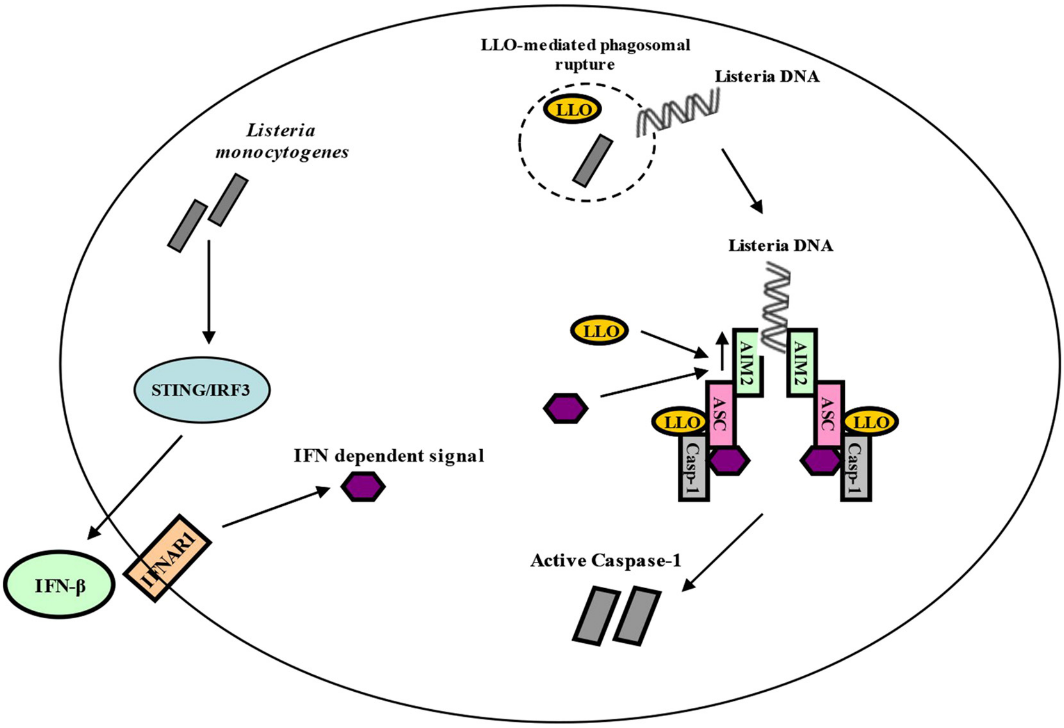

Fig. 1. Model of AIM2 inflammasome activation mechanism in *Listeria monocytogenes* infection. AIM2 can sense Listeria genomic DNA and induce the activation of caspase-1. The pore-forming toxin listeriolysin O (LLO) can upregulate the expression of AIM2, induce the ASC speck formation and release the bacterial genomic DNA to cytosol by mediating the phagosomal rupture. The activation of STING/IRF3 pathway results in the production of type-I IFN. The type I IFN dependent signal through IFNAR1 is essential for AIM2 activation by upregulating the level of AIM2 and mediating the ASC assembly.

line UACC-903, AIM2 was named absent in melanoma [17]. The restoration of AIM2 expression in melanoma cells can reverse its malignant phenotype. As an ALR, AIM2 can bind to DNA via its HIN200 domain and mediate ASC oligomerization to initiate the activation of a caspase-1-dependent inflammasome, leading to the secretion of the mature proinflammatory cytokines, interleukin-1β (IL-1β) and IL-18. The dsDNA-AIM2 inflammasome pathway is important for host cells to defend against bacterial and viral pathogens. The sensing of cytosolic double-stranded DNA can also activate the interferon (IFN)-stimulatory DNA (ISD) pathway, now known as the cGAS-STING-TBK1-IRF3 pathway. In this pathway, cyclic GMP-AMP synthase (cGAS) senses DNA independently of its sequence and then activates the adaptor stimulator of interferon genes (STING). STING subsequently activates the protein kinases IKK and TBK1, which in turn activate the transcrition factors NF-κB and interferon regulatory factor 3 (IRF3) to induce type I IFN production [18,19]. The effect of type I IFN signaling on bacterial infection in vivo can be beneficial or detrimental depending on the pathogen. Type I IFN signaling is protective in mice infected with *Streptococcus pneumoniae*, whereas pathogenic type I IFN signaling dominates the protective AIM2 inflammasome responses during *Francisella* infection [20]. Type I IFN signaling can regulate the activation of the AIM2 inflammasome upon *Listeria monocytogenes, Francisella* and *Streptococcus pneumoniae* infection. AIM2 protein expression is upregulated in bone marrow-derived macrophages (BMDMs) treated with IFN-β or infected with *Francisella* and *Listeria monocytogenes*. Compared with wild-type BMDMs, increased AIM2 expression was not observed in STING$^{-/-}$ or IFN-I receptor-deficient IFNAR$^{-/-}$ BMDMs [21]. In addition, *Francisella* infection of IRF3$^{-/-}$ macrophages, which are defective in the secretion of type I interferons, resulted in less efficient activation of the AIM2 inflammasome compared with that of wild-type macrophages. After treating these macrophages with IFN-β at the time of infection, AIM2 activation by *Francisella* infection was restored [22]. Furthermore, IFNAR1 blockade significantly reduced AIM2-mediated IL-18 production by *Streptococcus pneumonia* [23]. The interaction between these two intracellular DNA-sensing inflammatory pathways, the AIM2 inflammasome pathway and the cGAS-STING-TBK1-IRF3 pathway, may play an exquisite role in anti-infective immunity. In this review, we will elaborate on the activation and specific roles of AIM2 inflammasomes in recognition and host responses in diverse bacterial and virus infections.

2. The role of the AIM2 inflammasome in response to intracellular bacteria

2.1. *Listeria monocytogenes*

Listeria monocytogenes (L. monocytogenes) invades the cytoplasm of macrophages and activates multiple inflammasomes, including AIM2, NACHT, LRR and PYD domain-containing protein 3(NALP3), also known as NLRP3 and NLR family CARD domain-containing protein 4 (NLRC4) [24,25]. In NLRP3 and NLRC4 knockout macrophages, the secretion of IL-1β and IL-18 in response to L. *monocytogenes* was only slightly decreased relative to that of wild-type macrophages; however, the secretion of IL-1β and IL-18 was significantly decreased by knockdown of AIM2 [25]. In ASC knockout macrophages, the secretion of IL-1β and IL-18 was completely impaired, which suggests that AIM2 sensors also participate in inflammasome activation in an ASC-dependent manner. Several receptor candidates, including NLRP3, NLRC4 and AIM2, were used to reconstitute the inflammasome system in HEK293 cells, and the results suggested that AIM2 had the highest responsiveness to L. *monocytogenes* infection in HEK293 cells. NLRP3 and NLRC4 also participate in the response to bacterial infection [24]. *L. monocytogenes* replicates efficiently in the host. Continuous proliferation of L. *monocytogenes* in host macrophages might exhaust the nutrients and result in subsequent bacterial death or autolysis, accompanied by the breakdown of the cell wall. Lysis of L. *monocytogenes* in the cytoplasm of host cells may release bacterial DNA into the cytoplasm where it will be recognized by the AIM2 inflammasome. There is

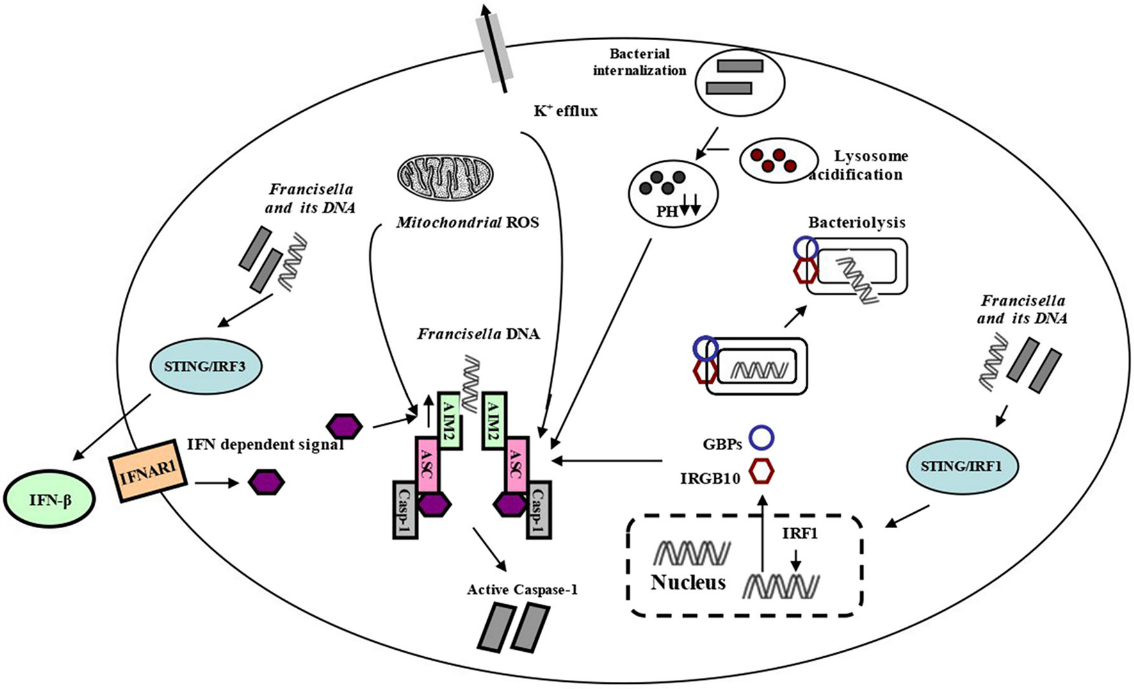

Fig. 2. Model of AIM2 inflammasome activation mechanism in *Francisella* infection. *Francisella* genomic DNA might be the ligand to activate AIM2 inflammasome. The activation of STING/IRF3 pathway results in the production of type-I IFN. The type I IFN dependent signal through IFNAR1 is essential for AIM2 activation by upregulating the level of AIM2 and mediating the ASC assembly. The STING/IRF1 pathway can also be activated. The interferon-inducible protein GBPs and IRGB10 can cause lysis of *Francisella* bacteria and leakage of bacterial DNA into the cytoplasm. Cytoplasmic potassium efflux is critical for AIM2 inflammasome activation by ASC pyroptosome formation and recruitment of caspase-1 to ASC oligomers. Bacterial internalization and lysosomal acidification are also required for activation of the AIM2 inflammasome. Mitochondrial ROS potentiate indirect activation of the AIM2 inflammasome.

evidence to suggest that L. *monocytogenes* genomic DNA is actually responsible for AIM2 inflammasome activation during infection [26–28], and the pore-forming toxin listeriolysin O (LLO) can upregulate the expression of AIM2 and induce ASC speck formation; In addition, bacterial genomic DNA can be released into the cytosol by LLO-mediated phagosomal rupture. Previous work also suggested that type I IFN signaling is essential for AIM2 activation in response to L. *monocytogenes* through the interferon-α/β receptor (IFNAR) [27,29] (Fig. 1).

2.2. Mycobacterium

M. tuberculosis DNA (Mtb DNA) present in the cytosol, colocalized with AIM2 suggesting that Mtb DNA could be recognized by AIM2 [30,31]. In addition, Mtb DNA alone could induce IL-1β/IL-18 secretion in an AIM2-dependent manner. These results suggest that *M. tuberculosis* infection could activate the AIM2 inflammasome by its genomic DNA. Bacterial escape from the phagosome to the cytosol may release cytosolic DNA that could activate the AIM2 inflammasome in *M. bovis*-infected macrophages. A recent report demonstrated that AIM2 inflammasome activation may require cytoplasmic potassium efflux in response to *M. bovis* infection. In addition, mycobacterial internalization was also required for *M. bovis* to trigger AIM2 inflammasome activation in macrophages because cytochalasin D, a phagocytosis inhibitor treatment, reduced *M. bovis*-induced IL-1β secretion significantly and decreased the mRNA expression level of AIM2 and ASC at the same time [30]. Although there are some reports that describe AIM2 inflammasome activation triggered by *Mycobacterium*, much remains unknown about how *Mycobacterium* delivers its genomic DNA into the cytosol and triggers or regulates the activation of the AIM2 inflammasome. In vivo experiments suggested that AIM2-deficient mice were highly susceptible to *M. tuberculosis*. The absence of AIM2 resulted in impaired production of IL-1β and IL-18 in serum. Mycobacterial antigen-specific production of IFN-γ was severely reduced in CD4$^+$ T cells derived from the spleen of *M. tuberculosis*-infected Aim2$^{-/-}$ mice, which means that AIM2 deficiency may result in impaired Th1 responses after *M. tuberculosis* infection [31].

2.3. Francisella

Francisella tularensis (*F. tularensis*) is an intracellular bacterium that can replicate in the host cytoplasm. In the macrophage cytosol, *F. tularensis* can be recognized by the AIM2 inflammasome, leading to the activation of the AIM2 inflammasome and the secretion of mature IL-1β and IL-18 [21,32]. The colocalization of bacterial DNA with endogenous AIM2 and the inflammasome adaptor ASC was observed in macrophages infected with *F. tularensis*. *F. novicida* can also activate the AIM2 inflammasome in dendritic cells, causing the secretion of IL-1β and rapid host cell death [33]. The replication of *F. novicida* is necessary for inflammasome activation in dendritic cells. The inflammasome activation induced by *F. novicida* in dendritic cells may be beneficial to bacterial clearance. *Francisella* infection can induce the release of interferon-β. Type-I IFN signaling is critical to AIM2 inflammasome activation in macrophages because IFNAR-deficient macrophages do not process caspase-1, release proinflammatory cytokines or die in response to *Francisella* [29]. In BMDCs from mice deficient for the type I interferon receptor (IFNAR$^{-/-}$ BMDCs), caspase-1-mediated cell death and IL-1β release were partially inhibited in response to *F. novicida* infection, which suggests that type I interferon signaling is partially required for AIM2 inflammasome activation in BMDCs. In fact, type I IFN (IFN-α and -β) secretion in response to *F. tularensis* does not require AIM2, but type I IFN can boost AIM2-dependent caspase-1 activation [32,34]. However, type I IFN signaling can mediate detrimental responses by inducing the activation of apoptotic caspases and cell death despite the protective AIM2 inflammasome response [20]. The guanylate-binding proteins (GBPs) and the interferon-inducible protein IRGB10 can promote AIM2 inflammasome activation during *F. novicida* by inducing

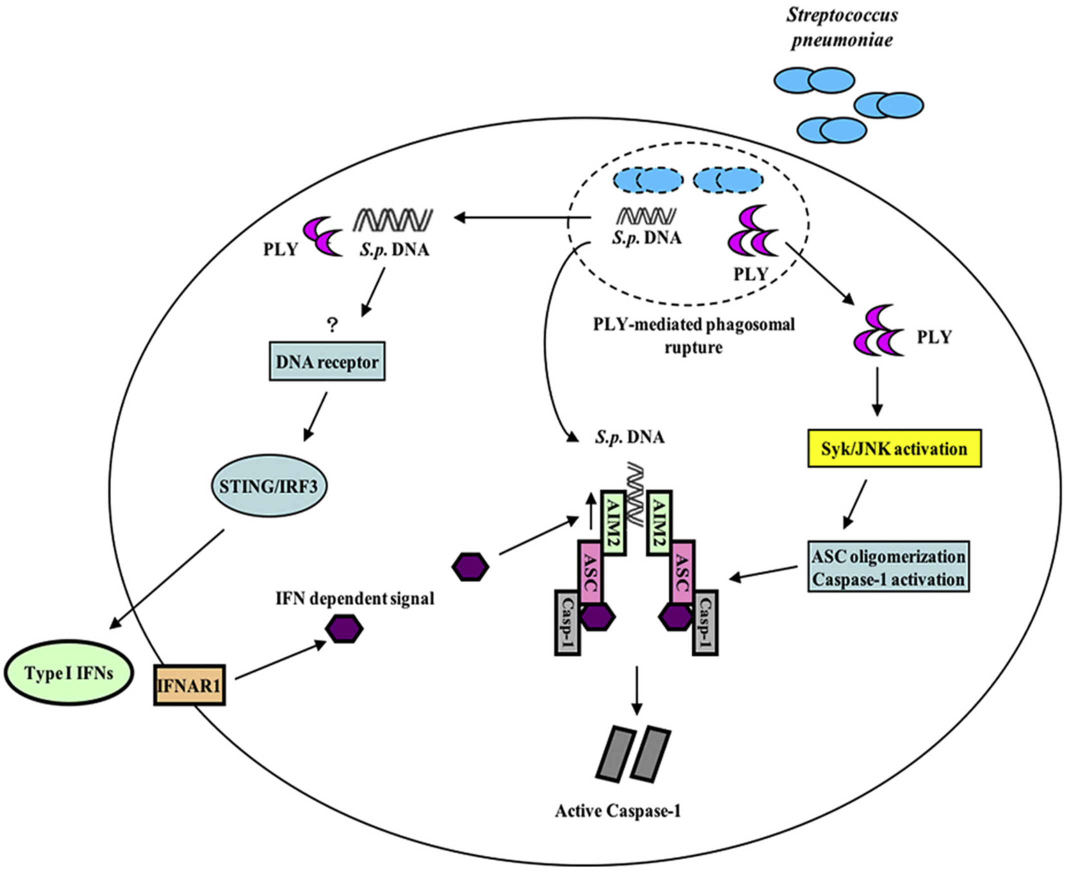

Fig. 3. Model of AIM2 inflammasome activation mechanism in *Streptococcus pneumoniae* infection. For extracellular bacteria, phagocytosis in macropahges is important for activation of the AIM2 inflammasome and caspase-1. *S. pneumoniae* genomic DNA might be the ligand for AIM2 inflammasome. The pneumolysin (PLY), a cytolysin, one of the most important virulence factors of *S. pneumonia* can rupture the phagosome, leading to the leakage of bacterial DNA into the cytoplasm. STING/IRF3 pathway and type I IFN signal can be activated by intracellular recognition of bacterial DNA and PLY. Type I IFN subsequently regulates the activation of the AIM2 inflammasome by upregulating AIM2 expression. Syk/JNK is involved in the activation of the AIM2 inflammasome by regulating caspase-1 activation and ASC oligomerization. PLY participates in syk/JNK activation process.

cytosolic bacteriolysis and DNA release [33,35–38]. Cytoplasmic potassium efflux is critical for the assembly of the AIM2 inflammasome and formation of ASC specks. Inhibition of potassium efflux by increasing the potassium concentration in the culture medium completely blocks ASC speck formation, caspase-1 activation and IL-1β secretion in NLRP3$^{-/-}$ macrophages. The actin oligomerization inhibitor cytochalasin D and the endosomal acidification inhibitors bafilomycin A or NH4Cl can markedly block the activation of caspase-1 and cell death by *Francisella*-infection, indicating that bacterial internalization and lysosomal acidification are all required for recognition of *Francisella* and activation of the AIM2 inflammasome [22]. Mitochondrial ROS mediate indirect activation of the AIM2 inflammasome. Inhibition of mitochondrial ROS by the specific ROS scavenger mitoTEMPO reduces the activation of caspase-1 and the secretion of IL-1β in *Francisella*-infected but NLRP3$^{-/-}$ bone marrow derived-macrophages (BMMs) [39] (Fig. 2).

3. The role of the AIM2 inflammasome in response to extracellular bacteria

3.1. Staphylococcus aureus

Staphylococcus aureus (S. aureus) elicits IL-1β production during the acute phase of infection in the central nervous system (CNS). ASC and caspase 1 KO mice were sensitive to *S. aureus* infection in the CNS with approximately 50% of mice succumbing to infection. The survival of NLRP3$^{-/-}$ mice during *S. aureus* infection was similar to that of WT mice, but AIM2 KO mice had similar disease patterns as ASC$^{-/-}$ mice. In addition to IL-1β, other key inflammatory mediators, including IL-6, CXCL1, CXCL10, and CCL2 in abscess homogenates were significantly reduced in the CNS of AIM2$^{-/-}$ and ASC$^{-/-}$ mice. However, these cytokines or chemokines were not dependent on inflammasome activation. These results demonstrate the critical role of the AIM2 inflammasome but not the NLRP3 inflammasome in acute *S. aureus* infection in the CNS. The lysis of *S. aureus* by host cells through phagocytosis or intracellular killing may lead to bacterial DNA release into the cytoplasm and subsequent AIM2 inflammasome activation. The intracellular survival phase of *S. aureus* contributes to the activation of cytosolic AIM2 activation [40].

3.2. Streptococcus pneumoniae

Streptococcus pneumonia (S. pneumonia) is a gram-positive, extracellular bacterium. Recent reports demonstrated that NLRP3 and AIM2 were required for the host to respond to *S. pneumonia* infection [41]. Caspase-1 activation was partially impaired in NLRP3$^{-/-}$ macrophages, but knockdown and knockout of AIM2 resulted in a remarkable decrease in caspase-1 activation in response to *S. pneumoniae*. These results suggest that AIM2 might be more important than NLRP3 in the response to *S. pneumoniae*. However, how AIM2 senses DNA during infection with *S. pneumonia* remains poorly understood. It has been hypothesized that pneumolysin (PLY), a cytolysin that is one of the most important virulence factors of *S. pneumonia,* can be released from autolyzed or killed bacteria in the phagosome. The released PLY might destabilize the membrane of phagosomes, leading to the leakage of bacterial DNA into the cytoplasm [42]. Activation of the AIM2 inflammasome is not specific during infection by intracellular parasitic microbes. Any other microbial pathogen that possesses the ability to deliver its DNA into the cytoplasm can also activate the AIM2 inflammasome. *S. pneumonia* infection can also induce the production of type I interferons (IFNs). It has been demonstrated that the AIM2 inflammasome rather than the NLRP3 inflammasome requires type I IFN signaling for activation [43] [23]. The Syk and JNK signaling pathways are also involved in AIM2 inflammasome activation in macrophages infected with *S. pneumonia* by regulating caspase-1 activation and ASC oligomerization. Pneumolysin (PLY) is essential for Syk/JNK activation in this process [44] (Fig. 3).

3.3. *Porphyromonas gingivalis*

Porphyromonas gingivalis (P. gingivalis) is involved in the pathogenesis of periodontitis [45]. *P. gingivalis* induces IL-1β secretion and inflammatory cell death via NLRP3 and AIM2 inflammasome activation. *P. gingivalis* DNA has been detected in the cytoplasm of THP-1 cells, which means that AIM2 might be activated by *P. gingivalis* DNA. In addition, *P. gingivalis* infection activates NLRP3 and AIM2 inflammasomes via the TLR2 and TLR4 pathways because knockdown of TLR2 and/or TLR4 with specific siRNAs inhibits *P. gingivalis*-induced caspase-1 activation and IL-1β maturation in THP-1 cells [46].

3.4. *Plasmodium falciparum*

Plasmodium falciparum (Pf) replicates inside red blood cells (RBCs) [47]. The lysis of parasitized RBCs often induces a proinflammatory cytokine storm characterized by excessive production of TNF-α, IFN-γ and IL-1β [48,49]. Accumulated reports have proven that Pf infection can activate both AIM2 and NLRP3 inflammasomes [50]. In vivo and in vitro results revealed that hemozoin (Hz) prepared from Pf cultures could induce proinflammatory responses via NLRP3 and AIM2 inflammasomes. Genomic DNA of *Pf* (*Pf* gDNA) can trigger the translocation of TLR9 to the membrane of the phagosomes, which may provide necessary signals for the initial synthesis of pro-IL-1β [50]. RBCs infected with Pf can also induce AIM2 activation in BMDMs. Similar to this result, gDNA and Hz can also activate the AIM2 inflammasome in BMDMs. Hz can damage the vacuolar or phagolysosomal membrane. In addition, Hz is also responsible for delivering DNA to the cytosol. In the cytoplasm, *Pf* gDNA dissociates from Hz and is recognized by AIM2 directly [50].

4. The role of the AIM2 inflammasome in responses to DNA viruses

The AIM2 inflammasome plays a critical role in the host defense against certain DNA viruses [51,52]. AIM2 can regulate the production of IL-1β in response to infection by vaccinia virus and murine cytomegalovirus (mCMV) [51]. Macrophages and dendritic cells lacking the AIM2 gene were not able to activate caspase-1 to cleave pro-IL-1β when infected with vaccinia virus or mCMV. Consistent with these in vitro results, reduced amounts of IL-18 were produced in the serum in mCMV-infected AIM2 knockout mice compared with wild-type controls. In addition, the reduced amount of IL-18 markedly impaired the production of splenic NK-cell IFN-γ in mice infected with mCMV. The lack of IL-18 and the production of NK-cell IFN-γ caused an elevation of the viral loads in the spleens of AIM2 knockout mice relative to that of the wild-type controls [51].

It should be noted that the AIM2 inflammasome is not able to sense all DNA viruses. For example, herpes simplex virus I (HSV-I), a DNA virus is sensed by IFI16 and NLRP3 but not AIM2. Two possible reasons for this outcome are as follows: 1) HSV-1 DNA is coated by a viral capsid and protected from AIM2 recognition in the cytoplasm; 2) the expression of IFI16 inhibits the synthesis of AIM2 in the host cell [53,54].

Hepatitis B virus (HBV) is a DNA virus. However, whether HBV infection activates the AIM2 inflammasome or not remains unknown. Recent reports demonstrated that there was a higher expression level of AIM2, IL-1β, and IL-18 in acute hepatitis B (AHB) patients PBMCs than in chronic hepatitis B (CHB) patients PBMCs [55]. The AIM2 mRNA level was significantly negatively correlated with hepatitis B virus (HBV) load and HBeAg in the serum. In addition, the AIM2 mRNA level was positively correlated with the clearance of HBV in the host. These findings suggest that the AIM2 inflammasome may play an important protective role during the AHB phase [56]. Among patients with HBV-associated glomerulonephritis, the expression of AIM2 was found to be significantly higher in the high HBV replication group than in the low HBV replication group. Therefore, inflammatory lesions may be associated with elevated AIM2 levels during HBV infection and replication [57].

Human papillomavirus (HPV) is a type of non-enveloped, double-stranded DNA (dsDNA) viruses that selectively infects keratinocytes in stratified epithelia [58]. A recent report suggested that AIM2 and IFI16 were present in HPV-positive skin lesions by immunohistochemistry [59]. HPV16 activates the AIM2 inflammasome in keratinocytes and the presence of cytosolic HPV16 DNA in biopsy samples has been confirmed by CISH staining. Cleaved IL-1β and mature caspase-1 have been detected in HPV-infected skin, which suggests inflammasome activation is induced by HPV viral DNA. Functional studies have proven that HPV16 DNA could trigger AIM2 inflammasome activation in normal human keratinocytes. Blocking IFI16 could increase the IL-1β secretion induced by HPV16 DNA, which suggests that there might be crosstalk between IFI16 and AIM2 in response to HPV infection. In addition, IFN-β secretion was found to be increased after AIM2 knockdown in keratinocytes, which suggests that AIM2 might act as a physiological inhibitor of IFN-β [59].

5. The role of the AIM2 inflammasome in response to RNA viruses

To date, little research has been performed on the activation of the AIM2 inflammasome induced by RNA viruses. It has been found that influenza virus infection can induce the activation of AIM2 in human primary alveolar type II cells (ATIIs) and alveolar macrophages (AMs) [60]. After AMs were infected with A/PR/8/34(PR8) viruses for 4 h, a significant elevation of AIM2 mRNA levels was detected compared with non-infected AMs. The elevation of AIM2 mRNA levels could be sustained for more than 24 h after PR8 infection, which suggests that AIM2 may play an important role during the early phase and late phase of influenza virus infection. In human AMs, knockdown of AIM2, NLRP3 and ASC by siRNA resulted in decreased secretion of TNF-α and RANTES, which suggests that AIM2 in combination with NLRP3 plays an important role in the host in response to influenza infection. There is no double- stranded DNA (dsDNA) phase during the replication cycle of influenza virus, and dsDNA is the only ligand of the AIM2 inflammasome; Thus, how influenza virus triggers the activation of the AIM2 inflammasome remains to be investigated. It can be assumed that the organelles or nucleus may be the source of the DNA that activates the AIM2 inflammasome in influenza infection. In fact, many reports have suggested that PB1-F2, an important virulence factor of influenza virus, interacts with the membrane of mitochondria (mt), which might cause mtDNA release, and mtDNA can trigger the activation of the AIM2 inflammasome [39,61,62]. Influenza virus infection often induces apoptosis of the cell [63–65], and the induced apoptosis may disrupt the integrity of the cell membrane and cause chromosomal DNA fragmentation and release. The released fragmented DNA or apoptotic infected cells may be taken up or phagocytosed by macrophages and consequently activate the AIM2 inflammasome.

Table 1
AIM2 inflammasome activation in different microbial pathogen infections.

Microbial pathogens	Activated inflammasome	Secretion of cytokines	Tissue origin	Pathway	Factors involved in the AIM2 activation mechanism	Ref.
Intracellular bacteria						
Listeria monocytogenes	NLRP3, NLRC4, AIM2	IL-1β, IL-18, TNF-α, type I IFNs	Mouse models	Canonical	Bacterial DNA;Type I IFN signals;LLO	[26–29]
Mycobacterium tuberculosis	NLRP3, AIM2	IL-1β, IL-18,IFN-β	Mouse models	Canonical	Bacterial DNA; Cytoplasmic potassium efflux; Mycobacterial internalization; but not IFN-β release	[30–31]
Francisella	AIM2	IL-1β, IL-18	Mouse models	Canonical	Bacterial DNA; Type I IFN signals; GBPs and IRGB10; Cytoplasmic potassium efflux; Mycobacterial internalization; Lysosomal acidification; Mitochondrial ROS	[21,22,29,32,33,38,39]
Extracellular bacteria						
Staphylococcus aureus	NLRP3, AIM2	IL-1β, IL-18	Mouse models	Canonical	Bacterial DNA; Others unknown	[40]
Streptococcus pneumoniae	NLRP3, AIM2	IL-1β, IL-18, Type I IFNs	Mouse models	Canonical	Bacterial DNA; Type I IFN signals; Pneumolysin (PLY)	[42,23]
Porphyromonas gingivalis	NLRP3, AIM2	IL-1β, IL-18	Human acute monocytic leukemia cell (THP-1 cell)	Canonical	Bacterial DNA;TLR2 and/or TLR4	[46]
Plasmodium falciparum	NLRP3, AIM2	IL-1β, IL-18	Mouse models	Canonical	Bacterial DNA; Others unknown	[50]
DNA viruses						
Cytomegalovirus	NLRP3, AIM2	IL-1β, IL-18, IFN-γ	Mouse models	Canonical	Viral dsDNA;Others unknown	[51]
Hepatitis B virus (HBV)	AIM2	IL-1β, IL-18	Human PBMCs; Human HGM cells; Human nephridial and hepatic tissue specimens	Canonical	Viral dsDNA;Others unknown	[56,57]
Papillomavirus (HPV)	AIM2, IFI16	IL-1β, IL-18	Human primary keratinocytes (NHEKs)	Canonical	Viral dsDNA;Others unknown	[59]
RNA viruses						
Influenza virus	AIM2, NLRP3	IL-1β, IL-18	Mouse model; Primary human and murine ATII cells and AMs	Noncanonical	Unknown	[60]

ATII cells: Alveolar type II cells AMs: Alveolar macrophages PBMCs: Peripheral blood mononuclear cells HGM cells: Human glomerular mesangial cells.
Canonical pathway: Microbial DNA triggers activation of the AIM2 inflammasome.
Noncanonical pathway: Host DNA from the nucleus or mitochondria may be the DNA ligand of the AIM2 inflammasome.

6. Regulation of inflammasome activation

For all bacterial pathogens and DNA viruses, DNA is always found in the cytoplasm of the cell during the process of AIM2 inflammasome activation [51,52], but the challenging question is why only a small portion of DNA-containing pathogens, especially DNA viruses, activate the AIM2 inflammasome. There must be some unknown mechanisms for the microbes to evade the activation of the inflammasome. Bacterial escape from the vacuole and the release of genomic DNA into the cytoplasm are two necessary factors for the AIM2 inflammasome activation during infection. Recent reports have suggested that certain bacteria may encode virulence factors that can escape detection from the AIM2 inflammasome [66]. Some strains of *F. tularensis* encode a clustered, regularly interspaced, short palindromic repeat-CRISPR associated system (CRISPR-Cas), which can strengthen the integrity of the bacterial membrane [67]. By this system, the strain can prevent excessive DNA release and minimize the amount of DNA ligands available to AIM2 in the cytoplasm. *L. pneumophila* can prevent rupture of the Legionella-containing vacuole by encoding the effector protein SDHA (succinate dehydrogenase complex flavoprotein subunit A), which is part of the Dot/Icm type IVB secretion system [68]. Some DNA viruses protect their genomic DNA from AIM2 recognition by coating it with a viral capsid. Inhibiting the synthesis of AIM2 may be another strategy for some pathogens to escape detection by AIM2 [54]. Type I interferon signaling may also contribute to AIM2 inflammasome activation [23,29,34,69]. The microbes may regulate the activation of the AIM2 inflammasome by regulating type-I signaling.

7. The AIM2 inflammasome regulates Caspase-3/8/9

Formerly, the AIM2 inflammasome complex had only been ascribed to caspase-1 activation. A recent report suggested that *F. tularensis* infection triggered AIM2/ASC-dependent caspase-3-mediated apoptosis in caspase-1-deficient macrophages [16,70]. AIM2/ASC-dependent caspase-1-independent activation of caspase-8- and caspase-9-mediated cell death was also observed in *F. tularensis*-infected cells [16]. Caspase-8 interacts with ASC, and the colocalization of active caspase-8 with AIM2/ASC speck has also been identified; thus, the AIM2/ASC complex may act as a novel caspase-8 activation platform, and activated caspase-8 then acts as the apical caspase in the AIM2/ASC dependent apoptotic pathways [71]. The AIM2 inflammasome activates caspase-8 and -1, which may lead to both apoptotic and pyroptotic cell death at the same time. The balance between pyroptosis and apoptosis is determined by the amount of DNA in the cell. Apoptosis requires a lower transfected DNA concentration than pyroptosis, which has a higher threshold for activation [71]. These works strongly demonstrate the crosstalk between inflammasome components and apoptosis.

8. Conclusion and future perspectives

It is well known that AIM2 plays a critical role in caspase-1 activation in response to intracellular parasitic pathogens such as *F.tularensis*, *L. monocytogenes* and some DNA viruses [51,52,71,72]. However, recent reports have proven that the AIM2 inflammasome also responds to some extracellular bacteria, including *S. pneumonia* and *S. aureus* [71]. These reports extend the function and role of the AIM2 inflammasome in response to microbial infection in the host (Table 1). Delivery of microbial DNA into the cytoplasm is the decisive factor in the activation of AIM2. In addition to microbial genomic DNA, organelles of host cells, such as the nucleus and mitochondria, can also act as sources of the DNA ligand of AIM2. According to some recent reports, the AIM2 inflammasome also plays a detrimental role in the pathogenesis of arthritis, erythematosus and other autoimmune diseases [73–77]. These clinical findings demonstrate that the AIM2 inflammasome can recognize endogenous DNA. The activation of AIM2 upon influenza infection means that the AIM2 inflammasome is involved in the immune response to an RNA virus infection [60]. All of these results suggest that the ligand of the AIM2 inflammasome might come from multiple sources, but adequate and direct evidence is needed to prove this hypothesis.

In addition, some reports have suggested that the inhibition of NLRP3 or IFI16 could increase the expression of AIM2 [53,78,79], so the cross talk mechanism between the AIM2 inflammasome and NLRP3 or IFI16 needs to be investigated further. TLR2 and/or TLR4 participate in the AIM2 inflammasome activation during *P. gingivalis* infection, while translocation of TLR9 is necessary for Pf gDNA-induced AIM2 inflammasome activation [46]. These results suggest that there is crosstalk between AIM2 and TLRs. Some reports have pointed out that type-I interferon may have a positive or negative correlation with the AIM2 inflammasome in response to different microbes [71], the underlying mechanism of which also needs to be investigated. In addition, the correlation between the AIM2 inflammasome and the recently identified type III interferon also needs to be investigated.

Conflicts of interest

The authors declare there are no conflicts of interest.

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References

[1] C.A. Janeway Jr., R. Medzhitov, Innate immune recognition, Annu. Rev. Immunol. 20 (2002) 197–216.
[2] S. Akira, Pathogen recognition by innate immunity and its signaling, Proc. Jpn. Acad. B Phys. Biol. Sci. 85 (4) (2009) 143–156.
[3] S. Akira, S. Uematsu, O. Takeuchi, Pathogen recognition and innate immunity, Cell 124 (4) (2006) 783–801.
[4] S. Akira, K. Takeda, T. Kaisho, Toll-like receptors: critical proteins linking innate and acquired immunity, Nat. Immunol. 2 (8) (2001) 675–680.
[5] T.B. Geijtenbeek, S.I. Gringhuis, Signalling through C-type lectin receptors: shaping immune responses, Nat. Rev. Immunol. 9 (7) (2009) 465–479.
[6] Y.M. Loo, M. Gale Jr., Immune signaling by RIG-I-like receptors, Immunity 34 (5) (2011) 680–692.
[7] L. Franchi, J.H. Park, M.H. Shaw, N. Marina-Garcia, G. Chen, Y.G. Kim, G. Nunez, Intracellular NOD-like receptors in innate immunity, infection and disease, Cell. Microbiol. 10 (1) (2008) 1–8.
[8] T.D. Kanneganti, M. Lamkanfi, G. Nunez, Intracellular NOD-like receptors in host defense and disease, Immunity 27 (4) (2007) 549–559.
[9] M.H. Shaw, T. Reimer, Y.G. Kim, G. Nunez, NOD-like receptors (NLRs): bona fide intracellular microbial sensors, Curr. Opin. Immunol. 20 (4) (2008) 377–382.
[10] V. Hornung, A. Ablasser, M. Charrel-Dennis, F. Bauernfeind, G. Horvath, D.R. Caffrey, E. Latz, K.A. Fitzgerald, AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC, Nature 458 (7237) (2009) 514–518.
[11] T. Jin, A. Perry, J. Jiang, P. Smith, J.A. Curry, L. Unterholzner, Z. Jiang, G. Horvath, V.A. Rathinam, R.W. Johnstone, V. Hornung, E. Latz, A.G. Bowie, K.A. Fitzgerald, T.S. Xiao, Structures of the HIN domain: DNA complexes reveal ligand binding and activation mechanisms of the AIM2 inflammasome and IFI16 receptor, Immunity 36 (4) (2012) 561–571.
[12] D. Goubau, J. Rehwinkel, C. Reis e Sousa, PYHIN proteins: center stage in DNA sensing, Nat. Immunol. 11 (11) (2010) 984–986.
[13] F. Martinon, K. Burns, J. Tschopp, The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta, Mol. Cell 10 (2) (2002) 417–426.
[14] E. Latz, T.S. Xiao, A. Stutz, Activation and regulation of the inflammasomes, Nat. Rev. Immunol. 13 (6) (2013) 397–411.
[15] J. Masumoto, T.A. Dowds, P. Schaner, F.F. Chen, Y. Ogura, M. Li, L. Zhu, T. Katsuyama, J. Sagara, S. Taniguchi, D.L. Gumucio, G. Nunez, N. Inohara, ASC is an activating adaptor for NF-kappa B and caspase-8-dependent apoptosis, Biochem. Biophys. Res. Commun. 303 (1) (2003) 69–73.
[16] R. Pierini, C. Juruj, M. Perret, C.L. Jones, P. Mangeot, D.S. Weiss, T. Henry, AIM2/ASC triggers caspase-8-dependent apoptosis in *Francisella*-infected caspase-1-deficient macrophages, Cell Death Differ. 19 (10) (2012) 1709–1721.
[17] K.L. DeYoung, M.E. Ray, Y.A. Su, S.L. Anzick, R.W. Johnstone, J.A. Trapani,

P.S. Meltzer, J.M. Trent, Cloning a novel member of the human interferon-inducible gene family associated with control of tumorigenicity in a model of human melanoma, Oncogene 15 (4) (1997) 453–457.

[18] G.N. Barber, STING-dependent cytosolic DNA sensing pathways, Trends Immunol. 35 (2) (2014) 88–93.

[19] X.D. Li, J. Wu, D. Gao, H. Wang, L. Sun, Z.J. Chen, Pivotal roles of cGAS-cGAMP signaling in antiviral defense and immune adjuvant effects, Science 341 (6152) (2013) 1390–1394.

[20] Q. Zhu, S.M. Man, R. Karki, R.K.S. Malireddi, T.D. Kanneganti, Detrimental type I interferon signaling dominates protective AIM2 inflammasome responses during *Francisella novicida* infection, Cell Rep. 22 (12) (2018) 3168–3174.

[21] J.W. Jones, N. Kayagaki, P. Broz, T. Henry, K. Newton, K. O'Rourke, S. Chan, J. Dong, Y. Qu, M. Roose-Girma, V.M. Dixit, D.M. Monack, Absent in melanoma 2 is required for innate immune recognition of *Francisella tularensis*, Proc. Natl. Acad. Sci. U. S. A. 107 (21) (2010) 9771–9776.

[22] T. Fernandes-Alnemri, J.W. Yu, C. Juliana, L. Solorzano, S. Kang, J. Wu, P. Datta, M. McCormick, L. Huang, E. McDermott, L. Eisenlohr, C.P. Landel, E.S. Alnemri, The AIM2 inflammasome is critical for innate immunity to *Francisella tularensis*, Nat. Immunol. 11 (5) (2010) 385–393.

[23] R. Fang, H. Hara, S. Sakai, E. Hernandez-Cuellar, M. Mitsuyama, I. Kawamura, K. Tsuchiya, Type I interferon signaling regulates activation of the absent in melanoma 2 inflammasome during Streptococcus pneumoniae infection, Infect. Immun. 82 (6) (2014) 2310–2317.

[24] J. Wu, T. Fernandes-Alnemri, E.S. Alnemri, Involvement of the AIM2, NLRC4, and NLRP3 inflammasomes in caspase-1 activation by *Listeria monocytogenes*, J. Clin. Immunol. 30 (5) (2010) 693–702.

[25] S. Kim, F. Bauernfeind, A. Ablasser, G. Hartmann, K.A. Fitzgerald, E. Latz, V. Hornung, *Listeria monocytogenes* is sensed by the NLRP3 and AIM2 inflammasome, Eur. J. Immunol. 40 (6) (2010) 1545–1551.

[26] S.E. Warren, A. Armstrong, M.K. Hamilton, D.P. Mao, I.A. Leaf, E.A. Miao, A. Aderem, Cutting edge: cytosolic bacterial DNA activates the inflammasome via Aim2, J. Immunol. 185 (2) (2010) 818–821.

[27] K. Tsuchiya, H. Hara, I. Kawamura, T. Nomura, T. Yamamoto, S. Daim, S.R. Dewamitta, Y. Shen, R. Fang, M. Mitsuyama, Involvement of absent in melanoma 2 in inflammasome activation in macrophages infected with *listeria monocytogenes*, J. Immunol. 185 (2) (2010) 1186–1195.

[28] J. Eitel, N. Suttorp, B. Opitz, Innate immune recognition and inflammasome activation in listeria monocytogenes infection, Front. Microbiol. 1 (2010) 149.

[29] T. Henry, A. Brotcke, D.S. Weiss, L.J. Thompson, D.M. Monack, Type I interferon signaling is required for activation of the inflammasome during Francisella infection, J. Exp. Med. 204 (5) (2007) 987–994.

[30] Y. Yang, X. Zhou, M. Kouadir, F. Shi, T. Ding, C. Liu, J. Liu, M. Wang, L. Yang, X. Yin, D. Zhao, The AIM2 inflammasome is involved in macrophage activation during infection with virulent *Mycobacterium* bovis strain, J. Infect. Dis. 208 (11) (2013) 1849–1858.

[31] H. Saiga, S. Kitada, Y. Shimada, N. Kamiyama, M. Okuyama, M. Makino, M. Yamamoto, K. Takeda, Critical role of AIM2 in *Mycobacterium tuberculosis* infection, Int. Immunol. 24 (10) (2012) 637–644.

[32] K. Belhocine, D.M. Monack, Francisella infection triggers activation of the AIM2 inflammasome in murine dendritic cells, Cell. Microbiol. 14 (1) (2012) 71–80.

[33] E. Meunier, P. Wallet, R.F. Dreier, S. Costanzo, L. Anton, S. Ruhl, S. Dussurgey, M.S. Dick, A. Kistner, M. Rigard, D. Degrandi, K. Pfeffer, M. Yamamoto, T. Henry, P. Broz, Guanylate-binding proteins promote activation of the AIM2 inflammasome during infection with *Francisella novicida*, Nat. Immunol. 16 (5) (2015) 476–484.

[34] R. Pierini, M. Perret, S. Djebali, C. Juruj, M.C. Michallet, I. Forster, J. Marvel, T. Walzer, T. Henry, ASC controls IFN-gamma levels in an IL-18-dependent manner in caspase-1-deficient mice infected with *Francisella novicida*, J. Immunol. 191 (7) (2013) 3847–3857.

[35] K.A. Fitzgerald, V.A. Rathinam, GBPs take AIM at Francisella, Nat. Immunol. 16 (5) (2015) 443–444.

[36] S.M. Man, D.E. Place, T. Kuriakose, T.D. Kanneganti, Interferon-inducible guanylate-binding proteins at the interface of cell-autonomous immunity and inflammasome activation, J. Leukoc. Biol. 101 (1) (2017) 143–150.

[37] S.M. Man, R. Karki, R.K. Malireddi, G. Neale, P. Vogel, M. Yamamoto, M. Lamkanfi, T.D. Kanneganti, The transcription factor IRF1 and guanylate-binding proteins target activation of the AIM2 inflammasome by Francisella infection, Nat. Immunol. 16 (5) (2015) 467–475.

[38] S.M. Man, R. Karki, M. Sasai, D.E. Place, S. Kesavardhana, J. Temirov, S. Frase, Q. Zhu, R.K.S. Malireddi, T. Kuriakose, J.L. Peters, G. Neale, S.A. Brown, M. Yamamoto, T.D. Kanneganti, IRGB10 Liberates Bacterial Ligands for Sensing by the AIM2 and Caspase-11-NLRP3 Inflammasomes, Cell 167 (2) (2016) 382–396 e17.

[39] D.D. Crane, T.J. Bauler, T.D. Wehrly, C.M. Bosio, Mitochondrial ROS potentiates indirect activation of the AIM2 inflammasome, Front. Microbiol. 5 (2014) 438.

[40] R. Hanamsagar, A. Aldrich, T. Kielian, Critical role for the AIM2 inflammasome during acute CNS bacterial infection, J. Neurochem. 129 (4) (2014) 704–711.

[41] A. Rabes, N. Suttorp, B. Opitz, Inflammasomes in pneumococcal infection: innate immune sensing and bacterial evasion strategies, Curr. Top. Microbiol. Immunol. 397 (2016) 215–227.

[42] R. Fang, K. Tsuchiya, I. Kawamura, Y. Shen, H. Hara, S. Sakai, T. Yamamoto, T. Fernandes-Alnemri, R. Yang, E. Hernandez-Cuellar, S.R. Dewamitta, Y. Xu, H. Qu, E.S. Alnemri, M. Mitsuyama, Critical roles of ASC inflammasomes in caspase-1 activation and host innate resistance to Streptococcus pneumoniae infection, J. Immunol. 187 (9) (2011) 4890–4899.

[43] U. Koppe, K. Hogner, J.M. Doehn, H.C. Muller, M. Witzenrath, B. Gutbier, S. Bauer, T. Pribyl, S. Hammerschmidt, J. Lohmeyer, N. Suttorp, S. Herold, B. Opitz, Streptococcus pneumoniae stimulates a STING- and IFN regulatory factor 3-dependent type I IFN production in macrophages, which regulates RANTES production in macrophages, cocultured alveolar epithelial cells, and mouse lungs, J. Immunol. 188 (2) (2012) 811–817.

[44] S. Feng, Q. Huang, C. Ye, R. Wu, G. Lei, J. Jiang, T. Chen, Y. Peng, R. Fang, Syk and JNK signaling pathways are involved in inflammasome activation in macrophages infected with Streptococcus pneumoniae, Biochem. Biophys. Res. Commun. 507 (1–4) (2018) 217–222.

[45] A. Amano, Molecular interaction of Porphyromonas gingivalis with host cells: implication for the microbial pathogenesis of periodontal disease, J. Periodontol. 74 (1) (2003) 90–96.

[46] E. Park, H.S. Na, Y.R. Song, S.Y. Shin, Y.M. Kim, J. Chung, Activation of NLRP3 and AIM2 inflammasomes by Porphyromonas gingivalis infection, Infect. Immun. 82 (1) (2014) 112–123.

[47] G. Dhangadamajhi, S.K. Kar, M. Ranjit, The survival strategies of malaria parasite in the red blood cell and host cell polymorphisms, Malar. Res. Treat. 2010 (2010) 973094.

[48] G.E. Grau, H. Heremans, P.F. Piguet, P. Pointaire, P.H. Lambert, A. Billiau, P. Vassalli, Monoclonal antibody against interferon gamma can prevent experimental cerebral malaria and its associated overproduction of tumor necrosis factor, Proc. Natl. Acad. Sci. U. S. A. 86 (14) (1989) 5572–5574.

[49] D. Kwiatkowski, M. Nowak, Periodic and chaotic host-parasite interactions in human malaria, Proc. Natl. Acad. Sci. U. S. A. 88 (12) (1991) 5111–5113.

[50] P. Kalantari, R.B. DeOliveira, J. Chan, Y. Corbett, V. Rathinam, A. Stutz, E. Latz, R.T. Gazzinelli, D.T. Golenbock, K.A. Fitzgerald, Dual engagement of the NLRP3 and AIM2 inflammasomes by plasmodium-derived hemozoin and DNA during malaria, Cell Rep. 6 (1) (2014) 196–210.

[51] V.A. Rathinam, Z. Jiang, S.N. Waggoner, S. Sharma, L.E. Cole, L. Waggoner, S.K. Vanaja, B.G. Monks, S. Ganesan, E. Latz, V. Hornung, S.N. Vogel, E. Szomolanyi-Tsuda, K.A. Fitzgerald, The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses, Nat. Immunol. 11 (5) (2010) 395–402.

[52] A.M. Krieg, AIMing 2 defend against intracellular pathogens, Nat. Immunol. 11 (5) (2010) 367–369.

[53] K.E. Johnson, L. Chikoti, B. Chandran, Herpes simplex virus 1 infection induces activation and subsequent inhibition of the IFI16 and NLRP3 inflammasomes, J. Virol. 87 (9) (2013) 5005–5018.

[54] S.R. Paludan, A.G. Bowie, K.A. Horan, K.A. Fitzgerald, Recognition of herpesviruses by the innate immune system, Nat. Rev. Immunol. 11 (2) (2011) 143–154.

[55] W. Du, J. Zhen, Z. Zheng, S. Ma, S. Chen, Expression of AIM2 is high and correlated with inflammation in hepatitis B virus associated glomerulonephritis, J. Inflamm. 10 (1) (2013) 37.

[56] D.L. Wu, G.H. Xu, S.M. Lu, B.L. Ma, N.Z. Miao, X.B. Liu, Y.P. Cheng, J.H. Feng, Z.G. Liu, D. Feng, L. Na, W.Q. Li, Y.R. Zhao, Correlation of AIM2 expression in peripheral blood mononuclear cells from humans with acute and chronic hepatitis B, Hum. Immunol. 74 (5) (2013) 514–521.

[57] J. Zhen, L. Zhang, J. Pan, S. Ma, X. Yu, X. Li, S. Chen, W. Du, AIM2 mediates inflammation-associated renal damage in hepatitis B virus-associated glomerulonephritis by regulating caspase-1, IL-1beta, and IL-18, Mediat. Inflamm. 2014 (2014) 190860.

[58] H. zur Hausen, Papillomaviruses in the causation of human cancers - a brief historical account, Virology 384 (2) (2009) 260–265.

[59] M. Reinholz, Y. Kawakami, S. Salzer, A. Kreuter, Y. Dombrowski, S. Koglin, S. Kresse, T. Ruzicka, J. Schauber, HPV16 activates the AIM2 inflammasome in keratinocytes, Arch. Dermatol. Res. 305 (8) (2013) 723–732.

[60] H. Zhang, J. Luo, J.F. Alcorn, K. Chen, S. Fan, J. Pilewski, A. Liu, W. Chen, J.K. Kolls, J. Wang, AIM2 inflammasome is critical for influenza-induced lung injury and mortality, J. Immunol. 198 (11) (2017) 4383–4393.

[61] H. Yamada, R. Chounan, Y. Higashi, N. Kurihara, H. Kido, Mitochondrial targeting sequence of the influenza A virus PB1-F2 protein and its function in mitochondria, FEBS Lett. 578 (3) (2004) 331–336.

[62] T. Yoshizumi, T. Ichinohe, O. Sasaki, H. Otera, S. Kawabata, K. Mihara, T. Koshiba, Influenza A virus protein PB1-F2 translocates into mitochondria via Tom40 channels and impairs innate immunity, Nat. Commun. 5 (2014) 4713.

[63] H. Fesq, M. Bacher, M. Nain, D. Gemsa, Programmed cell death (apoptosis) in human monocytes infected by influenza A virus, Immunobiology 190 (1–2) (1994) 175–182.

[64] V.S. Hinshaw, C.W. Olsen, N. Dybdahl-Sissoko, D. Evans, Apoptosis: a mechanism of cell killing by influenza A and B viruses, J. Virol. 68 (6) (1994) 3667–3673.

[65] I. Mori, T. Komatsu, K. Takeuchi, K. Nakakuki, M. Sudo, Y. Kimura, In vivo induction of apoptosis by influenza virus, J. Gen. Virol. 76 (1995) 2869–2873 Pt 11.

[66] S.M. Man, R. Karki, T.D. Kanneganti, AIM2 inflammasome in infection, cancer, and autoimmunity: role in DNA sensing, inflammation, and innate immunity, Eur. J. Immunol. 46 (2) (2016) 269–280.

[67] E. Schunder, K. Rydzewski, R. Grunow, K. Heuner, First indication for a functional CRISPR/Cas system in *Francisella tularensis*, Int. J. Med. Microbiol. 303 (2) (2013) 51–60.

[68] C.R. Harding, C.A. Stoneham, R. Schuelein, H. Newton, C.V. Oates, E.L. Hartland, G.N. Schroeder, G. Frankel, The Dot/Icm effector SdhA is necessary for virulence of *Legionella pneumophila* in *Galleria mellonella* and A/J mice, Infect. Immun. 81 (7) (2013) 2598–2605.

[69] V.A. Rathinam, S.K. Vanaja, K.A. Fitzgerald, Regulation of inflammasome signaling, Nat. Immunol. 13 (4) (2012) 333–342.

[70] V. Sagulenko, S.J. Thygesen, D.P. Sester, A. Idris, J.A. Cridland, P.R. Vajjhala, T.L. Roberts, K. Schroder, J.E. Vince, J.M. Hill, J. Silke, K.J. Stacey, AIM2 and NLRP3 inflammasomes activate both apoptotic and pyroptotic death pathways via

ASC, Cell Death Differ. 20 (9) (2013) 1149–1160.

[71] T. Grabinger, P. Peterburs, T. Brunner, dsDNA ASCs for caspase 8-mediated apoptosis, Cell Death Differ. 20 (9) (2013) 1128–1130.

[72] T. Fernandes-Alnemri, J.W. Yu, P. Datta, J. Wu, E.S. Alnemri, AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA, Nature 458 (7237) (2009) 509–513.

[73] L. Franchi, T. Eigenbrod, R. Munoz-Planillo, G. Nunez, The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis, Nat. Immunol. 10 (3) (2009) 241–247.

[74] J.M. Kahlenberg, M.J. Kaplan, The inflammasome and lupus: another innate immune mechanism contributing to disease pathogenesis? Curr. Opin. Rheumatol. 26 (5) (2014) 475–481.

[75] C. Conforti-Andreoni, P. Ricciardi-Castagnoli, A. Mortellaro, The inflammasomes in health and disease: from genetics to molecular mechanisms of autoinflammation and beyond, Cell. Mol. Immunol. 8 (2) (2011) 135–145.

[76] M. Lamkanfi, V.M. Dixit, Inflammasomes and their roles in health and disease, Annu. Rev. Cell Dev. Biol. 28 (2012) 137–161.

[77] T. Strowig, J. Henao-Mejia, E. Elinav, R. Flavell, Inflammasomes in health and disease, Nature 481 (7381) (2012) 278–286.

[78] N. Kerur, M.V. Veettil, N. Sharma-Walia, V. Bottero, S. Sadagopan, P. Otageri, B. Chandran, IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi sarcoma-associated herpesvirus infection, Cell Host Microbe 9 (5) (2011) 363–375.

[79] S. Veeranki, X. Duan, R. Panchanathan, H. Liu, D. Choubey, IFI16 protein mediates the anti-inflammatory actions of the type-I interferons through suppression of activation of caspase-1 by inflammasomes, PLoS One 6 (10) (2011) e27040.