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Interaction of Mycobacteria With Host Cell Inflammasomes

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The inflammasome complex is important for host defense against intracellular bacterial infections. *Mycobacterium tuberculosis* (Mtb) is a facultative intracellular bacterium which is able to survive in infected macrophages. Here we discuss how the host cell inflammasomes sense Mtb and other related mycobacterial species. Furthermore, we describe the molecular mechanisms of NLRP3 inflammasome sensing of Mtb which involve the type VII secretion system ESX-1, cell surface lipids (TDM/TDB), secreted effector proteins (LpqH, PPE13, EST12, EsxA) and double-stranded RNA acting on the priming and/or activation steps of inflammasome activation. In contrast, Mtb also mediates inhibition of the NLRP3 inflammasome by limiting exposure of cell surface ligands *via* its hydrolase, Hip1, by inhibiting the host cell cathepsin G protease *via* the secreted Mtb effector Rv3364c and finally, by limiting intracellular triggers (K^+ and Cl^- efflux and cytosolic reactive oxygen species production) *via* its serine/threonine kinase PknF. In addition, Mtb inhibits the AIM2 inflammasome activation *via* an unknown mechanism. Overall, there is good evidence for a tug-of-war between Mtb trying to limit inflammasome activation and the host cell trying to sense Mtb and activate the inflammasome. The detailed molecular mechanisms and the importance of inflammasome activation for virulence of Mtb or host susceptibility have not been fully investigated.

Keywords: Mycobacterium tuberculosis, inflammasome, NLRP3, AIM2, ESX-1, IL-1b, NTM = nontuberculous mycobacteria

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INTRODUCTION

Tuberculosis (TB) is a major cause of morbidity and mortality with approximately 10 million new cases and 1-2 million deaths, annually (1). The disease is caused by the human pathogen *Mycobacterium tuberculosis* (Mtb) which is transmitted *via* aerosol from the lung of an infected individual to the naïve bystander. Current chemotherapy leads to positive outcomes in about 85% of the patients but takes 6-9 months to complete and the success rate drops dramatically if drug resistant strains of Mtb are the cause of the infection (2). Consequently, the search for better antibiotics and more efficient treatment regiments is of great interest. In addition, host-directed therapy (HDT) is a complementary approach to improving clinical outcomes by targeting host signaling pathways that, for example, support bacterial replication or cause immune pathologies (3). For the latter approach to be successful, a more detailed understanding of host responses to infection with Mtb and their importance for host protection or susceptibility is required. The cytokine Interleukin (IL)-1β is of crucial importance for host resistance to Mtb. In this review we will provide some background information on mechanisms of inflammasome activation which leads

to the generation of IL-1β, summarize the findings of the importance of IL-1β for host resistance to Mtb infections and their potential for host-targeted therapeutic approaches and finally we will focus on how the inflammasome detects various mycobacterial species and how Mtb is able to inhibit inflammasome activation (summarized in **Table 1** and **Figure 2**).

OVERVIEW OF MECHANISMS OF INFLAMMASOME ACTIVATION AND ITS CONSEQUENCES

In this section we will provide a concise overview of the components and signaling pathways involving mainly two (NLRP3, AIM2) kinds of inflammasomes since they are most relevant to our subsequent discussion on interaction of mycobacteria with inflammasomes (see also **Figure 1**). We would encourage the interested reader to follow-up on this brief overview with any of the excellent specialized reviews on the topic for an in-depth discussion (27–36).

As opposed to the membrane-bound pathogen recognition receptors (PRRs) such as Toll-like receptors (TLRs) that survey extracellular pathogen components, the nucleotide binding and oligomerization domain-like receptors (NLRs, e.g. NLRP3) and Absent in Melanoma 2 (AIM2)-like receptors (ALRs, e.g. AIM2) survey the host cell cytosol for the presence of pathogens (27, 37–41). Upon binding of NLRs/ALRs to pathogen or danger associated molecular patterns (P/DAMP), they initiate the formation the inflammasome (Signal 2: **Figure 1**). IL-1β is a potent immunomodulator and its overproduction may cause rheumatoid arthritis and other pathologies (42, 43). Consequently, IL-1β production is highly regulated and in addition to the inflammasome activation pathway another signaling pathway (Signal 1: **Figure 1**) needs to be engaged to achieve production of mature IL-1β. This pathway involves other PRRs, for example, TLRs or cytokine receptors such as receptors for IL-1β and Tumor Necrosis Factor (TNF) which, after ligand binding, activate NFκB, resulting in the transcriptional activation of, for example, the *IL1B* gene to increase protein levels of pro-IL-1β (44). There is also a crosstalk of Signal 1 with Signal 2 *via* the activation of proteins that perform posttranslational modifications (PTM) of inflammasome components (44–46) (**Figure 1**).

Once Signal 1 and Signal 2 are activated, in case of AIM2 or NLRP3, they associate with the adapter molecule Apoptosis-associated speck-like protein containing a CARD (ASC) which recruits pro-caspase-1 into a complex that continues to oligomerize to form in some cases structures called "specks", measuring 1-2μm in diameter (47–49). The formed inflammasome complex supports the self-cleavage of pro-caspase-1 into active caspase-1 which cleaves pro-IL-1β and pro-IL-18 and gasdermin D (GSDMD) to release the N-terminal fragment that is capable of oligomerization and membrane pore formation (50–52). The GSDMD pores in the cell membrane will lead to pyroptosis and cytokine release but they do not allow for plasma membrane rupture and secretion of higher molecular weight proteins and protein complexes (e.g., HMGB1) (53) (**Figure 1**). More recently, a complementary role in pore generation after inflammasome activation has been determined for gasdermin E (54).

SIGNAL 2: ACTIVATION OF THE NLRP3 AND AIM2 INFLAMMASOMES

The activation of the NLRP3 inflammasome is complex and one of the reasons is that no ligand that physically binds to NLPR3 has yet been identified. Instead, the prevailing model is that NLRP3 is a stress sensor of the cell which reacts to the increase of various cellular stress signals (32) (**Figure 1**). A major trigger shared across many activating stimuli is the efflux of potassium ions (K^+) (55). Additional triggers are the efflux of chloride ions (Cl^-) (56–58), mobilization of intracellular calcium ions (Ca^{2+}) (59–61), increase in intracellular reactive oxygen species (ROS) (62) or the release of oxidized mitochondrial DNA (63) [for review (41, 45, 46, 64)] (**Figure 1**). The non-canonical NLRP3 inflammasome pathway (for review (65)) targets caspase-11 in mice and caspases-4/5 in humans (66) and is dependent on the TRIF-mediated induction of interferon (IFN) production and subsequent IFN-receptor mediated signaling (67, 68). Ultimately, the activation of non-canonical pathway is triggered by the presence of intracellular lipopolysaccharide (LPS) of gram-negative bacteria (69, 70) which directly binds to and activates caspases-4/5/11 (71) (**Figure 1**). IFN-stimulated genes, such as the family of guanylate-binding proteins (GBPs), are critical for non-canonical NLRP3 inflammasome activation (72, 73) *via* mechanisms that involve: attacking the outer membrane of cytosolic bacteria such as *Shigella* or *Fransicella* (74–76), releasing intracellular phagosomal bacteria (e.g. *Salmonella*) into the cytosol (73) or assembly to provide a platform for caspase-4 recruitment and activation on the surface of the bacteria (77, 78). Another IFN-stimulated gene product, IRGB10, is also involved in release LPS from intracellular bacteria (75). After activation, caspase-11, like caspase-1, cleaves GSDMD which will lead to pore formation and pyroptosis but not cytokine maturation (51, 52). The activation of the non-canonical pathway will ultimately also lead to efflux of K^+ which will activate the canonical NLRP3 inflammasome pathway (79) (**Figure 1**).

The signal transduction of the activation of the AIM2 inflammasome is fairly simple because it is mediated by the binding of the HIN-200 domain of AIM2 to DNA (80–82) (**Figure 1**). The pathogen DNA can be accumulating in the cytosol due to infection of the cell with viruses or they can be generated by degrading bacteria in the cytosol *via* action of GBPs and IRGB10 (73–76). Cell stress leading to the release of non-oxidized mitochondrial DNA can also activate the AIM2 inflammasome (83) (**Figure 1**).

Two other important aspects to inflammasome regulation, namely post translational modifications (PTMs) and

TABLE 1 | Summary overview of different mycobacterial species and effectors involved in activation of either NLRP3 or AIM2 inflammasome.

Pathogen	Strains	Inflammasome target	Cell Type/*in vivo*	Mechanism/Function/Triggers involved	Bacterial effector/mediators	References
M. tuberculosis	H37Rv	NLRP3	peritoneal exudate macrophages, BMDMs	Induction of Potassium efflux results in increased secretion of IL-1β and IL-18	RD1 Locus	(4)
M. tuberculosis	H37Rv	NLRP3	J774A.1, BMDMs, and THP-1 macrophages	Assembly of NLRP3 inflammasome complex (interacts with NATCH and LRR domains)	PPE13	(5)
M. tuberculosis	H37Rv	NLRP3	mouse retinal pigment epithelium (RPE) cells	Caspase-1 activation	EsxA and dsRNA	(6)
M. tuberculosis	H37Rv	NLRP3	PBMCs, THP-1 macrophages	Up-regulates expression of MFN2 and induces release of IL-1β	EsxA	(7)
M. tuberculosis	H37Rv ATCC 27294	NLRP3	Mouse peritoneal macrophages, PMA-differentiated THP1 cells, and BMDMs	Induces GSDMD mediated pyroptosis through interaction with RACK-1	Rv1579c (EST12)	(8)
M. tuberculosis	H37Rv	NLRP3	BMDMs	Phagocytosis and Potassium efflux	RD1 locus	(9)
M. tuberculosis	H37Rv ATCC 25618	NLRP3	THP-1 macrophages, BMDMs, BMDCs	induces Caspase-1 activation and IL-1β secretion	ESX-5a	(10)
M. tuberculosis	H37Rv	NLRP3	THP-1 macrophages, Human MDMs	Phagosomal damage, Syk activation, Lysosomal permeabilization	EsxA	(11)
M. marinum	E11 strain	NLRP3	Human primary Type 1 macrophages	Potassium efflux, ROS production and cathepsin B release	ESX-5	(12)
M. abscessus	ATCC 19977	NLRP3	Human MDMs, THP-1 macrophages	dectin-1/Syk-dependent signaling, expression of the cytoplasmic scaffold protein p62/SQSTM1 (p62) and Potassium efflux leads to activation of Caspase-1 and secretion of IL-1β	ND	(13)
M. kansasii	ATCC12478	NLRP3	THP-1 macrophages	Potassium efflux, lysosomal acidification, ROS production and cathepsin B release	possibly ESX-1/ EsxA	(14)
M. tuberculosis	H37Ra	NLRP3	Primary microglia	NF-Kb in signal 1 and P2X7R in signal 2	ND	(15)
M. tuberculosis	H37Rv	NLRP3	Ana-1 mouse macrophage cell line	Potassium efflux	LpqH	(16)
M. marinum	M-strain	NLRP3	BMDMs	induces Caspase-1 activation	ESX-1	(17)
M. marinum	M-strain	NLRP3	Female C57BL/6 (B6) mice and ASC-KO mice	Promotes secretion of IL-1β	ESX-1	(17)
M. marinum	M-strain	NLRP3	BMDMs	Promotes secretion of IL-1β and IL-18	ESX-1	(18)
M. tuberculosis	H37Rv ATCC 27294	NLRP3	THP-1 macrophages	induces Caspase-1 activation and IL-1β secretion	EsxA	(19)
M. tuberculosis	H37Rv	NLRP3	BMDMs/C57Bl/6 mice	Secretion of activated Cathepsin B into the cytosol	EsxA	(20)
M. abscessus	ATCC 19977	NLRP3	BMDMs, J774A.1	Induction of mtROS results in increased IL-1β secretion	enhanced cytosolic escape of bacteria	(21)
M. tuberculosis	H37Rv ATCC 25618	NLRP3	BMDCs	induces Caspase-1 activation and IL-1β secretion	partially ESX-1–dependent mechanism	(22)
M. smegmatis	mc2 155	AIM2	BMDCs	induction of IFN-β	partially ESX-1–dependent mechanism	(23)
M. fortuitum	ATCC 6841	AIM2	BMDCs	induction of IFN-β	ND	(23)
M. kansasii	ATCC 12478	AIM2	BMDCs	induction of IFN-β	ND	(23)
M. tuberculosis	H37Rv ATCC358121	AIM2	Peritoneal macrophages	induces Caspase-1 activation and IL-1β,IL-18 secretion	Mtb genomic DNA	(24)
M. bovis	Beijing strain	AIM2	BMDMs, J774A.1	Up-Regulates the mRNA Expression of AIM2 and ASC, requires potassium efflux and mycobacterial internalization but not Reactive Oxygen Species	ND	(25)
M. ulcerans	01G897 and 1615	NLRP3/1	BMDMs, hMDM/ C57Bl/6 mice	Toxin binding to TLR-2, membrane permeabilization and ROS production	mycolactone	(26)

'ND' denotes Not determined. 'FA' indicates first author.

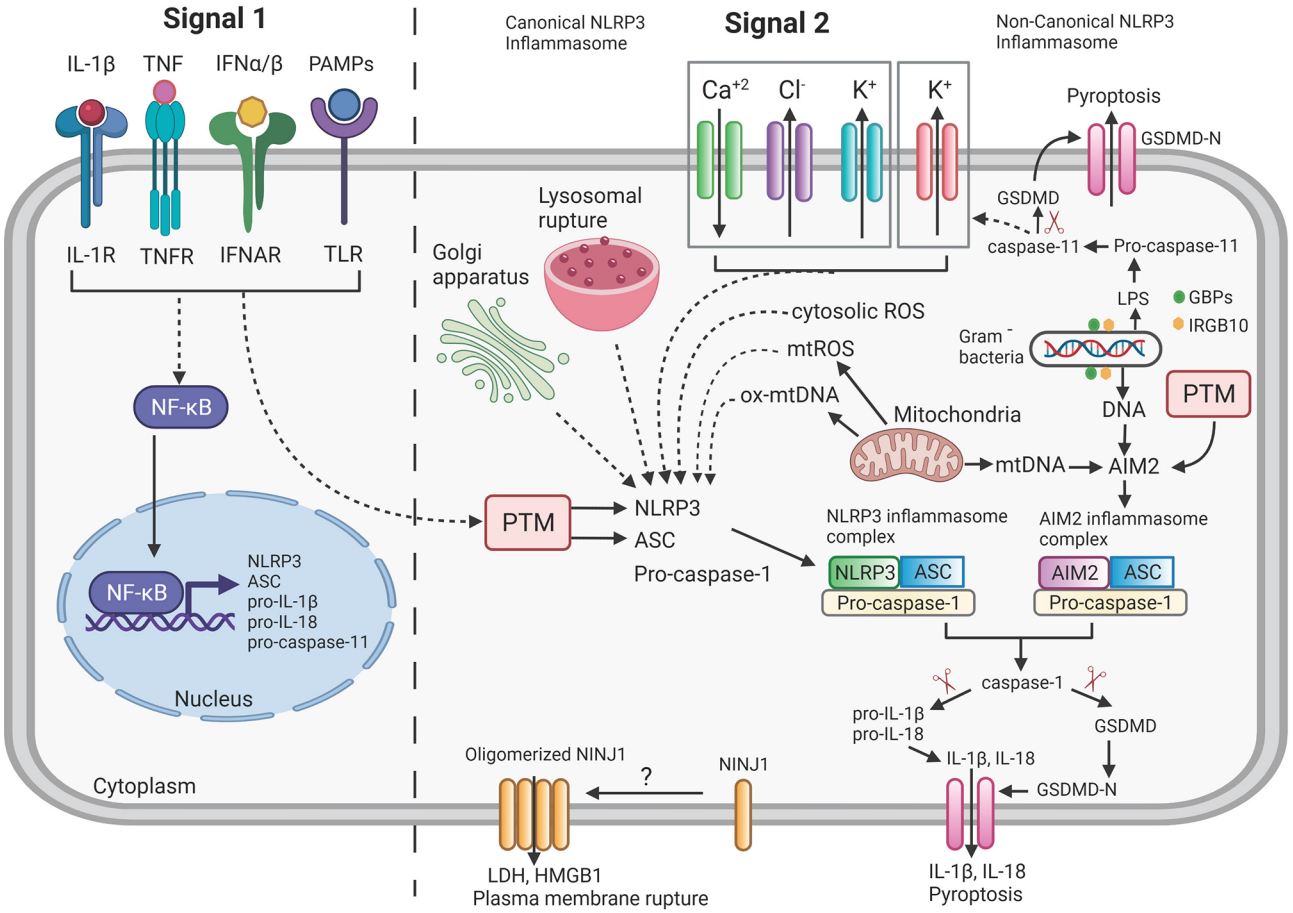

FIGURE 1 | Overview of mechanism of Inflammasome signaling pathway. NLRP3 and AIM2 inflammasome activation requires two distinct signals: Signal 1 (priming signal, left) is induced by the detection of pathogen-associated molecular patterns (PAMPs) or endogenous cytokines by the Toll-like receptor (TLR) or cytokine receptors (IL-1R, TNFR, IFNAR) and thus leading to increased transcription of NLRP3, ASC, pro-IL-1β, pro-IL-18 and pro-caspase-11 through activation of NF-κB. Signal 2 (activation signal, right) for the NLRP3 inflammasome is triggered by various stimuli such as potassium (K^+) efflux, chloride (Cl^-) efflux, calcium (Ca^{+2}) influx, oxidized mitochondrial DNA (ox-mtDNA), lysosomal rupture and intracellular reactive oxygen species (ROS) production. All these triggers lead to oligomerization and assembly of NLRP3 inflammasome complex. AIM2 directly recognizes either DNA released from Gram negative bacteria or mtDNA released from mitochondria and lead to assembly of AIM2 inflammasome complex. Activated inflammasome complexes (NLRP3 or AIM2) recruit and cleave pro-caspase-1 to active caspase-1 that further results in the proteolytic cleavage of pro-IL-1β and pro-IL-18 to the mature forms IL-1β and IL-18. Caspase-1 also cleaves gasdermin D (GSDMD) to its pore-forming N-terminal fragment GSDMD-N which results in pyroptosis. Ninjurin-1 (NINJ1) by unknown mechanism as indicated by "?" oligomerizes and forms a pore to facilitate release of LDH, HMGB1 and the accumulation of these pores ultimately led to plasma membrane rupture which is not achieved by the GSDMD-N pores. Post-translational modifications (PTM) of cytosolic sensors (NLRP3/AIM2) and adaptor protein (ASC) regulate the activity of inflammasome. Gram negative bacteria are lysed to releases LPS and DNA *via* a mechanism requiring various interferon-inducible Guanylate-binding proteins (GBPs) and IRGB10. The LPS binds to pro-caspase-11 to initiate autocleavage into active caspase-11 which further cleaves GSDMD to GSDMD-N and results in pyroptosis (indicated as Non-Canonical NLRP3 inflammasome) and increased efflux of K^+, thus further activating the canonical NLRP3 inflammasome pathway (dashed lines = indirect interaction; solid lines = direct interaction; arrowhead = activation). Created with Biorender.com.

intracellular location of inflammasome components, will not be discussed in detail here because very little is known about the effect of mycobacterial infection on these two parameters. PTMs in inflammasome activation involves phosphorylation, ubiquitination, sumoylation, S-nitrosylation and ADP-ribosylation of inflammasome components which may lead to either activation or inhibition of the inflammasome formation (44–46, 64, 84). Consequently, the proteins involved in mediating the PTMs are themselves important components of the inflammasome regulatory network. In addition, the subcellular localization of inflammasome components and their association with specific organelles impact activation of the inflammasome (35, 46) (**Figure 1**).

INFLAMMASOME-INDEPENDENT PRODUCTION OF IL-1β

It is important to mention that in certain settings mature IL-1β and IL-18 can be generated mostly without the activation of the inflammasome [for review (85, 86)]. The inflammasome-

independent IL-1β and IL-18 production is most relevant in an *in vivo* setting where neutrophils dominate (85, 86). The proteases produced in neutrophils involved in cleavage of pro-IL-1β are: proteinase 3 (87, 88), zinc-dependent metalloproteinase meprin A and its monomer meprin α (89), matrix metalloproteinases-2, -3 and -9 (90) and granzyme A (91).

Another pathway for inflammasome independent generation of mature IL-1β and IL-18 is *via* activation of the caspase-8 and its subsequent cleavage of pro-IL-1β and pro-IL-18 (31, 92). One possible pathway for caspase-8 activation is through ligand binding to TLR3 or TLR4 which leads to recruitment of TRIF (Toll/IL-1R domain-containing adapter-inducing IFN-β) and subsequent recruitment of receptor interacting protein 1/receptor interacting protein serine/threonine kinase 1 (RIP1/RIPK1), FAS-associated death domain (FADD) and caspase-8 (93–95). The TNF receptor family member Fas can also activate the FADD/caspase-8 pathway to induce mature IL-1β and IL-18 (96, 97). Other studies also implicated the RIPK3 in the caspase-8 activation pathway (98, 99).

Another inflammasome-independent pathway involving caspase-8 is important for IL-1β and IL-18 production in response to fungal pathogens (100). Dectin-1 signals *via* the tyrosine kinase SYK to induce the formation of a CARD9, Bcl-10, MALT1 and caspase-8 complex which recruits the ASC protein to finally mediate cleavage of pro-IL-1β and -IL-18 (100, 101). Active caspase-8 cleaves pro-IL-1β at the same site that caspase-1 does (93).

THE IMPACT OF IL-1β ON HOST RESPONSE DURING MTB INFECTION

Protective Role of IL-1β During Mtb Infections

The role of IL-1β throughout infection of the host with Mtb is complex with some evidence in support of a host protective role and other data supporting a role in increasing host susceptibility (3). First, we will discuss the data demonstrating that IL-1β is of importance for host resistance against infections with Mtb and the possible mechanisms (3, 102–106). Mouse studies demonstrate the hyper susceptibility of mice deficient in the expression of either IL-1α/-β or the IL-1β receptor (107–112). The mechanism of protection conferring host resistance by IL-1β has been proposed to involve cell intrinsic mechanisms *via* the increase in host cell apoptosis (113) or autophagy signaling (114). The inflammasome activation has been linked to increasing maturation of Mtb-containing phagosomes and thus limiting bacterial growth (115, 116). Nevertheless, another study demonstrates that cell intrinsic mechanisms are not how IL-1β confers host resistance but instead it is mediated *via trans*-protection of infected cells (117). Although the precise mechanism is unclear, *in vivo*, a major function of IL-1β seems to be to suppress necrosis of lung cells (110, 118). This seems counterintuitive since inflammasome-mediated IL-1β production is associated with cell death (pyroptosis) but it was shown that, at least in the mouse model, IL-1β production is independent of the inflammasome during Mtb infections (111).

It is well-established that, at least partially, the protective effect of IL-1β *in vivo* is linked to its capacity to suppress IFN-β expression since increased IFN-β production increases host susceptibility (for review (3, 102, 104, 106, 119, 120). Importantly, IL-1β can suppress IFN-β expression and vice versa (121). This interdependence can be exploited for HDT approaches to boost IL-1β production, reduce IFN-β expression and reduce the associated morbidities and mortalities (118). Interestingly, IFN-β-mediated signaling is associated with increased necrotic cell death during *ex vivo* Mtb infections which could provide a mechanism for the *in vivo* observed immunopathologies associated with high IFN-β expression (122). Mtb clinical isolates associated with severe TB evade NLRP3 inflammasome activation suggesting a host protective role of IL-1β (123). Macrophages isolated from patients with inflammatory disease carrying gain-of-function genetic variants in inflammasome genes (NLRP3 and/or CARD8) subsequently infected with Mtb displayed increased growth restriction of Mtb in human macrophages (116). In the zebrafish/Mmar infection model, treatment with the drug clemastine modulates the host innate immunity *via* potentiation of P2RX7 that enhances calcium transients within infected macrophages *in vivo*. P2RX7 potentiation augments inflammasome activation, resulting in constraint of mycobacterial growth in zebrafish larvae (124).

Detrimental Role of IL-1β During Mtb Infections

In contrast, other data from mouse and human studies point towards a role of IL-1β in increasing host susceptibility (3). Some of the strongest evidence for a positive correlation between increased IL-1β and severity of disease in humans comes from several studies analyzing genetic variability and clinical outcomes. The analysis of single nucleotide polymorphisms (SNP) in the human *IL1B* gene identified 3 SNPs in the genes promoter region that results in increased IL-1β expression and was associated with more severe tuberculosis possibly due to the increased infiltration of neutrophils (125). A polymorphism in the IL-1 receptor agonist (*IL1RA*) gene resulted in population with decreased *IL1RA* and increased *IL1B* gene expression that was more commonly found in patients with tuberculoid pleurisy (126). Furthermore, several studies using the mouse model suggest a detrimental role of IL-1β to host defense. For example, it was demonstrated that the primary protective mechanism of nitric oxide (NO) during Mtb infection is not antibacterial activity but instead the suppression of inflammasome activation (127, 128). MCC950 inhibits the NLRP3 inflammasome activation in Mtb-infected BMDMs and results in decreased survival of Mtb in addition to reduced processing of IL-1β (129).

In conclusion, it is very likely that, similar to the situation with TNF and IFN-β (130, 131), also for the production of the IL-1β the Goldilocks principle applies with just the right amount of cytokine being produced in the right context at the right time during infection in order to produce a host protective outcome.

INFLAMMASOME RECOGNITION OF MYCOBACTERIA

Recognition of Mtb by the NLRP3 Inflammasome

Different mycobacterial species express different proteins and lipids which may affect their recognition by NLR/ALR proteins (132) (**Table 1**). Secretion of proinflammatory mature IL-1β or IL-18 during Mtb infection requires activation of NLRP3 inflammasome (9–11, 17, 19, 22, 133). The activation of the NLRP3 inflammasome after Mtb infection is conserved across various cell types: mouse bone marrow derived macrophages (BMDMs) (4, 5, 8–10, 20), peritoneal exudate macrophages (4, 8), THP-1 human macrophages (5, 7, 8, 10, 11, 19), mouse retinal pigment epithelium (RPE) cells (6), primary microglia (15), Ana-1 mouse macrophage (16), mouse bone marrow derived dendritic cells (BMDCs) (10, 22), J774A.1 mouse macrophages (5), PBMCs (7) and human monocyte derived macrophages (hMDMs) (11) (see also **Table 1**). The adaptor ASC, NLRP3 and caspase-1/11 are required for the secretion of IL-1β in Mtb-infected BMDCs (22). Mtb infection induces increased K^+ and Cl^- efflux but does not affect Ca^{2+} flux (134). The phagosomal and mitochondrial ROS are not involved in the activation of the NLRP3 inflammasome upon Mtb infection but instead it is cytosolic ROS, generated by the xanthine oxidase (XO) (134). Interestingly, plasma membrane damage mediated by ESX-1 system triggers increase in K^+ efflux, consequently activating the NLRP3 inflammasome and pyroptosis, which permits the spreading of Mtb to neighboring cells (135).

Recognition of NTM by the NLRP3 Inflammasome

The activation of the NLRP3 inflammasome has also been demonstrated for non-tuberculous mycobacteria (NTM) species including *Mycobacterium marinum* (Mmar) (12, 17), *Mycobacterium abscessus* (Mab) (13, 21) and *Mycobacterium kansasii* (Mkan) (14) and *Mycobacterium ulcerans* (26) (**Table 1**). More specifically, Mab leads to caspase-1 activation and release of IL-1β in human macrophages. Dectin-1/Syk-dependent signaling, increased expression of the cytoplasmic scaffold protein p62/SQSTM1 and potassium efflux are implicated in Mab mediated NLRP3 inflammasome activation (13). Consistently, it has been demonstrated that Mab results in increased production of IL-1β in murine macrophages (21). Mab induces mitochondrial ROS and thereby leads to enhanced NLRP3 inflammasome activation (21). A recent study has demonstrated that infection of microglia with the attenuated Mtb H37Ra strain triggers NLRP3 mediated secretion of IL-1β and IL-18 (15). Moreover, they also found that by inhibiting NF-κB (signal 1) and P2X7R (signal 2) they can alter the secretion of IL-1β and IL-18 and thereby regulate the NLRP3 inflammasome pathway in microglia during Mtb infection (15) (**Table 1**). Interestingly, irrespective of the overexpression of NLRP3 and inflammatory caspases-4/5 detected in the lepromatous pole, low expression of caspase-1, IL-1β, and IL-18 were observed in leprosy and therefore these results indicate that NLRP3 inflammasome does not actively contribute to the innate immune response in leprosy, suggesting immune evasion of *M. leprae* (136).

Recognition of Mycobacteria by the AIM2 Inflammasome

In addition to NLRP3 inflammasome, different reports have implicated the critical role for the AIM2 inflammasome following mycobacterial infection. Activation of AIM2 inflammasome has been reported in several cell types during infection with various mycobacterial species, including *Mycobacterium smegmatis* (Msme) (23), *Mycobacterium fortuitum* (Mfor) and Mkan in BMDCs (23) (**Table 1**). In BMDCs about 40–50% of the production of IL-1β following Msme, Mfor, and Mkan infection was dependent on the AIM2 inflammasome and moreover there was an inverse correlation between virulence of the mycobacterial species and the amount of IL-1β release, with the least virulent species inducing the highest levels of IL-1β (23). *Mycobacterium bovis* (Mbov) infection activated the AIM2 inflammasome in BMDMs and J774A.1 mouse macrophage (25) (**Table 1**). Mbov infection augments the mRNA expression of AIM2 and ASC in both BMDMs and J774A.1 mouse macrophage (25). Potassium efflux and mycobacterial escape into the cytosol are the two essential triggers in the activation of AIM2 inflammasome during Mbov infection. Additionally, infection of J774A.1 mouse macrophage with Mbov results in activation of caspase-1 as early as 6h post-infection (25). The transfection of Mtb genomic DNA into LPS-primed peritoneal macrophages results in AIM2-dependent caspase-1 activation and subsequent secretion of mature IL-1β and IL-18 (24). This is not surprising since AIM2 recognizes any type of dsDNA but interesting because Mtb does not activate the AIM2 inflammasome upon infection of BMDCs or BMDMs (23).

ACTIVATION OF THE NLRP3 INFLAMMASOME BY MYCOBACTERIAL PROTEINS AND LIPIDS

Mtb contains several secretion systems to export proteins into the cell well and beyond (137, 138). In order for these proteins to potentially reach the host cell cytosol, the ESX-1-secreted effector EsxA is involved in permeabilizing the phagosomal membrane (**Figure 2**) (139, 140). A small number of mycobacterial secreted protein effectors have been identified that are involved in activation of NLRP3 inflammasome (5–8, 10, 11, 16, 19, 20) (**Figure 2** and **Table 1**).

PPE13

The Proline-Proline-Glutamate (PPE) family protein, PPE13, participates in the assembly of NLRP3 inflammasome complex *via* its C-terminal repetitive major polymorphic tandem repeat (MPTR) domain by directly interacting with the NACHT and Leucine-rich repeat (LRR) domains of NLRP3 (5) (**Figure 2** and **Table 1**). A recombinant Msme strain expressing the Mbov PPE13 induces increased cell death and increased secretion of IL-1β in J774A.1, BMDMs, and THP-1 macrophages but to different

levels depending on the cell type (5). The release of IL-1β was dependent on activation of NLRP3 inflammasome as confirmed by caspase-1 and NLRP3 inflammasome inhibitor studies (5). The role of PPE13 in inflammasome signaling needs further validation by creating a gene specific knockout in Mtb.

EST12

Recent studies show that *Rv1579c*, located within the Mtb H37Rv region of difference 3 (RD3), encodes for a protein (EST12) which acts as a pyroptosis-inducing protein (8) (**Figure 2** and **Table 1**). Indeed, EST12 interacts with the host protein receptor for activated C kinase 1 (RACK1) and forms a EST12-RACK1 complex in macrophages. The EST12-RACK1 dimer recruits the deubiquitinase UCHL5 to stimulate the K48-linked deubiquitination of NLRP3 and consequently triggers the NLRP3 inflammasome mediated pyroptosis and IL-1β secretion (8) (**Figure 2**). Mice infected with an Mtb strain lacking EST12 showed significant increase in the bacterial growth in the lungs and lower levels of serum IL-1β compared to wild-type Mtb-infected mice. Consistently, mice infected with BCG or Msme strains overexpressing EST12 showed lower bacterial burden in lungs or spleen and increased levels of IL-1β compared to mice infected with control bacteria. Consequently, Mtb EST12 increases mycobacterial clearance in mice and is responsible to activate the host's immunity (8). It will be interesting to see in future studies which Mtb secretion system is responsive for the secretion of EST12.

LpqH

The Mtb lipoprotein, LpqH, activates the NLRP3 inflammasome *via* a mechanism that involves activation of the TLR-2 receptor (16) (**Figure 2** and **Table 1**). The treatment of LPS-primed Ana-1 mouse macrophages with purified LpqH protein results in increased expression of NLRP3, ASC and caspase-1 proteins in

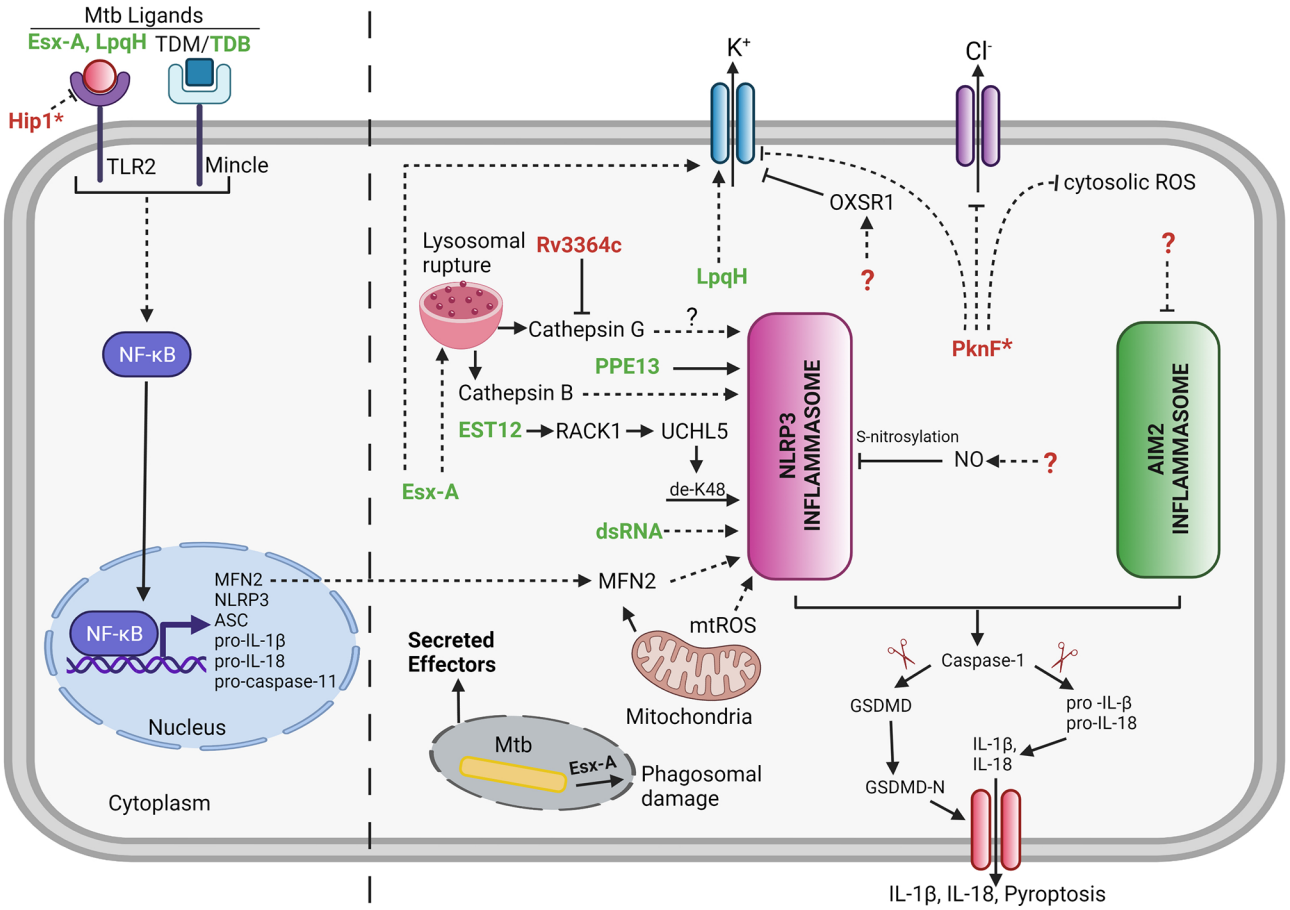

FIGURE 2 | Mycobacterial effectors involved in regulation of host cell inflammasome. Several Mtb effectors either secreted or non-secreted (as indicated by *) are known to be implicated in manipulation of the host cell inflammasome pathway. Bold green color denotes the Mtb effectors involved either directly or indirectly in activation of inflammasome. Bold red color denotes the Mtb effectors involved in inhibition of inflammasome. Unknown Mtb effectors are represented by ? (dashed lines = indirect interaction; solid lines = direct interaction; arrowhead = activation; blunt end = inhibition). LpqH,19 kDa Lipoprotein antigen precursor; PPE13, PPE family protein 13; EST12, Estimated 12kDa (Rv1579c); EsxA, 6 kDa Early secretory antigenic target; dsRNA, double stranded Ribonucleic Acid; TDB, Trehalose-6,6-dibehenate; TDM, Trehalose dimycolate; PknF, Protein kinase F; Hip1, Hydrolase important for pathogenesis 1; NO, Nitric Oxide; RACK1, Receptor for Activated C Kinase 1; UCHL5, Ubiquitin C-Terminal Hydrolase L5; MFN2, Mitofusin 2; OXSR1, Oxidative Stress Responsive Kinase 1. Created with Biorender.com.

a dose-dependent manner (16). Moreover, potassium efflux acts as an important trigger for LpqH-mediated activation of the NLRP3 inflammasome (16). However, the underlying mechanism of how LpqH influences potassium efflux has not been explored in this study. The work was performed in mouse macrophages and thus further validation in human macrophages would be valuable. It will also be crucial to test a *lpqH* deletion mutant of Mtb for changes in NLRP3 inflammasome activation to confirm that the observed activity of purified proteins is conserved within the context of a whole bacterium.

ESX-1 and ESX-5

The Mtb RD1 locus which encodes for the ESX-1 secretion system is required for activation of NLRP3 inflammasome and subsequent release of IL-1β in human PBMCs, THP-1 cells and mouse BMDMs and retinal pigment epithelium (RPE) cells (4, 6, 7, 9, 11, 14, 19, 20) (**Figure 2** and **Table 1**). The ESX-5a is a duplicated region of 4 genes out of the ESX-5 secretion system which is important for the secretion of subset of ESX-5-secreted proteins and its deletion results in reduced inflammasome activation (10) (**Table 1**).

EsxA

EsxA is one of the main substrates secreted by the ESX-1 system and consequently many studies have been performed by adding purified EsxA to cells during *ex vivo* experimentations. EsxA interacts with TLR-2 and TLR-4 receptors to induce host cell signaling (141–144). One report shows that treatment of mouse RPE cells with different doses of EsxA results in caspase-1 activation in a dose dependent manner and that this activation is dependent on TLR/MyD88 signaling and the NLRP3 inflammasome (6). Other studies reveal that stimulation of either PBMCs (7) or THP-1 macrophages (7, 19) with EsxA results in increased release of proinflammatory cytokine IL-1β. Furthermore, stimulation of PBMCs and THP-1 derived macrophages with either Mtb protein EsxA or heat inactivated Mtb lysates induces increase in expression of MFN2 and results in increased release of IL-1β. Therefore, these findings suggest that MFN2 is required for the assembly and activation of NLRP3 inflammasome during Mtb infection (7). Transcriptional profiling in human PBMCs from active tuberculosis patients and healthy controls determined that a mitochondrial outer membrane protein, MFN2 expression was significantly upregulated in TB patients compared to healthy controls (7). Intriguingly, another study reported the importance of EsxA and RD1 locus in secretion of IL-1β, since BMDMs when infected with Mtb strains lacking *esxA* or RD1 showed a significant reduction in the secretion of IL-1β compared to the BMDMs infected with Mtb (20). EsxA was partially responsible for the release of mature cathepsin B by the lysosomes during Mtb infection and further leads to NLRP3 inflammasome activation in BMDMs (20). In addition to lysosomal permeabilization, EsxA also triggers phagosome damage and Syk activation in human macrophages that result in NLRP3 mediated necrotic cell death (11). Additionally, EsxA facilitates the translocation of other immunostimulatory Mtb components such as Ag85 into the macrophage cytosol, resulting in increased activation of caspase-1 and subsequent secretion of IL-1β (19).

Critical role for the ESX-1/EsxA in NLRP3 activation has also been reported during the infection with non-tuberculous mycobacteria species including Mmar (12, 17, 18), and Mkan (14) (**Table 1**). In addition to ESX-1, ESX-5 secreted substrates also play a role in activation of NLRP3 inflammasome in response to infection with Mmar (12) (**Table 1**). Additionally, transfection of mouse RPE cells with mycobacterial dsRNA induces NLRP3 inflammasome-dependent caspase-1 activation *via* an uncharacterized mechanism (6).

TDB/TDM

The role of mycobacterial cell wall lipids in NLRP3 inflammasome activation has also been studied in addition to mycobacterial secreted effector proteins (145). Trehalose-6,6'-dibehenate (TDB), a synthetic analogue of Trehalose-6,6'-dimycolate (TDM) also known as mycobacterial cord factor has been developed as an effective adjuvant for tuberculosis subunit vaccine and both act as a potent proinflammatory pathogen-associated molecular pattern (PAMP) which is recognized by macrophage inducible C-type lectin (Mincle) receptor on innate immune cells and triggers host innate immune response. TDB induces the NLRP3/ASC/Caspase-1 mediated increase in production of IL-1β in BMDCs. Activation of NLRP3 inflammasome by TDB involves numerous triggers such as lysosomal permeabilization, increased ROS generation and increased potassium efflux (145).

It is important to remember that the NLRP3 inflammasome is acting most likely as the cells stress or danger sensor and thus any bacterial induction of the NRLP3 inflammasome might not be mediated by a direct interaction with the inflammasome complex but through interaction with other cellular components/pathways that then trigger the stress/danger signal.

AIM2 INFLAMMASOME INHIBITION BY MTB

Mycobacterial extracellular DNA enters the host cell cytosol in an ESX-1 secretion system dependent manner (146). Intriguingly, AIM2 recognizes and binds to cytosolic DNA of intracellular pathogens such as *Francisella* and *Listeria* (82, 147) and even Mtb (24). However, AIM2 is not activated during the course of *ex vivo* Mtb H37Rv infection of BMDM and BMDCs (23). Nonvirulent mycobacterial species such as Msme induce the activation of AIM2 inflammasome in contrast to virulent Mtb that inhibits the AIM2 inflammasome activation induced by either Msme or AIM2 agonists (23). Moreover, Mtb-mediated AIM2 inflammasome inhibition is dependent on a functional ESX-1 secretion system since infection with the Mtb strain deficient in *esxA* fails to inhibit IL-1β secretion induced by Msme (23). Intriguingly, Mtb inhibits the secretion of IFN-β in infected cells, which may provide one of the mechanisms to suppresses the activation of AIM2 inflammasome (23).

Consequently, co-secretion of a putative AIM2 inhibitor and/or IFN-β inhibitor through ESX-1 secretion system into the host cell cytosol together with cytosolic Mtb DNA may play an important role in Mtb-mediated evasion of AIM2 inflammasome activation. The inhibition of the AIM2 inflammasome activation might be of importance for virulence of Mtb because *aim2*$^{-/-}$ mice are highly susceptible to Mtb infections and showing impaired production of pro-inflammatory cytokines IL-1β and IL-18 (24). An area of interest will be the discovery of the Mtb genes involved in the AIM2 inflammasome inhibition in order to assess the importance of AIM2-inflammasoem evasion for the virulence of Mtb.

NLRP3 INFLAMMASOME INHIBITION BY MTB

Mtb PknF

As discussed before many studies have shown that Mtb causes NLRP3 inflammasome activation and even that the deletion of certain Mtb genes led to an increased activation of the NLRP3 inflammasome (**Figure 2** and **Table 1**). Nevertheless, not until recently was it shown that Mtb infection can inhibit activation of the NLRP3 inflammasome *via* either LPS/Nigericin or LPS/ATP stimuli (134). Mtb inhibits the NLRP3 inflammasome activation *via* a mechanism that is independent of the ESX-1 secretion system which is opposed to the capacity of Mtb to inhibit the AIM2 inflammasome in an ESX-1 dependent mechanism (23, 134). Mtb infection inhibits the LPS/ATP-induced K^+ efflux and increase in xanthine oxidase (XO) activity leading to decreased cytosolic ROS levels (134). The Mtb serine threonine kinase, PknF, mediates inhibition of NLRP3 inflammasome dependent production of IL-1β and pyroptosis in both mouse and human derived primary macrophages (134). Moreover, K^+ efflux, Cl^{2+} efflux and ROS generation are implicated in the PknF-mediated NLRP3 inflammasome inhibition (134) (**Figure 2**). Additionally, the Mtb *pknF* mutant induces an increase in the XO activity compared to Mtb-infected cells and thus increasing XO-mediated ROS production (134). Altogether it seems that PknF is inhibiting the exact NLRP3 inflammasome activation pathway that is being only slightly activated upon Mtb infection.

Mtb Zmp1

The BCG gene *zmp1* encodes a zinc metalloprotease that has been shown to inhibit the NLRP3 inflammasome dependent processing of IL-1β (115). However, these findings could not be independently confirmed since generation of the *zmp1* Mtb deletion mutant strain did not show any effect on pyroptosis, on the caspase-1 activation nor the release of IL-1β (11). The inconsistency between these two publications might be due to a difference in the background of the *zmp1* mutant strain because most of the studies performed by Master et al. were done using the BCG strain that, unlike Mtb, lacks a functional ESX-1 secretion system. Another possibility may be the difference in cell types used to study the strains lacking *zmp1*.

Mtb Hip1 and Rv3364c

The Mtb serine hydrolase, Hip1, inhibits the NLRP3 inflammasome activation by dampening the TLR2-dependent cell signaling in BMDMs (148) (**Figure 2**). Hip1 not only affects the secretion of inflammasome dependent cytokines but also result in decrease of other proinflammatory cytokines thus suggesting Hip1 modulates the proinflammatory responses in macrophages by preventing the activation of TLR2 dependent cell signaling (148). The mechanism involves Hip1-mediated proteolytical cleavage of GroEL2 from multimer to monomer and the cleaved monomeric GroEL2 subsequently contributes to dampening of proinflammatory responses in macrophages mediated by TLR2 signaling (149). Therefore, it is not possible to attribute the *in vivo* attenuation of the *hip1* Mtb deletion mutant to its increase in inflammasome activation since also other important proinflammatory cytokines such as TNF are upregulated (148).The Mtb protein, Rv3364c, binds to and inhibits the membrane associated host serine protease cathepsin G which leads to suppression of caspase-1 activity and pyroptosis in macrophages (150) (**Figure 2**).

Nitric Oxide (NO)

Host cell derived NO acts as a negative regulator of NLRP3 inflammasome activation and inhibits processing of IL-1β (127, 151) (**Figure 2**). Stimulation of Mtb-infected macrophages with IFN-γ showed iNOS-dependent thiol nitrosylation of NLRP3 which leads to inhibition of NLRP3 inflammasome dependent maturation of IL-1β and minimize inflammatory tissue damage during chronic Mtb infection (127). Indeed, the NO-mediated nitrosylation inhibits the assembly of NLRP3 inflammasome complex (127, 151).

OXSR1

During mycobacterial infection, a host serine/threonine protein kinase, the oxidative stress responsive kinase 1 (OXSR1), inhibits K^+ channels responsible for K^+ efflux (152). Indeed, the mycobacterial infection leads to the upregulation of host OXSR1 and this host cell manipulation is dependent on the mycobacterial ESX-1 secretion system. The immunomodulatory role of OXSR1 is conserved in both zebrafish and humans (152). Furthermore, inhibition or depletion of OXSR1 results in diminished levels of intracellular potassium and hence limits the growth of mycobacteria. Therefore, targeting of OXSR1 might be a valuable approach for host-directed therapy. Micheliolide (MCL), a sesquiterpene lactone, act as an anti-inflammatory molecule by inhibiting PI3K/Akt/NF-κB and NLRP3 inflammasome signaling during Mtb infection (153). However, previous report showed that RAW264.7 cells do not release mature IL-1β since they do not express ASC as determined by immunoblot analysis with an ASC-specific antibody (154). The study by Zhang et al. did not address this problem since all experiments were performed in RAW264.7 macrophages and hence there remains some questions on the validity of their results.

Overall, there has been notable progress but still the molecular mechanisms by which Mtb evades NLRP3

inflammasome activation and the importance of this manipulation for virulence of Mtb remain poorly understood.

CONCLUSION

Since we last reviewed the literature on the subject of Mtb-host cell inflammasome interactions in 2013 (155) a tremendous amount of progress has been made in our understanding of the molecular mechanisms of inflammasome activation and subsequent pathways of pyroptosis induction (**Figure 1**). Also, our knowledge of the role of IL-1β during Mtb infections has been greatly expended. Nevertheless, important questions remain; for example, what is the *in vivo* mechanisms of host resistance that is mediated by IL-1β? We know that protective effects are mediated by bystander cells but what is IL-1β/IL-1β-signaling doing onto those cells that conveys the protective effect? We now know that Mtb is able to inhibit the AIM2- and NLRP3-inflammasome during *ex vivo* infections (**Figure 2**) but is there a role for the inflammasome for increasing host resistance or susceptibility during *in vivo* Mtb infections? The herein described progress made in identifying various Mtb effectors activating or inhibiting the host cell inflammasome (**Figure 2** and **Table 1**) and the subsequent availability of specific Mtb mutants perturbing the inflammasome activation will provide the tools necessary to start answering that question.

AUTHOR CONTRIBUTIONS

SR and VB wrote and edited the manuscript. SR created the figures and table. All authors contributed to the article and approved the submitted version.

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