

REVIEW

Innate immunity in tuberculosis: host defense vs pathogen evasion

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The major innate immune cell types involved in tuberculosis (TB) infection are macrophages, dendritic cells (DCs), neutrophils and natural killer (NK) cells. These immune cells recognize the TB-causing pathogen *Mycobacterium tuberculosis* (Mtb) through various pattern recognition receptors (PRRs), including but not limited to Toll-like receptors (TLRs), Nod-like receptors (NLRs) and C-type lectin receptors (CLRs). Upon infection by Mtb, the host orchestrates multiple signaling cascades via the PRRs to launch a variety of innate immune defense functions such as phagocytosis, autophagy, apoptosis and inflammasome activation. In contrast, Mtb utilizes numerous exquisite strategies to evade or circumvent host innate immunity. Here we discuss recent research on major host innate immune cells, PRR signaling, and the cellular functions involved in Mtb infection, with a specific focus on the host's innate immune defense and Mtb immune evasion. A better understanding of the molecular mechanisms underlying host–pathogen interactions could provide a rational basis for the development of effective anti-TB therapeutics.

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INTRODUCTION

Infection with *Mycobacterium tuberculosis* (Mtb) was responsible for ~10.4 million new tuberculosis (TB) cases and 1.4 million TB deaths worldwide in 2015, according to a report from the World Health Organization.¹ The successful establishment of Mtb infection largely depends on its early interactions with host innate immune cells, such as macrophages, dendritic cells (DCs), neutrophils and natural killer (NK) cells.² These immune cells express a variety of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), Nod-like receptors (NLRs) and C-type lectin receptors (CLRs), all of which have been implicated in the recognition and uptake of Mtb.³ These receptors are also involved in the initiation of various innate immune defense-associated cellular functions, such as

phagocytosis, autophagy, apoptosis and inflammasome activation.^{4,5}

Mtb is an extremely successful intracellular pathogen that has co-evolved with its host for eons. The host immune cells are triggered into a non-sterilizing control of Mtb, which causes a latent Mtb infection that maintains equilibrium between the host and the pathogen via granuloma formation. The reactivation rates of latent TB range from 5 to 10% per lifespan in patients. The failure of the host cells to restrain Mtb growth results in granulomatous lesions with more necrotic macrophage death and increased inflammatory cell recruitment. This evasion of the host immunity reflects the highly evolved and multifactorial ability of pathogenic mycobacteria to survive and persist within host cells. The intricate

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mechanisms that *Mtb* has developed to evade host innate immunity include cytosolic escape, the restricted production of antimicrobial peptides, blockade of phagosome maturation, apoptosis, inflammasome activation and modulation of autophagy. These strategies and measures also limit the development of adaptive immune responses during *Mtb* infection.^{6–8} In this review, we highlight recent research regarding major innate immune cells, PRR signaling pathways and the cellular functions involved in the innate immune defense against *Mtb*. We also describe evidence demonstrating that *Mtb* modulates the host innate immune defense functions to its own benefit. A better understanding of the molecular mechanisms underlying the intricate and dynamic interactions between the host and *Mtb* is crucial to the development of better drugs and vaccines for the prevention and treatment of TB.

INNATE IMMUNE CELLS IN TB

The major innate immune cell types involved in *Mtb* infection include macrophages, DCs, neutrophils and NK cells. Several innate-like cells are also involved in the host defense against *Mtb*, including non-conventional T cells such as mucosal-associated invariant T (MAIT) cells, CD1-restricted lymphocytes and NKT cells.^{9–11} Furthermore, other cell types (such as airway epithelial cells and mast cells) that are not classically defined as immune cells have also been shown to contribute to early immune responses against *Mtb*. During *Mtb* infection, different cell types play distinct but overlapping roles and are readily manipulated by *Mtb*. Here we focus only on the regulatory roles of the classically defined major innate immune cells (including macrophages, DCs, neutrophils and NK cells) during *Mtb* infection.

Macrophages

Macrophages play a central role in mycobacterial pathogenesis since they are the primary cellular niche for *Mtb* during both early and chronic infection.¹² Macrophages can eliminate *Mtb* via multiple mechanisms, including the production of oxygen and nitrogen components and cytokines, phagosome acidification and the autophagy of intracellular *Mtb*, among other processes. *Mtb* is phagocytosed by alveolar macrophages, which are the first cells to encounter the pathogen and recruit different types of macrophages, such as monocyte-derived macrophages, during early infection.¹³ The recognition of pathogen-associated molecular patterns (PAMPs) from *Mtb* (such as glycolipids, lipoproteins and carbohydrates) by macrophage PRRs (such as TLRs, NLRs and CLRs) induces a network of coordinated signaling pathways that leads to distinct gene expression profiles in macrophages at different stages of infection.³ Gene profiling studies have provided evidence for the importance of inflammatory cytokines, including IFN- γ , IL-12, IL-1 β and macrophage inflammatory protein-1 α (MIP-1 α /CCL3) in the defense against *Mtb* infection.¹⁴ Multiple macrophage functions (including phagocytosis, autophagy and antimicrobial peptide production) can be enhanced by vitamin D treatment.^{15–17} The development and function of macrophages are shaped by micro-environmental signals, which drive

macrophage differentiation, with the M1 and M2 populations being the two extreme phenotypes of the macrophage polarization spectrum.^{18,19} Normally, classically activated M1 macrophages, which are key effectors of the host response against intracellular bacteria and produce immune-stimulatory cytokines, are induced by microbial stimuli (for example, LPS) or cytokines (for example, IFN γ , TNF α and GM-CSF). In contrast, the alternatively activated M2 macrophages, which are poor antigen-presenting cells and suppressors of Th1 responses, are induced by IL-4 and IL-13 as well as IL-10 and TGF β .²⁰ These additional macrophage populations have been shown to play important roles in maintaining the tight balance between exacerbated pathology and control of mycobacterial growth. For example, mice deficient in Arg1, a hallmark enzyme of M2 macrophages, demonstrate better protection against *Mtb* infection.²¹ In the context of active TB, human monocytes are predisposed to differentiate toward M2-like macrophages characterized by the CD16⁺CD163⁺MerTK⁺pSTAT3⁺ phenotype and increased protease-dependent motility, pathogen permissivity and immunomodulation.²² M2 macrophages can be induced by mycobacterial DnaK (heat shock protein 70, Hsp70) in an IL-10-dependent manner.²³ Myeloid-derived suppressor cells (MDSCs), which represent an innate immune cell population consisting of granulocytic CD15⁺ G-MDSCs and monocytic CD14⁺ M-MDSCs, have been described as lung-residing myeloid-derived suppressors induced during TB that can provide a niche for mycobacteria survival. Therefore, MDSCs can be considered novel targets for host-directed therapy in TB.²⁴ More recently, another population of macrophages termed myeloid suppressor cells (MSCs), which suppress T-cell responses via the secretion of IL-10 and TGF- β , has emerged as a novel class of immune cells that exhibits suppressive function and regulates the infection and inflammation associated with TB.²⁵ Histopathologically, TB has long been characterized by granulomas that contain a broad spectrum of transformed macrophages, such as multinucleated giant cells, epithelioid cells and foam cells.^{26,27} Foamy macrophages, which exhibit an attenuated ability to mediate phagocytosis accompanied by reduced antigen processing capacity and increased secretion of TGF- β , can be induced by multiple *Mtb* triggers, including mycolic acids, lipopeptides and early secretory antigen-6 (ESAT-6).^{27,28} More recently, it was reported that TLR2 signaling promotes macrophage polyploidy and suppresses genomic instability by regulating Myc and ATR expression, indicating that in the presence of persistent inflammatory stimuli, pathways involved in developing cancer cells surprisingly instruct a polyploid macrophage fate and regulate granulomatous tissue remodeling.^{28,29} Interestingly, emerging evidence suggests that *Mtb* pathogenicity is intimately associated with its capacity to regulate host cell metabolism.³⁰ Upon *Mtb* infection, mononuclear phagocytes accumulate a stearic acid derivative, which promotes phagocyte differentiation into macrophages and enhances the effector function of phagocytes against *Mtb*.³¹ Furthermore, *Mtb* ESAT-6 was found to induce metabolic flux perturbations to drive foamy

macrophage differentiation.²⁸ More in-depth studies are needed to identify additional Mtb effectors and signaling pathways that regulate macrophage functions and metabolism. This understanding may allow the development of novel approaches to control TB via modulation of macrophage phenotype, form, metabolism and function.

Dendritic cells

DCs play a central role in Mtb antigen presentation and are thus critical in bridging innate and adaptive immunity.³² Monocyte-derived human DCs express mannose receptors (MRs) and DC-specific ICAM-grabbing nonintegrin (DC-SIGN), which are capable of recognizing Mtb ligands, such as Mtb lipoprotein *lprG* and hexamannosylated phosphatidylinositol mannosides (PIMs).^{33–35} Freshly isolated human lung dendritic cells express DC-SIGN, and Mtb-derived material was detected in CD14 (–) HLA-DR (+) DC-SIGN (+) cells in lymph nodes (LNs) from TB patients, suggesting that the DC-SIGN-mediated entry of Mtb in DCs could influence pathogen persistence and host immunity.³³

Roberts and colleagues³⁶ found that Mtb-infected DCs exhibit reduced surface expression of the β (2) (CD18) integrin and have a reduced ability to reach the lymph nodes and initiate an adaptive immune response. In later studies, a population of DCs that contribute to the priming of CD4⁺ T cells during *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) infection was discovered. Basically, these DCs transport bacilli into the draining lymph node in an IL-1R-MyD88-dependent manner.³⁷ During Mtb infection, ligation of DC-SIGN by Mtb mannose-capped lipoarabinomannan (ManLAM) induces the production of the anti-inflammatory cytokine IL-10, which impairs DC maturation and the expression of co-stimulatory molecules. ManLAMs are also capable of inducing a negative signal that inhibits IL-12 production, suggesting that Mtb modulates DC functions to prevent the optimal induction of adaptive immunity.³⁸ Another study showed that PE27 from Mtb elicits Th1-polarized immune responses via DC activation during Mtb infection, suggesting that PE27 could be an effective Mtb vaccine candidate.³⁹ This induction of DC maturation by PE27 is mediated by TLR4 binding and the subsequent activation of extracellular-regulated protein kinases (ERKs), p38 mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) signaling. In addition, RpfE, a latency-associated member of the Rpf family from Mtb, is also a potential effective Mtb vaccine because of its ability to activate DC maturation by promoting the expression of surface molecules and the production of IL-6, IL-1 β , IL-23p19, IL-12p70 and TNF- α but not of IL-10.⁴⁰ Furthermore, Mtb Rv2463 and Rv3416 can downregulate the expression of neural precursor cell expressed developmentally downregulated 8 (NEDD8) with a concomitant upregulation of SUMO/sentrin-specific peptidase family member 8 (SEN8). RNAi-mediated knockdown of NEDD8 and SEN8 differentially regulated oxidative burst, apoptosis and autophagy in DCs, suggesting that Mtb exploits neddylation to its advantage to delay the induction of protective responses, thereby

contributing to its long-term survival in the host.⁴¹ Another recent study reported increased expression of CD13 on DCs during Mtb infection and enhanced T-cell activation after anti-CD13 antibody treatment, suggesting that CD13 is positively involved in Mtb pathogenesis. Therefore, targeting the CD13 receptor may help reduce the ability of Mtb to inhibit T-cell activation, but the specific Mtb effectors modulating CD13 expression are currently unknown.⁴² More questions remain regarding the mechanisms by which Mtb manipulates DCs and the consequences of that manipulation on the nature and kinetics of the adaptive immune responses toward Mtb.

Neutrophils

Neutrophils are the first cells to infiltrate the lungs after Mtb infection and are the most abundant cell type appearing in the bronchoalveolar lavage and the sputum of the active pulmonary TB patients. These cells play a very complex role in the pathology of TB. Their recruitment to the lung and their pathologic roles are regulated by various cytokines and chemokines,^{43,44} alarmins (such as S100A8/A9 proteins)⁴⁵ and intrinsically expressed miRNAs (such as miR-223).⁴⁶ The factors released by neutrophils during respiratory bursts, such as elastase, collagenase and myeloperoxidase, indiscriminately damage bacterial and host cells. Thus, neutrophils constitute a potent population of effector cells that can mediate both anti-mycobacterial activity and immunopathology during Mtb infection.⁴⁷ The potential of neutrophils to release enzymes that lead to the destruction of pulmonary parenchyma, such as arginase and matrix metalloproteinase-9 (MMP-9 and gelatinase B), is shared by other innate immune cells and epithelial cells affected by Mtb.^{48,49} Previous studies have demonstrated an inverse correlation between the development of pulmonary TB and the number of neutrophils in the peripheral blood of the close contacts of active TB patients. In addition, *in vitro* neutrophil depletion from whole blood led to a failure to control Mtb growth.⁵⁰ Apoptotic neutrophils and purified neutrophil granules, both of which contain active antimicrobial peptides, can be taken up by macrophages and lead to the inhibition of bacterial replication.⁵¹ Interestingly, transcriptional profiling studies have shown that cell surface expression of programmed death ligand 1 (PD-L1) by neutrophils was primarily responsible for high levels of PD-L1 expression in the whole blood of active TB patients, suggesting that neutrophils are implicated in a more immune-regulatory role during Mtb infection.⁵² Furthermore, although autophagy-related gene 5 (Atg5) is dispensable in alveolar macrophages during Mtb infection, a loss of Atg5 in neutrophils can sensitize mice to Mtb. These findings argue for a shift in the focus onto the macroautophagy-independent roles of Atg5 in controlling resistance to Mtb infection *in vivo*.⁵³ Another study found that CD73 (also called ecto-5'-nucleotidase) limits the early influx of neutrophils into the lungs without affecting bacterial growth and dissemination, supporting the view that CD73 fine-tunes anti-mycobacterial immune responses.⁵⁴ Neutrophils can also be actively manipulated by Mtb. For example, Mtb induces neutrophil necrosis and prevents apoptosis dependent on

region of difference 1 (RD-1)-encoded virulence factors.⁵⁵ More recently, ESAT-6 protein, which is secreted by a type VII secretion system (ESX) encoded by RD1 in *Mtb*, was demonstrated to induce an intracellular Ca^{2+} overload followed by necrosis and the formation of neutrophil extracellular traps (NET) characterized by extruded DNA and myeloperoxidase.⁵⁶ Furthermore, neutrophils are involved in the induction of adaptive immunity and are critical for granuloma cavitation during *Mtb* infection.^{57,58} Future work is warranted to identify additional mycobacterial effectors of neutrophil necrosis and determine whether pharmacologic intervention targeting neutrophil necrosis could alter uncontrolled inflammation and immunopathology during *Mtb* infection.

Natural killer cells

NK cells are granular innate lymphocytes that possess potent cytolytic capacity. NK cells act early during infection and are not MHC-restricted.⁵⁹ Various *Mtb* cell wall components, such as mycolic acids, are direct ligands for the natural cytotoxicity receptor (NCR) NKp44 on NK cells. NK cells isolated from healthy donors can lyse infected monocytes and reduce *Mtb* intracellular growth.⁶⁰ NK cells are required for mycobacterial resistance in T-cell-deficient mice, suggesting an important role for NK cells in combating *Mtb* infection in immune-compromised individuals.⁶¹ NK cells can control mycobacterial growth indirectly via immune stimulation through macrophage activation and directly via cytotoxic mechanisms, including the production of cytoplasmic granules containing perforin, granzyme and granzyme. Additionally, NK cells can produce IFN- γ and IL-22, which can inhibit *Mtb* intracellular growth by enhancing phagolysosomal fusion. NK cells can also promote $\gamma\delta$ T-cell proliferation by producing CD54, TNF α , GM-CSF and IL-12.⁵⁹ In addition to early innate immune functions, NK cells are found in mature granulomatous lesions in the lungs of *Mtb*-infected patients. There are indications that NK cells may be functionally impaired during TB.⁶² Patients newly diagnosed with pulmonary TB display decreased frequencies of NK cell subsets, concurrent with decreased expression of NKp30 and NKp46, which are capable of increasing the expression of granzyme and perforin through the MAP kinase signaling pathway.^{63,64} Anti-TB treatment regimens leading to reductions in mycobacterial load partially restore NK cell cytolytic capabilities. It was demonstrated that glutathione (GSH) could partially inhibit intracellular *Mtb* growth through bacteriostatic mechanisms.⁶⁵ Interestingly, both NK cell function and intracellular GSH levels are compromised in HIV-infected individuals, suggesting that GSH could be a potential immune adjuvant for TB treatment, particularly in individuals suffering from HIV.⁶⁶ A better understanding of the exact roles and molecular mechanisms of NK cells in anti-mycobacterial immunity is needed, and this knowledge may open new possibilities for NK cell-based therapeutic strategies for TB treatment.

INNATE IMMUNE SIGNALING PATHWAYS IN TB

The first step in the activation of innate immune responses during *Mtb* infection begins with pathogen recognition. During phagocytosis, conserved PAMPs on the surface of *Mtb* are recognized by PRRs on the host cells. A variety of PRRs have been shown to recognize mycobacterial PAMPs, such as TLRs, NLRs, CLRs, scavenger receptors (for example, MSR1, MARCO and CD36), CD14 receptors, AIM2 and AhR.^{67–71} Different innate immune cells use distinct receptors or combinations of receptors to identify and phagocytose *Mtb*, although the pathogen may preferentially target specific receptors to manipulate the host immune responses and promote their own intracellular survival.^{3,6} In addition, accumulating data suggest that protein modification systems, such as the ubiquitin system, play a pivotal role in the regulation of PRR signaling networks.⁷² Here we focus primarily on the recent progress in understanding the major PRR signaling pathways (including the TLR, NLR and CLR pathways) and their regulatory roles during *Mtb* infection.

TLR signaling

TLRs are a family of type I transmembrane proteins that contain leucine-rich repeats and recognize PAMPs from pathogens and Toll-interleukin 1 receptor (TIR) domains. TLRs are responsible for recruitment of the downstream adapters, including MYD88 (myeloid differentiation primary response protein 88), TRIF (TIR domain-containing adapter protein inducing IFN- β), TIRAP (TIR domain-containing adapter protein) and TRAM (TRIF-related adapter molecule). Depending on their cellular localization and agonists, the TLRs fall into two groups: plasma membrane-anchored TLRs (TLR1, 2, 4, 5 and 6), which mainly recognize microbial membrane components such as the gram-negative bacterial endotoxin lipopolysaccharides (LPS) and endosomal TLRs (TLR3, 7, 8 and 9), which predominantly detect microbial nucleic acids.⁷³ Upon pathogen infection, different TLRs recruit distinct adapter molecules to relay signals to downstream molecules, which results in the activation of multiple signaling pathways such as the NF- κ B, MAPK and PI3K/Akt pathways. These events culminate with the induction of pro-inflammatory cytokines and/or type I IFNs. Changes in the expression and/or activation status of TLRs can serve as useful markers of the immunological status in TB patients.⁷⁴ Mice deficient in the TLR adapter molecule MYD88 are highly susceptible to *Mtb* infection, suggesting a major role for this pathway in the innate defense against *Mtb*.⁷⁵ TLR2^{-/-} mice exhibit defective granuloma formation following *Mtb* infection and have a greatly enhanced susceptibility to infection compared with WT mice. Consistently, TLR2 polymorphisms in humans are associated with enhanced susceptibility to pulmonary TB.⁷⁶ Genetic polymorphisms in TLR4 are linked to an increased susceptibility to and severity of pulmonary TB in an Asian population in India.⁷⁷ TLR7 and TLR8 genetic polymorphisms are also associated with susceptibility to *Mtb* infection. Individuals with the TLR7 IVS2-151A/TLR8-129C genotype show increased phagocytosis and lower levels of immune activation due to a

blockade of phagosome–lysosome fusion.⁷⁸ Mice lacking TLR9 succumb to Mtb infection earlier than do WT mice.⁷⁹ However, there is conflicting evidence concerning the protective effects of TLR signaling during Mtb infection. For example, the results from a previous study demonstrated that MyD88, but not TLR2, TLR4 or TLR9, is critical for triggering macrophage effector mechanisms upon Mtb infection.⁸⁰ Another study indicated that during Mtb infection, cytokines can be generated via a TLR- and caspase-1-independent mechanism.⁸¹ Mtb expresses many diverse lipoproteins and lipoglycans that can be recognized by different TLRs. For example, TLR2 recognizes products encoded by IqH (19-kDa lipoprotein).⁸² TLR3 regulates mycobacterial RNA-induced IL-10 production through the PI3K/AKT signaling pathway.⁸³ The Mtb recombinant leucine-responsive regulatory protein (rLrp) inhibits pro-inflammatory cytokine production and downregulates macrophage antigen presentation via TLR2-mediated activation of the PI3K/AKT pathway.⁸⁴ Previous research from our lab revealed that Mtb-secreted proteins such as PtpA and Mce3E modulate TLR signaling by targeting the downstream molecules involved in the NF- κ B and MAPK pathways.^{85,86} Interestingly, a recent study demonstrated that G protein-coupled receptor 160 (GPR160) regulates mycobacteria entry into macrophages by activating MAPK/ERK signaling, which suggests a crosstalk between the GPCR and TLR signaling pathways during mycobacterial infection.⁸⁷ Further in-depth studies of the underlying mechanisms of the interactions between TLR signaling pathways and Mtb components are warranted.

NLR signaling

The NLR family members, which include NOD1, NOD2, NLRP3 and NLRC4, are intracellular proteins involved in the recognition of microbial components and the activation of inflammatory pathways that protect against invading pathogens.⁸⁸ Mtb is able to escape from phagosomes into macrophage cytosol via a pathway that is dependent on the ESAT-6 secretion system-1 (ESX-1).⁸⁹ Thus, it is not surprising that cytosolic PRRs, such as NOD1/2, are involved in the innate detection of Mtb. An important role for NOD2 in the recognition of and defense against Mtb has been demonstrated using NOD2^{-/-} mice.⁹⁰ In addition, activation of NOD2 by muramyl dipeptide in human alveolar macrophages infected with Mtb was shown to increase intracellular control of bacterial growth and recruitment of autophagy-associated proteins to the bacteria-containing autophagosome, highlighting the possibility of a PRR-dependent mechanism for autophagy activation.⁹¹ Furthermore, three common non-synonymous polymorphisms in the NOD2 gene were associated with a genetic susceptibility to TB in a study of an African–American population from the United States.⁹² An association was also found between TB susceptibility and the NOD2 synonymous Arg5878Arg SNP in the Chinese Han population.⁹³ More recently, many studies have examined the role of other NLRs (particularly NLRP3) and effectors of the inflammasome during Mtb infection. For example, Mtb

ESAT-6 was found to potently activate the NLRP3/ASC inflammasome in macrophages, leading to IL-1 β release and pyroptosis.⁹⁴ Another study demonstrated that mice that were genetically deficient in the production of or response to IL-1 β have increased susceptibility to acute disease following Mtb infection; this phenotype appears to be independent of TLRs, NLRP3, caspase-1 or ASC.⁹⁵ Thus, inflammasome activation may be triggered by Mtb in some situations to promote persistent infection rather than as a virulence mechanism. Despite the rapid progress made in the discovery of new NLRs and their roles in host defense against Mtb infection, on a mechanistic level, there is still much to be learned about the signaling pathways induced by each NLR. In addition, it remains to be investigated whether any Mtb effector proteins interact with the effector domains (such as PYD domain) of NLRs to potentially regulate NLR signaling. Unraveling the regulatory functions and mechanisms that control NLR signaling during Mtb infection will undoubtedly be an exciting field of research in the coming years.

CLR signaling

CLR receptors are a class of PRRs that also include collectins, selectins, phagocytic receptors and proteoglycans and have been classified into at least 17 groups. Many CLRs have been associated with responses to mycobacteria, such as MR, DC-SIGN, Mincle, Dectin-1, Dectin-2, Dectin-3 (also called macrophage C-type lectin, MCL), CL-LK (the heteromeric complex of CL-L1 and CL-K1) and dendritic cell immunoreceptor (DCIR). CLRs are characterized by the presence of one or more carbohydrate recognition domains that can bind to carbohydrate molecules, lipids, proteins and inorganic compounds in a Ca²⁺-dependent or Ca²⁺-independent manner. CLRs have been increasingly recognized to play an important role in modulating Mtb-mediated immune responses, and Mtb surface ligands, including ManLAM and cord factor, are important immune modulators that can be directly recognized by several CLRs.⁹⁶ MR binds to ManLAM mannose caps and mediates phagocytosis of mycobacteria by human macrophages.⁹⁷ ManLAM also binds to DC-SIGN to stimulate the production of immunosuppressive IL-10 by LPS-activated monocyte-derived dendritic cells.⁹⁸ Mincle, a macrophage-inducible CLR, was identified as the mammalian receptor for trehalose 6, 6'-dimycolate (TDM, also known as cord factor) from Mtb.⁹⁹ Dectin-1, in cooperation with TLR2, can activate pro-inflammatory macrophage responses upon mycobacterial infection,¹⁰⁰ but there is also evidence suggesting that Dectin-1 makes a minor contribution to Mtb susceptibility in mice.¹⁰¹ Dectin-2 contributes to host immunity against mycobacterial infection by functioning as a direct receptor for Mtb ManLAM.¹⁰² Interestingly, both Mincle and Dectin-3 are required for immune responses against TDM from Mtb, and Dectin-3 was found to positively regulate Mincle expression, thereby amplifying Mincle-mediated signaling.^{103,104} Collectin CL-LK was identified as a novel soluble C-type lectin able to bind to ManLAM.¹⁰⁵ More recently, the C-type lectin receptor DCIR, which belongs to the Dectin-2 family, was demonstrated

to modulate immunity to TB by sustaining type I interferon signaling in dendritic cells. However, the Mtb ligand of DCIR remains to be identified.¹⁰⁶ Further elucidation of Mtb recognition by CLR and their crosstalk with other PRRs on immune cells is important for a better understanding of the Mtb-induced host innate immune responses.

CELLULAR FUNCTIONS ASSOCIATED WITH INNATE IMMUNE DEFENSE IN TB

In addition to eliciting inflammatory cytokine and chemokine production, pathogen recognition by innate immune cells triggers a cascade of cellular events, such as phagocytosis, autophagy, apoptosis and inflammasome activation, to control or eliminate invading pathogens and to augment antigen presentation, thereby contributing to the induction of adaptive immunity.^{5,107} In contrast, sly intracellular pathogens such as Mtb also endeavor to manipulate host cellular functions through diverse effectors that target key signaling pathways and nodes.^{7,8} Here we focus on the regulatory roles of cellular functions, including phagocytosis, autophagy, apoptosis and inflammasome activation, during Mtb infection. Other cellular mechanisms, such as the production of reactive oxygen and nitrogen species, antigen presentation and major histocompatibility complex class II expression and trafficking, are also considered to play important roles in Mtb infection and are covered extensively elsewhere,^{108,109} but they are not discussed here.

Phagocytosis

Upon invading host cells through phagocytosis, Mtb can replicate within infected cells by arresting phagosome maturation. This mechanism allows the pathogen to avoid exposure to lysosomal hydrolases, low pH conditions and other bactericidal lysosomal components.¹¹⁰ Numerous mycobacterial factors have been identified as inhibitors of phagosome maturation. Mtb PIMs were found to inhibit phagosome acidification by promoting fusion between phagosome and early endosomes.¹¹¹ How PIMs trigger early endosome fusion remains to be fully elucidated, but the process may involve Rab14, a small GTPase that is specifically recruited by mycobacteria to favor phagosome-early endosome fusion and block phagosome acidification.¹¹² Mtb ManLAM has also been demonstrated to limit phagosome maturation by binding to MR.⁹⁷ Mycobacterial phagosomes were found to retain coronin-1 (also called TACO) on the cytoplasmic faces of their limiting membranes, whereas phagosomes that undergo fusion with lysosomes tend to rapidly lose association with this protein.¹¹³ More recently, the serine/threonine kinase PknG from Mtb was identified as a potential effector that inhibits phagosome-lysosome fusion.¹¹⁴ Subsequent studies identified a small secreted protein tyrosine phosphatase PtpA that inhibits vacuolar acidification by binding to the H-subunit of the macrophage vacuolar-H⁺-ATPase.¹¹⁵ In addition, an acid- and phagosome-regulated (*aprABC*) locus was discovered to respond to acidic stress within the phagosome in virulent mycobacteria. The genes mediating this process require acid sensing by the phoPR

operon, which leads to *aprABC* expression and the modulation of cell wall lipid synthesis and sequestration, thus enabling Mtb survival under low pH conditions.¹¹⁶ Another study provided evidence demonstrating that the antiviral interferon-induced transmembrane (IFITM) proteins participate in the restriction of mycobacterial growth by mediating endosomal maturation. IFITM3 interacts with v-ATPase and potentially stabilizes its association with endosomal membranes.^{117,118} Interestingly, it was demonstrated that PPE57, which plays a role in macrophage phagocytosis, is able to recognize TLR2 and induce macrophage activation by augmenting the expression of several cell surface molecules (CD40, CD80, CD86 and MHC class II) and pro-inflammatory cytokines (TNF- α , IL-6 and IL-12p40) in macrophages, suggesting that the PPE57 protein could be a potential antigen for the development of an efficient vaccine against Mtb.¹¹⁹ However, the mechanisms by which Mtb inhibits phagosome maturation remain incompletely understood and have been an area of ongoing active investigation.

Autophagy

Autophagy is a homeostatic and inducible intracellular process by which cells eliminate damaged organelles, protein aggregates and intracellular pathogens. Autophagy is initiated by the formation of a double-membrane-enclosed structure that forms an autophagic vacuole.¹²⁰ Nutrient starvation or treatment with IFN- γ or rapamycin can induce autophagy in Mtb-infected cells, and phagosomes containing the bacilli acquire lysosomal markers and become acidified during this process.¹²¹ Mtb localization to autophagosomes in infected macrophages is markedly increased by treating the cells with LPS, which indicated a TLR4-mediated pathway for the induction of autophagy.¹²² Animals lacking autophagic functionality in myeloid cells only (*Atg5flox/flox LysMCre*) are acutely susceptible to Mtb infection and have unrestrained bacterial replication, increased inflammatory cytokine production and large focal pulmonary abscesses.¹²³ The immunity-related GTPase family M (IRGM) gene encodes a GTP-binding protein that induces autophagy,¹²⁴ and variations in the promoter region of the IRGM gene have been associated with an increased risk of TB.^{125,126} Another study further suggested that IRGM genetic variants differ between active TB and latent TB infection (LTBI), revealing that the IRGM genotype probably determines whether TB progresses from LTBI into active TB.¹²⁷ In addition, ESAT-6 was found to insert into membranes and damage the phagosomal membrane, which provides a signal for autophagy induction. Adapter proteins, such as NDP52 and p62, recognize the damage and stimulate LC3 binding to the phagosome membrane to capture Mtb within an autophagosome.¹²⁸ Interestingly, cyclic-di-adenosine monophosphate (C-di-AMP), which is a bacterial secondary messenger, is also a key mycobacterial PAMP that drives host type I IFN responses and autophagy.¹²⁹ When autophagy is not activated by starvation or other stimuli, Mtb takes advantage of both Rab GTPases and autophagy to establish an ideal replicative niche, thus promoting its intracellular survival. In Mtb-containing phagosomes, Rab5 is recruited at early stages,

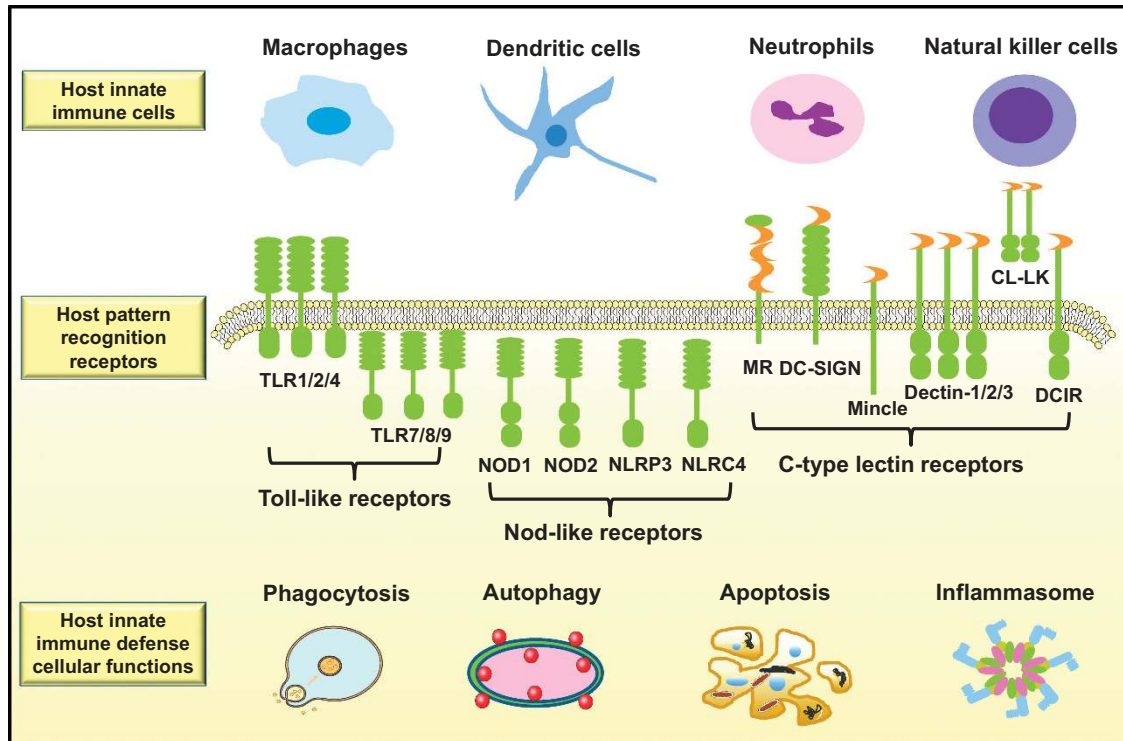


Figure 1 Major host immune cells, pattern recognition receptors and cellular functions involved in innate immune defense against *Mtb*. *Mtb* mainly infects innate immune cells, including macrophages, dendritic cells, neutrophils and natural killer cells. Those immune cells recognize *Mtb* through various pattern recognition receptors, including Toll-like receptors (such as TLR1, TLR2, TLR4, TLR7, TLR8 and TLR9), Nod-like receptors (such as NOD1, NOD2, NLRP3 and NLRC4) and C-type lectin receptors (such as MR, DC-SIGN, Mincle, Dectin-1 and Dectin-2, Dectin-3, CL-LK and DCIR). During *Mtb* infection, the host orchestrates signaling from those PRRs and launches a variety of cellular functions, such as phagocytosis, autophagy, apoptosis and inflammasome activation, to control or eliminate *Mtb*.

and *Mtb* inhibits the fusion of lysosomes with phagosomes by selectively excluding the GTPase Rab7 (which is a late endosomal marker) and lysosome-associated membrane protein-1 (LAMP1) while retaining the GTPase Rab5 on the phagosome.¹³⁰ Rab22a prevents the acquisition of Rab7 and inhibits maturation into the late endosomal/lysosomal compartment.¹³¹ EEA1 is also crucial for phagosomal maturation and its recruitment to *Mtb*-containing phagosomes is altered.¹³² In addition, Rab10 was found to be acquired even before Rab5, thus acting upstream and modulating the maturation of *Mtb*-containing phagosomes.¹³³ Multiple *Mtb* molecules have been shown to inhibit phagosomal maturation. For example, enhanced intracellular survival (EIS) from *Mtb* was shown to inhibit phagosome maturation, reactive oxygen species production, and autophagy through the direct acetylation of a c-Jun N-terminal kinase (JNK)-specific phosphatase.¹³⁴ Another study demonstrated that EIS protein upregulates IL-10 via Ac-H3 and thus activates the Akt/mTOR/p70S6K pathway.¹³⁵ The secreted acid phosphatase (SapM) protein from *Mtb* was shown to be indispensable for arresting phagosomal maturation and promoting pathogen growth in guinea pig tissues.¹³⁶ LrpG (also called P27) has been suggested to be able to block phagosome–lysosome fusion by modulating the traffic machinery in macrophages.¹³⁷ *Mtb* phthiocerol dimycocerosate (PDIM) was demonstrated to contribute to

phagosomal escape and host cell exit by *Mtb*.¹³⁸ The autophagy-associated protein Atg5 was found to play a unique role in protection against *Mtb* by preventing polymorphonuclear-mediated immunopathology. Loss of Atg5 in polymorphonuclear cells can sensitize mice to *Mtb* infection; thus, autophagy is both antibacterial and anti-inflammatory by suppressing bacilli growth and protecting against tissue necrosis and lung pathology.⁵³ Despite our growing understanding of the regulatory roles of autophagy during *Mtb* infection, many unresolved questions remain to be explored. For instance, what dynamic and spatio-temporal patterns are adopted by different *Mtb* effector proteins during their collaborative efforts to fine-tune host autophagy to benefit *Mtb* infection? Nevertheless, many studies have demonstrated the potential for autophagy-based therapies to target *Mtb*,¹²¹ and exploiting autophagy may open new avenues to boost host immunity against *Mtb*.

Apoptosis

Apoptosis, a crucial host defense mechanism against pathogens, involves many components and complex signaling pathways. In contrast to necrosis, which is a form of traumatic cell death, apoptosis is a highly regulated and controlled process. The two best-understood activation mechanisms of apoptosis are the extrinsic pathway and the intrinsic pathway (also called the mitochondrial pathway). The extrinsic pathway is activated by

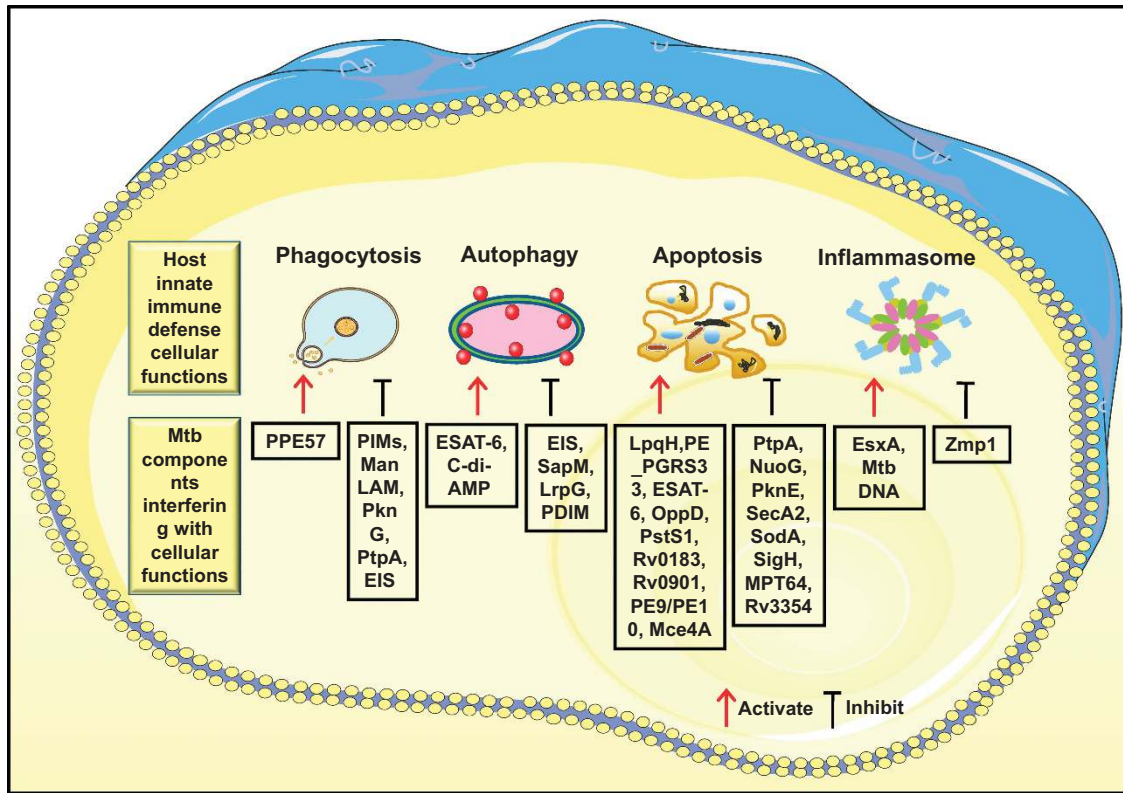


Figure 2 Mtb components interfering with host cellular functions. During Mtb infection, multiple Mtb components interfere (either activate or inhibit) with host cellular functions (such as phagocytosis, autophagy, apoptosis and inflammasome activation) to help the pathogen evade or circumvent host innate immunity. For example, PPE57 promotes phagocytosis, whereas PIMs, ManLAM, PknG, PtpA and EIS inhibit the complete phagocytosis of macrophages through arresting phagosome maturation; ESAT-6 and C-di-AMP activate, whereas EIS, SapM, LrpG and PDIM inhibit autophagy. Many Mtb components can either activate (including LpqH, PE_PGRS33, ESAT-6, OppD, PstS1, Rv0183, Rv0901, PE9/PE10 and Mce4A) or inhibit (including PtpA, NuoG, PknE, SecA2, SodA, SigH, MPT64 and Rv3354) apoptosis; EsxA and Mtb DNA can activate, whereas Zmp1 can inhibit inflammasome activation.

extracellular ligands and initiated by cell surface death receptors (such as TNF receptors and Fas receptors), which leads to the formation of the death-inducing signaling complex. The intrinsic pathway is activated by intracellular signals and depends on the release of proteins from the intermembrane mitochondrial space.¹³⁹ In addition to restricting Mtb growth during the early phase of infection, apoptosis also plays an important role in the induction of the acquired cellular immune response and leads to cell death under certain circumstances.¹⁴⁰ The general perception is that apoptosis blockade and induction of necrosis may be one of the main strategies by which Mtb evades or delays antigen presentation.¹³⁹ Mtb is a successful intracellular pathogen that has evolved multiple effective mechanisms to manipulate host apoptosis, and many Mtb effectors have been associated with apoptosis pathways. The reported anti-apoptotic Mtb antigens include PtpA, NuoG, PknE, SecA2, SodA, SigH, MPT64 and Rv3354.^{141–148} The Mtb known pro-apoptotic antigens include LpqH (19-kDa lipoprotein), PE_PGRS33, ESAT-6, OppD, PstS1, Rv0183, Rv0901, PE9/PE10 and Mce4A.^{149–158} TLRs are important for triggering apoptosis in Mtb-infected cells. For example, Mtb LpqH induces macrophage cell death in a TLR2-dependent manner.¹⁵⁹ Another study demonstrated that the

PE/PPE complex PE9/PE10 induces macrophage apoptosis via TLR4 engagement.¹⁵⁶ Interestingly, a recent study from our lab demonstrated that TRIM27 restricts the survival of mycobacteria in macrophages by promoting JNK/p38 MAPK pathway activation and cell apoptosis, whereas Mtb PtpA antagonizes those TRIM27-promoted innate immune responses by competitively binding to the RING domain of TRIM27, indicating a dynamic antagonism between Mtb and its host during infection.¹⁶⁰ Taken together, the ability to precisely modulate the outcome of apoptosis is an important immune evasion strategy adopted by Mtb, suggesting that the interactions between Mtb and host cells during apoptosis could be leveraged to develop better measures to prevent TB. Despite the substantially increased knowledge of how the apoptosis signaling pathways are widely used as targets for Mtb effectors to enhance intracellular survival and pathogenesis, several important issues remain unresolved, such as how different Mtb effector proteins coordinate and temporally regulate apoptosis during host defense against Mtb infection *in vivo*.

Inflammasome activation

During microbial infection, certain members of the NLR family (such as NLRP3 and NLRC4) and the cytosolic DNA sensor

AIM2 assemble into a multimeric inflammasome complex to mediate the activation of inflammatory caspase-1. This, in turn, leads to maturation of the pro-inflammatory cytokines IL-1 β and IL-18 and induction of pyroptosis, which is a form of necrotic and inflammatory programmed cell death that is induced by inflammatory caspases.¹⁶¹ Pyrin domain-containing inflammasomes, including NLRP3 and AIM2, signal through the adapter protein ASC (apoptosis-associated speck-like protein containing a CARD) to recruit caspase-1. By contrast, the CARD domain-containing inflammasome NLRC4 can signal directly to caspase-1, which results in pyroptosis, as well as indirectly through ASC to augment IL-1 β and IL-18 secretion.¹⁶² Macrophages from individuals that carry a combined polymorphism (Q705K) in the *NLRP3* gene together with a variant in *CARD8* are able to better restrict mycobacterial growth.¹⁶³ The mycobacterial ESX-1 secretion system was demonstrated to be an important trigger of the IL-1 β response in macrophages, and the membrane-lytic capability of EsxA was shown to directly promote the activation of the NLRP3 inflammasome.⁹⁴ Potassium efflux is also important for activating the NLRP3 inflammasome, and Nek7 was identified as an essential molecule that acts upstream of the NLRP3 inflammasome.^{164,165} The AIM2 inflammasome was also implicated in the intracellular recognition of Mtb, and AIM2 can be directly engaged by mycobacterial genomic DNA.⁷⁰ The inflammasome response can be modulated by the effector proteins secreted by Mtb. For example, Mtb Rv0198c (*Zmp1*) plays a critical role in preventing caspase-1-dependent activation and the secretion of IL-1 β . *Zmp1*-deleted Mtb-triggered activation of the inflammasome, resulting in an increased release of IL-1 β , enhanced maturation of Mtb-containing phagosomes, improved mycobacterial clearance by macrophages and bacterial load reduction in the lungs of infected mice. Thus, *Zmp1* is an important virulence factor and represents a potentially useful drug target.¹⁶⁶ Mtb may also prevent the activation of the AIM2 by limiting type I IFN production in infected cells dependent on its ESX-1 secretion system, suggesting that prophylactic strategies employing recombinant BCG expressing innate ligands, which are efficient in inducing inflammasome formation, can boost its protective efficacy against Mtb.¹⁶⁷ Deciphering the interplay between the pathways involved in inflammasome activation during Mtb infection represents an important challenge and great opportunity for treating TB.

CONCLUSIONS

The innate immune cells, signaling pathways and cellular functions that are involved in the early phases of Mtb infection are crucial in limiting disease and serve as potent regulators of antigen-specific adaptive immunity (Figure 1). Innate immune cells are uniquely positioned to determine the balance between protective and pathogenic immune responses in TB. TB disease results when the pathological responses that promote lung damage and chronic inflammation dominate over protective responses that limit disease and eliminate bacteria. However, Mtb can evade antimicrobial immune responses and disrupt

the crosstalk between innate immunity and adaptive immunity, thereby tilting the balance toward pathological consequences rather than protective immune responses (Figure 2). It is clear from increasing experimental evidence and clinical observations that Mtb controls host innate immunity by dictating a sophisticated program that involves multiple host signaling pathways and cellular functions. As Mtb infection remains a global public health problem in an era of increasing antibiotic resistance, a more comprehensive understanding of the extraordinarily complex Mtb–host relationship during Mtb infection will provide new potential targets for effective host-directed therapies or adjuvant treatments for TB.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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