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REVIEW

# Innate immunity in tuberculosis: host defense *vs* pathogen evasion

Cui Hua Liu[1,2], Haiying Liu[3] and Baoxue Ge[4]

**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

[1]CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China; [2]Savaid Medical School, University of Chinese Academy of Sciences, Beijing 101408, China; [3]MOH Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, and Center for Tuberculosis Research, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100176, China and [4]Shanghai Key Lab of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China
Correspondence: Professor CH Liu, PhD, CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China.
Email: liucuihua@im.ac.cn
or Associate Professor H Liu, PhD, MOH Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, and Center for Tuberculosis Research, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100176, China.
Email: haiyingbj@gmail.com
or Professor B Ge, PhD, Shanghai Key Lab of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China.
Email: gebaoxue@sibs.ac.cn
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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-1β and macrophage inflammatory protein-1α (MIP-1α/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, IFNγ, TNFα 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 TGFβ.[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 colleagues[36] 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-κB (NF-κB) 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-1β, 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 (SENP8). RNAi-mediated knockdown of NEDD8 and SENP8 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, granulysin 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 γδ T-cell proliferation by producing CD54, TNFα, 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 granulysin 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-κB, 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 lpqH (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-κB 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 susceptibly 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-1β release and pyroptosis.[94] Another study demonstrated that mice that were genetically deficient in the production of or response to IL-1β 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 $Ca^{2+}$-dependent or $Ca^{2+}$-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 CLRs 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,

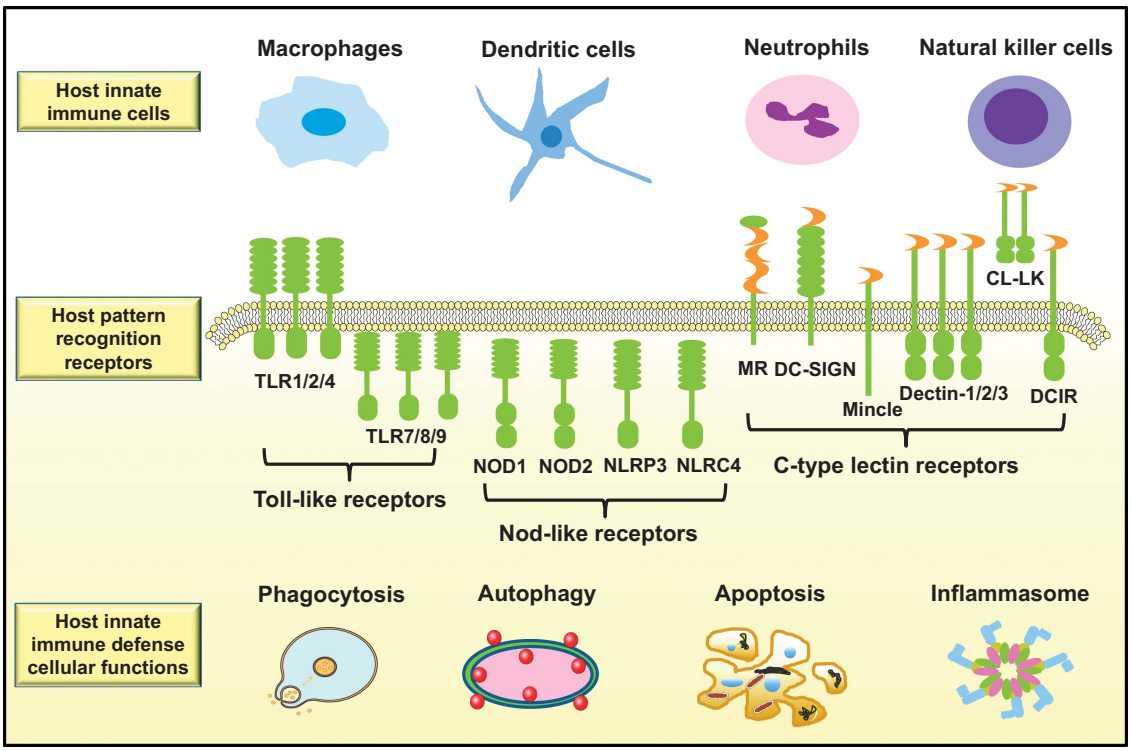


**Figure 1** Major host immune cells, pattern recognition receptors and cellular functions involved in innate immune defense against Mtb. Mtb mainly infects innate immune cells, including macrophages, dendritic cells, neutrophils and natural killer cells. Those immune cells recognize Mtb through various 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

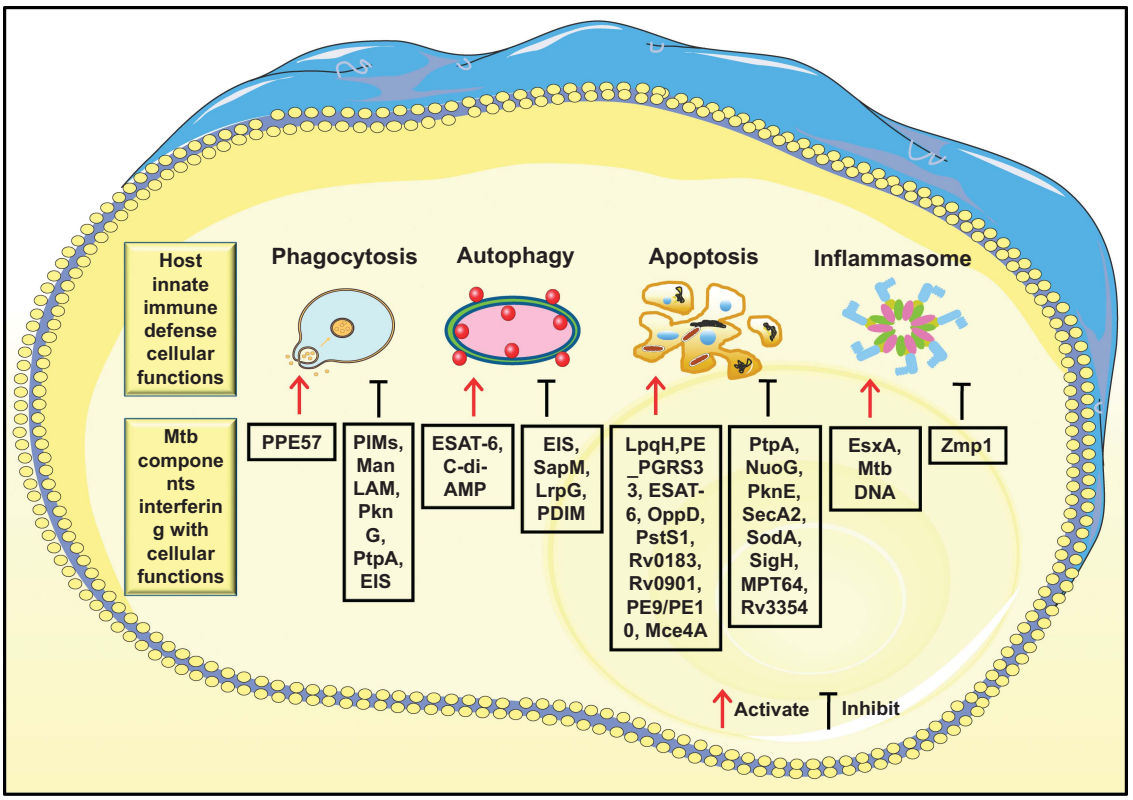


**Figure 2** Mtb components interfering with host cellular functions. During Mtb infection, multiple Mtb components interfere (either activate or inhibit) with host cellular functions (such as phagocytosis, autophagy, apoptosis and inflammasome activation) to help the pathogen evade or circumvent host 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-1β 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-1β 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-1β 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-1β. Zmp1-deleted Mtb-triggered activation of the inflammasome, resulting in an increased release of IL-1β, 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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1 World Health Organization. *Global Tuberculosis Report 2016*. WHO: Geneva, Switzerland, 2016.
2 Sia JK, Georgieva M, Rengarajan J. Innate immune defenses in human tuberculosis: an overview of the interactions between mycobacterium tuberculosis and innate immune cells. *J Immunol Res* 2015; **2015**: 747543.
3 Killick KE, Ni Cheallaigh C, O'Farrelly C, Hokamp K, MacHugh DE, Harris J. Receptor-mediated recognition of mycobacterial pathogens. *Cell Microbiol* 2013; **15**: 1484–1495.
4 Lerner TR, Borel S, Gutierrez MG. The innate immune response in human tuberculosis. *Cell Microbiol* 2015; **17**: 1277–1285.
5 Khan N, Vidyarthi A, Javed S, Agrewala JN. Innate immunity holding the flanks until reinforced by adaptive immunity against mycobacterium tuberculosis infection. *Front Microbiol* 2016; **7**: 328.
6 Mortaz E, Adcock IM, Tabarsi P, Masjedi MR, Mansouri D, Velayati AA *et al*. Interaction of pattern recognition receptors with mycobacterium tuberculosis. *J Clin Immunol* 2015; **35**: 1–10.
7 Korb VC, Chuturgoon AA, Moodley D. Mycobacterium tuberculosis: manipulator of protective immunity. *Int J Mol Sci* 2016; **17**: 131.
8 Goldberg MF, Saini NK, Porcelli SA. Evasion of innate and adaptive immunity by *Mycobacterium tuberculosis*. *Microbiol Spectr* 2014; **2**: 5.
9 Gold MC, Napier RJ, Lewinsohn DM. MR1-restricted mucosal associated invariant T (MAIT) cells in the immune response to *Mycobacterium tuberculosis*. *Immunol Rev* 2015; **264**: 154–166.
10 Van Rhijn I, Moody DB. CD1 and mycobacterial lipids activate human T cells. *Immunol Rev* 2015; **264**: 138–153.
11 Arora P, Foster EL, Porcelli SA. CD1d and natural killer T cells in immunity to *Mycobacterium tuberculosis*. *Adv Exp Med Biol* 2013; **83**: 199–223.
12 McClean CM, Tobin DM. Macrophage form, function, and phenotype in mycobacterial infection: lessons from tuberculosis and other diseases. *Pathog Dis* 2016; **74**: 7.
13 Cadena AM, Flynn JL, Fortune SM. The importance of first impressions: early events in *Mycobacterium tuberculosis* infection influence outcome. *MBio* 2016; **7**: e00342–16.

14 Cappelli G, Volpe P, Sanduzzi A, Sacchi A, Colizzi V, Mariani F. Human macrophage gamma interferon decreases gene expression but not replication of *Mycobacterium tuberculosis*: analysis of the host-pathogen reciprocal influence on transcription in a comparison of strains H37Rv and CMT97. *Infect Immun* 2001; **69**: 7262–7270.
15 Fabri M, Stenger S, Shin DM, Yuk JM, Liu PT, Realegeno S *et al.* Vitamin D is required for IFN-gamma-mediated antimicrobial activity of human macrophages. *Sci Transl Med* 2011; **3**: 104ra2.
16 Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *J Immunol* 2007; **179**: 2060–2063.
17 Jo EK. Innate immunity to mycobacteria: vitamin D and autophagy. *Cell Microbiol* 2010; **12**: 1026–1035.
18 Murray PJ. Macrophage polarization. *Annu Rev Physiol* 2017; **79**: 541–566.
19 Ginhoux F, Schultze JL, Murray PJ, Ochando J, Biswas SK. New insights into the multidimensional concept of macrophage ontogeny, activation and function. *Nat Immunol* 2016; **7**: 34–40.
20 Sica A, Erreni M, Allavena P, Porta C. Macrophage polarization in pathology. *Cell Mol Life Sci* 2015; **72**: 4111–4126.
21 Duque-Correa MA, Kuhl AA, Rodriguez PC, Zedler U, Schommer-Leitner S, Rao M *et al.* Macrophage arginase-1 controls bacterial growth and pathology in hypoxic tuberculosis granulomas. *Proc Natl Acad Sci USA* 2014; **111**: E4024–E4032.
22 Lastrucci C, Benard A, Balboa L, Pingris K, Souriant S, Poincloux R *et al.* Tuberculosis is associated with expansion of a motile, permissive and immunomodulatory CD16(+) monocyte population via the IL-10/STAT3 axis. *Cell Res* 2015; **25**: 1333–1351.
23 Lopes RL, Borges TJ, Zanin RF, Bonorino C. IL-10 is required for polarization of macrophages to M2-like phenotype by mycobacterial DnaK (heat shock protein 70). *Cytokine* 2016; **85**: 123–129.
24 Knaul JK, Jorg S, Oberbeck-Mueller D, Heinemann E, Scheuermann L, Brinkmann V *et al.* Lung-residing myeloid-derived suppressors display dual functionality in murine pulmonary tuberculosis. *Am J Respir Crit Care Med* 2014; **190**: 1053–1066.
25 Khan A, Hunter RL, Jagannath C. Emerging role of mesenchymal stem cells during tuberculosis: the fifth element in cell mediated immunity. *Tuberculosis* 2016; **101S**: S45–S52.
26 Feng Y, Dorhoi A, Mollenkopf HJ, Yin H, Dong Z, Mao L *et al.* Platelets direct monocyte differentiation into epithelioid-like multinucleated giant foam cells with suppressive capacity upon mycobacterial stimulation. *J Infect Dis* 2014; **210**: 1700–1710.
27 Peyron P, Vaubourgeix J, Poquet Y, Levillain F, Botanch C, Bardou F *et al.* Foamy macrophages from tuberculous patients' granulomas constitute a nutrient-rich reservoir for *M. tuberculosis* persistence. *PLoS Pathog* 2008; **4**: e1000204.
28 Singh V, Kaur C, Chaudhary VK, Rao KV, Chatterjee S. *M. tuberculosis* secretory protein ESAT-6 induces metabolic flux perturbations to drive foamy macrophage differentiation. *Sci Rep* 2015; **5**: 12906.
29 Herrtwich L, Nanda I, Evangelou K, Nikolova T, Horn V, Sagar *et al.* DNA damage signaling instructs polyploid macrophage fate in granulomas. *Cell* 2016; **167**: 1264–80 e18.
30 Mehrotra P, Jamwal SV, Saquib N, Sinha N, Siddiqui Z, Manivel V *et al.* Pathogenicity of *Mycobacterium tuberculosis* is expressed by regulating metabolic thresholds of the host macrophage. *PLoS Pathog* 2014; **10**: e1004265.
31 Mosquera-Restrepo SF, Caro AC, Pelaez-Jaramillo CA, Rojas M. Mononuclear phagocyte accumulates a stearic acid derivative during differentiation into macrophages. Effects of stearic acid on macrophage differentiation and *Mycobacterium tuberculosis* control. *Cell Immunol* 2016; **303**: 24–33.
32 Prendergast KA, Kirman JR. Dendritic cell subsets in mycobacterial infection: control of bacterial growth and T cell responses. *Tuberculosis* 2013; **93**: 115–122.
33 Tailleux L, Schwartz O, Herrmann JL, Pivert E, Jackson M, Amara A *et al.* DC-SIGN is the major *Mycobacterium tuberculosis* receptor on human dendritic cells. *J Exp Med* 2003; **197**: 121–127.
34 Carroll MV, Sim RB, Bigi F, Jakel A, Antrobus R, Mitchell DA. Identification of four novel DC-SIGN ligands on *Mycobacterium bovis* BCG. *Protein Cell* 2010; **1**: 859–870.
35 Driessen NN, Ummels R, Maaskant JJ, Gurcha SS, Besra GS, Ainge GD *et al.* Role of phosphatidylinositol mannosides in the interaction between mycobacteria and DC-SIGN. *Infect Immun* 2009; **77**: 4538–4547.
36 Roberts LL, Robinson CM. Mycobacterium tuberculosis infection of human dendritic cells decreases integrin expression, adhesion and migration to chemokines. *Immunology* 2014; **141**: 39–1451.
37 Bollampalli VP, Harumi Yamashiro L, Feng X, Bierschenk D, Gao Y, Blom H *et al.* BCG skin infection triggers IL-1R-MyD88-dependent migration of EpCAMlow CD11bhigh skin dendritic cells to draining lymph node during CD4+ T-cell priming. *PLoS Pathog* 2015; **11**: e1005206.
38 Nigou J, Zelle-Rieser C, Gilleron M, Thurnher M, Puzo G. Mannosylated lipoarabinomannans inhibit IL-12 production by human dendritic cells: evidence for a negative signal delivered through the mannose receptor. *J Immunol* 2001; **166**: 7477–7485.
39 Kim WS, Kim JS, Cha SB, Kim SJ, Kim H, Kwon KW *et al.* Mycobacterium tuberculosis PE27 activates dendritic cells and contributes to Th1-polarized memory immune responses during in vivo infection. *Immunobiology* 2016; **221**: 440–453.
40 Choi HG, Kim WS, Back YW, Kim H, Kwon KW, Kim JS *et al.* Mycobacterium tuberculosis RpfE promotes simultaneous Th1- and Th17-type T-cell immunity via TLR4-dependent maturation of dendritic cells. *Eur J Immunol* 2015; **45**: 1957–1971.
41 Chadha A, Mehto S, Selvakumar A, Vashishta M, Kamble SS, Popli S *et al.* Suppressive role of neddylation in dendritic cells during Mycobacterium tuberculosis infection. *Tuberculosis* 2015; **95**: 599–607.
42 Kuo CP, Chang KS, Hsu JL, Tsai IF, Lin AB, Wei TY *et al.* Analysis of the immune response of human dendritic cells to Mycobacterium tuberculosis by quantitative proteomics. *Proteome Sci* 2016; **14**: 5.
43 Nouailles G, Dorhoi A, Koch M, Zerrahn J, Weiner J, Fae KC *et al.* CXCL5-secreting pulmonary epithelial cells drive destructive neutrophilic inflammation in tuberculosis. *J Clin Invest* 2014; **124**: 1268–1282.
44 Niazi MK, Dhulekar N, Schmidt D, Major S, Cooper R, Abeijon C *et al.* Lung necrosis and neutrophils reflect common pathways of susceptibility to Mycobacterium tuberculosis in genetically diverse, immune-competent mice. *Dis Model Mech* 2015; **8**: 1141–1153.
45 Gopal R, Monin L, Torres D, Slight S, Mehra S, McKenna KC *et al.* S100A8/A9 proteins mediate neutrophilic inflammation and lung pathology during tuberculosis. *Am J Respir Crit Care Med* 2013; **188**: 1137–1146.
46 Dorhoi A, Iannaccone M, Farinacci M, Fae KC, Schreiber J, Moura-Alves P *et al.* MicroRNA-223 controls susceptibility to tuberculosis by regulating lung neutrophil recruitment. *J Clin Invest* 2013; **123**: 4836–4848.
47 Dallenga T, Schaible UE. Neutrophils in tuberculosis–first line of defence or booster of disease and targets for host-directed therapy? *Pathog Dis* 2016; **7**: 3.
48 Elkington PT, Green JA, Emerson JE, Lopez-Pascua LD, Boyle JJ, O'Kane CM *et al.* Synergistic up-regulation of epithelial cell matrix metalloproteinase-9 secretion in tuberculosis. *Am J Respir Cell Mol Biol* 2007; **37**: 431–437.
49 Hesse M, Modolell M, La Flamme AC, Schito M, Fuentes JM, Cheever AW *et al.* Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/type 2 cytokines in vivo: granulomatous pathology is shaped by the pattern of L-arginine metabolism. *J Immunol* 2001; **167**: 6533–6544.
50 Martineau AR, Newton SM, Wilkinson KA, Kampmann B, Hall BM, Nawroly N *et al.* Neutrophil-mediated innate immune resistance to mycobacteria. *J Clin Invest* 2007; **117**: 1988–1994.
51 Tan BH, Meinken C, Bastian M, Bruns H, Legaspi A, Ochoa MT *et al.* Macrophages acquire neutrophil granules for antimicrobial activity against intracellular pathogens. *J Immunol* 2006; **177**: 1864–1871.
52 McNab FW, Berry MP, Graham CM, Bloch SA, Oni T, Wilkinson KA *et al.* Programmed death ligand 1 is over-expressed by neutrophils in the blood of patients with active tuberculosis. *Eur J Immunol* 2011; **41**: 1941–1947.
53 Kimmey JM, Huynh JP, Weiss LA, Park S, Kambal A, Debnath J *et al.* Unique role for ATG5 in neutrophil-mediated immunopathology during *M. tuberculosis* infection. *Nature* 2015; **528**: 565–569.
54 Petit-Jentreau L, Jouvion G, Charles P, Majlessi L, Gicquel B, Tailleux L. Ecto-5'-nucleotidase (CD73) deficiency in Mycobacterium tuberculosis-infected mice enhances neutrophil recruitment. *Infect Immun* 2015; **83**: 3666–3674.

55 Corleis B, Korbel D, Wilson R, Bylund J, Chee R, Schaible UE. Escape of Mycobacterium tuberculosis from oxidative killing by neutrophils. *Cell Microbiol* 2012; **14**: 1109–1121.
56 Francis RJ, Butler RE, Stewart GR. Mycobacterium tuberculosis ESAT-6 is a leukocidin causing Ca2+ influx, necrosis and neutrophil extracellular trap formation. *Cell Death Dis* 2014; **5**: e1474.
57 Blomgran R, Ernst JD. Lung neutrophils facilitate activation of naive antigen-specific CD4+ T cells during Mycobacterium tuberculosis infection. *J Immunol* 2011; **186**: 7110–7119.
58 Ong CW, Elkington PT, Brilha S, Ugarte-Gil C, Tome-Esteban MT, Tezera LB *et al.* Neutrophil-derived MMP-8 drives AMPK-dependent matrix destruction in human pulmonary tuberculosis. *PLoS Pathog* 2015; **11**: e1004917.
59 Allen M, Bailey C, Cahatol I, Dodge L, Yim J, Kassissa C *et al.* Mechanisms of control of Mycobacterium tuberculosis by NK cells: role of glutathione. *Front Immunol* 2015; **6**: 508.
60 Esin S, Counoupas C, Aulicino A, Brancatisano FL, Maisetta G, Bottai D *et al.* Interaction of Mycobacterium tuberculosis cell wall components with the human natural killer cell receptors NKp44 and Toll-like receptor 2. *Scand J Immunol* 2013; **77**: 460–469.
61 Feng CG, Kaviratne M, Rothfuchs AG, Cheever A, Hieny S, Young HA *et al.* NK cell-derived IFN-gamma differentially regulates innate resistance and neutrophil response in T cell-deficient hosts infected with Mycobacterium tuberculosis. *J Immunol* 2006; **177**: 7086–7093.
62 Portevin D, Via LE, Eum S, Young D. Natural killer cells are recruited during pulmonary tuberculosis and their *ex vivo* responses to mycobacteria vary between healthy human donors in association with KIR haplotype. *Cell Microbiol* 2012; **14**: 1734–1744.
63 Lu CC, Wu TS, Hsu YJ, Chang CJ, Lin CS, Chia JH *et al.* NK cells kill mycobacteria directly by releasing perforin and granulysin. *J Leukoc Biol* 2014; **96**: 1119–1129.
64 Bozzano F, Costa P, Passalacqua G, Dodi F, Ravera S, Pagano G *et al.* Functionally relevant decreases in activatory receptor expression on NK cells are associated with pulmonary tuberculosis in vivo and persist after successful treatment. *Int Immunol* 2009; **21**: 779–791.
65 Guerra C, Johal K, Morris D, Moreno S, Alvarado O, Gray D *et al.* Control of Mycobacterium tuberculosis growth by activated natural killer cells. *Clin Exp Immunol* 2012; **168**: 142–152.
66 Bhaskar A, Munshi M, Khan SZ, Fatima S, Arya R, Jameel S *et al.* Measuring glutathione redox potential of HIV-1-infected macrophages. *J Biol Chem* 2015; **290**: 1020–1038.
67 Court N, Vasseur V, Vacher R, Fremond C, Shebzukhov Y, Yeremeev VV *et al.* Partial redundancy of the pattern recognition receptors, scavenger receptors, and C-type lectins for the long-term control of Mycobacterium tuberculosis infection. *J Immunol* 2010; **184**: 7057–7070.
68 Bowdish DM, Gordon S. Conserved domains of the class A scavenger receptors: evolution and function. *Immunol Rev* 2009; **227**: 19–31.
69 Bowdish DM, Sakamoto K, Kim MJ, Kroos M, Mukhopadhyay S, Leifer CA *et al.* MARCO, TLR2, and CD14 are required for macrophage cytokine responses to mycobacterial trehalose dimycolate and Mycobacterium tuberculosis. *PLoS Pathog* 2009; **5**: e1000474.
70 Saiga H, Kitada S, Shimada Y, Kamiyama N, Okuyama M, Makino M *et al.* Critical role of AIM2 in Mycobacterium tuberculosis infection. *Int Immunol* 2012; **24**: 637–644.
71 Moura-Alves P, Fae K, Houthuys E, Dorhoi A, Kreuchwig A, Furkert J *et al.* AhR sensing of bacterial pigments regulates antibacterial defence. *Nature* 2014; **512**: 387–392.
72 Li J, Chai QY, Liu CH. The ubiquitin system: a critical regulator of innate immunity and pathogen-host interactions. *Cell Mol Immunol* 2016; **13**: 560–576.
73 Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol* 2010; **11**: 373–384.
74 Saraav I, Singh S, Sharma S. Outcome of Mycobacterium tuberculosis and Toll-like receptor interaction: immune response or immune evasion? *Immunol Cell Biol* 2014; **92**: 741–746.
75 Sugawara I, Yamada H, Mizuno S, Takeda K, Akira S. Mycobacterial infection in MyD88-deficient mice. *Microbiol Immunol* 2003; **47**: 841–847.
76 Drennan MB, Nicolle D, Quesniaux VJ, Jacobs M, Allie N, Mpagi J *et al.* Toll-like receptor 2-deficient mice succumb to Mycobacterium tuberculosis infection. *Am J Pathol* 2004; **164**: 49–57.
77 Najmi N, Kaur G, Sharma SK, Mehra NK. Human Toll-like receptor 4 polymorphisms TLR4 Asp299Gly and Thr399Ile influence susceptibility and severity of pulmonary tuberculosis in the Asian Indian population. *Tissue Antigens* 2010; **76**: 102–109.
78 Lai YF, Lin TM, Wang CH, Su PY, Wu JT, Lin MC *et al.* Functional polymorphisms of the TLR7 and TLR8 genes contribute to Mycobacterium tuberculosis infection. *Tuberculosis* 2016; **98**: 125–131.
79 Carvalho NB, Oliveira FS, Duraes FV, de Almeida LA, Florido M, Prata LO *et al.* Toll-like receptor 9 is required for full host resistance to Mycobacterium avium infection but plays no role in induction of Th1 responses. *Infect Immun* 2011; **79**: 1638–1646.
80 Holscher C, Reiling N, Schaible UE, Holscher A, Bathmann C, Korbel D *et al.* Containment of aerogenic Mycobacterium tuberculosis infection in mice does not require MyD88 adaptor function for TLR2, -4 and -9. *Eur J Immunol* 2008; **38**: 680–694.
81 Mayer-Barber KD, Barber DL, Shenderov K, White SD, Wilson MS, Cheever A *et al.* Caspase-1 independent IL-1beta production is critical for host resistance to Mycobacterium tuberculosis and does not require TLR signaling in vivo. *J Immunol* 2010; **184**: 3326–3330.
82 Pecora ND, Gehring AJ, Canaday DH, Boom WH, Harding CV. Mycobacterium tuberculosis LprA is a lipoprotein agonist of TLR2 that regulates innate immunity and APC function. *J Immunol* 2006; **177**: 422–429.
83 Bai W, Liu H, Ji Q, Zhou Y, Liang L, Zheng R *et al.* TLR3 regulates mycobacterial RNA-induced IL-10 production through the PI3K/AKT signaling pathway. *Cell Signal* 2014; **26**: 942–950.
84 Liu Y, Li JY, Chen ST, Huang HR, Cai H. The rLrp of Mycobacterium tuberculosis inhibits proinflammatory cytokine production and down-regulates APC function in mouse macrophages via a TLR2-mediated PI3K/Akt pathway activation-dependent mechanism. *Cell Mol Immunol* 2016; **13**: 729–746.
85 Wang J, Li BX, Ge PP, Li J, Wang Q, Gao GF *et al.* Mycobacterium tuberculosis suppresses innate immunity by coopting the host ubiquitin system. *Nat Immunol* 2015; **16**: 237–245.
86 Li J, Chai QY, Zhang Y, Li BX, Wang J, Qiu XB *et al.* Mycobacterium tuberculosis Mce3E suppresses host innate immune responses by targeting ERK1/2 signaling. *J Immunol* 2015; **194**: 3756–3767.
87 Yang H, Liu H, Chen H, Mo H, Chen J, Huang X *et al.* G protein-coupled receptor160 regulates mycobacteria entry into macrophages by activating ERK. *Cell Signal* 2016; **28**: 1145–1151.
88 Kim YK, Shin JS, Nahm MH. NOD-like receptors in infection, immunity, and diseases. *Yonsei Med J* 2016; **57**: 5–14.
89 Simeone R, Bobard A, Lippmann J, Bitter W, Majlessi L, Brosch R *et al.* Phagosomal rupture by Mycobacterium tuberculosis results in toxicity and host cell death. *PLoS Pathog* 2012; **8**: e1002507.
90 Divangahi M, Mostowy S, Coulombe F, Kozak R, Guillot L, Veyrier F *et al.* NOD2-deficient mice have impaired resistance to Mycobacterium tuberculosis infection through defective innate and adaptive immunity. *J Immunol* 2008; **181**: 7157–7165.
91 Juarez E, Carranza C, Hernandez-Sanchez F, Leon-Contreras JC, Hernandez-Pando R, Escobedo D *et al.* NOD2 enhances the innate response of alveolar macrophages to Mycobacterium tuberculosis in humans. *Eur J Immunol* 2012; **42**: 880–889.
92 Austin CM, Ma X, Graviss EA. Common nonsynonymous polymorphisms in the NOD2 gene are associated with resistance or susceptibility to tuberculosis disease in African Americans. *J Infect Dis* 2008; **197**: 1713–1716.
93 Pan H, Dai Y, Tang S, Wang J. Polymorphisms of NOD2 and the risk of tuberculosis: a validation study in the Chinese population. *Int J Immunogenet* 2012; **39**: 233–240.
94 Mishra BB, Moura-Alves P, Sonawane A, Hacohen N, Griffiths G, Moita LF *et al.* Mycobacterium tuberculosis protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. *Cell Microbiol* 2010; **12**: 1046–1063.
95 McElvania Tekippe E, Allen IC, Hulseberg PD, Sullivan JT, McCann JR, Sandor M *et al.* Granuloma formation and host defense in chronic Mycobacterium tuberculosis infection requires PYCARD/ASC but not NLRP3 or caspase-1. *PLoS One* 2010; **5**: e12320.

96 Goyal S, Klassert TE, Slevogt H. C-type lectin receptors in tuberculosis: what we know. *Med Microbiol Immunol* 2016; **205**: 513–535.
97 Kang PB, Azad AK, Torrelles JB, Kaufman TM, Beharka A, Tibesar E *et al.* The human macrophage mannose receptor directs Mycobacterium tuberculosis lipoarabinomannan-mediated phagosome biogenesis. *J Exp Med* 2005; **202**: 987–999.
98 Geurtsen J, Chedammi S, Mesters J, Cot M, Driessen NN, Sambou T *et al.* Identification of mycobacterial alpha-glucan as a novel ligand for DC-SIGN: involvement of mycobacterial capsular polysaccharides in host immune modulation. *J Immunol* 2009; **183**: 5221–5231.
99 Matsunaga I, Moody DB. Mincle is a long sought receptor for mycobacterial cord factor. *J Exp Med* 2009; **206**: 2865–2868.
100 Yadav M, Schorey JS. The beta-glucan receptor dectin-1 functions together with TLR2 to mediate macrophage activation by mycobacteria. *Blood* 2006; **108**: 3168–3175.
101 Marakalala MJ, Guler R, Matika L, Murray G, Jacobs M, Brombacher F *et al.* The Syk/CARD9-coupled receptor Dectin-1 is not required for host resistance to Mycobacterium tuberculosis in mice. *Microbes Infect* 2011; **13**: 198–201.
102 Yonekawa A, Saijo S, Hoshino Y, Miyake Y, Ishikawa E, Suzukawa M *et al.* Dectin-2 is a direct receptor for mannose-capped lipoarabinomannan of mycobacteria. *Immunity* 2014; **41**: 402–413.
103 Miyake Y, Masatsugu OH, Yamasaki S. C-type lectin receptor MCL facilitates mincle expression and signaling through complex formation. *J Immunol* 2015; **194**: 5366–5374.
104 Wilson GJ, Marakalala MJ, Hoving JC, van Laarhoven A, Drummond RA, Kerscher B *et al.* The C-type lectin receptor CLECSF8/CLEC4D is a key component of anti-mycobacterial immunity. *Cell Host Microbe* 2015; **17**: 252–259.
105 Troegeler A, Lugo-Villarino G, Hansen S, Rasolofo V, Henriksen ML, Mori K *et al.* Collectin CL-LK is a novel soluble pattern recognition receptor for Mycobacterium tuberculosis. *PLoS ONE* 2015; **10**: e0132692.
106 Troegeler A, Mercier I, Cougoule C, Pietretti D, Colom A, Duval C *et al.* C-type lectin receptor DCIR modulates immunity to tuberculosis by sustaining type I interferon signaling in dendritic cells. *Proc Natl Acad Sci USA* 2017; **114**: E540–E549.
107 Korbel DS, Schneider BE, Schaible UE. Innate immunity in tuberculosis: myths and truth. *Microbes Infect* 2008; **10**: 995–1004.
108 Hmama Z, Pena-Diaz S, Joseph S, Av-Gay Y. Immunoevasion and immunosuppression of the macrophage by Mycobacterium tuberculosis. *Immunol Rev* 2015; **264**: 220–232.
109 Hussain Bhat K, Mukhopadhyay S. Macrophage takeover and the host-bacilli interplay during tuberculosis. *Future Microbiol* 2015; **10**: 853–872.
110 Weiss G, Schaible UE. Macrophage defense mechanisms against intracellular bacteria. *Immunol Rev* 2015; **264**: 182–203.
111 Vergne I, Fratti RA, Hill PJ, Chua J, Belisle J, Deretic V. Mycobacterium tuberculosis phagosome maturation arrest: mycobacterial phosphatidylinositol analog phosphatidylinositol mannoside stimulates early endosomal fusion. *Mol Biol Cell* 2004; **15**: 751–760.
112 Kyei GB, Vergne I, Chua J, Roberts E, Harris J, Junutula JR *et al.* Rab14 is critical for maintenance of Mycobacterium tuberculosis phagosome maturation arrest. *EMBO J* 2006; **25**: 5250–5259.
113 Ferrari G, Langen H, Naito M, Pieters J. A coat protein on phagosomes involved in the intracellular survival of mycobacteria. *Cell* 1999; **97**: 435–447.
114 Walburger A, Koul A, Ferrari G, Nguyen L, Prescianotto-Baschong C, Huygen K *et al.* Protein kinase G from pathogenic mycobacteria promotes survival within macrophages. *Science* 2004; **304**: 1800–1804.
115 Wong D, Bach H, Sun J, Hmama Z, Av-Gay Y. Mycobacterium tuberculosis protein tyrosine phosphatase (PtpA) excludes host vacuolar-H+-ATPase to inhibit phagosome acidification. *Proc Natl Acad Sci USA* 2011; **108**: 19371–19376.
116 Abramovitch RB, Rohde KH, Hsu FF, Russell DG. aprABC: a Mycobacterium tuberculosis complex-specific locus that modulates pH-driven adaptation to the macrophage phagosome. *Mol Microbiol* 2011; **80**: 678–694.
117 Wee YS, Roundy KM, Weis JJ, Weis JH. Interferon-inducible transmembrane proteins of the innate immune response act as membrane organizers by influencing clathrin and v-ATPase localization and function. *Innate Immun* 2012; **18**: 834–845.
118 Diamond MS, Farzan M. The broad-spectrum antiviral functions of IFIT and IFITM proteins. *Nat Rev Immunol* 2013; **13**: 46–57.
119 Xu Y, Yang E, Huang Q, Ni W, Kong C, Liu G *et al.* PPE57 induces activation of macrophages and drives Th1-type immune responses through TLR2. *J Mol Med* 2015; **93**: 645–662.
120 Kimmey JM, Stallings CL. Bacterial pathogens versus autophagy: implications for therapeutic interventions. *Trends Mol Med* 2016; **22**: 1060–1076.
121 Bento CF, Empadinhas N, Mendes V. Autophagy in the fight against tuberculosis. *DNA Cell Biol* 2015; **34**: 228–242.
122 Xu Y, Fattah EA, Liu XD, Jagannath C, Eissa NT. Harnessing of TLR-mediated autophagy to combat mycobacteria in macrophages. *Tuberculosis* 2013; **93 (Suppl)**: S33–S37.
123 Castillo EF, Dekonenko A, Arko-Mensah J, Mandell MA, Dupont N, Jiang S *et al.* Autophagy protects against active tuberculosis by suppressing bacterial burden and inflammation. *Proc Natl Acad Sci USA* 2012; **109**: E3168–E3176.
124 Chauhan S, Mandell MA, Deretic V. Mechanism of action of the tuberculosis and Crohn disease risk factor IRGM in autophagy. *Autophagy* 2016; **12**: 429–431.
125 Yuan L, Ke Z, Ma J, Guo Y, Li Y. IRGM gene polymorphisms and haplotypes associate with susceptibility of pulmonary tuberculosis in Chinese Hubei Han population. *Tuberculosis* 2016; **96**: 58–64.
126 Singh SB, Davis AS, Taylor GA, Deretic V. Human IRGM induces autophagy to eliminate intracellular mycobacteria. *Science* 2006; **313**: 1438–1441.
127 Lu Y, Li Q, Peng J, Zhu Y, Wang F, Wang C *et al.* Association of autophagy-related IRGM polymorphisms with latent versus active tuberculosis infection in a Chinese population. *Tuberculosis* 2016; **97**: 47–51.
128 Zhang L, Zhang H, Zhao Y, Mao F, Wu J, Bai B *et al.* Effects of Mycobacterium tuberculosis ESAT-6/CFP-10 fusion protein on the autophagy function of mouse macrophages. *DNA Cell Biol* 2012; **31**: 171–179.
129 Dey B, Dey RJ, Cheung LS, Pokkali S, Guo H, Lee JH *et al.* A bacterial cyclic dinucleotide activates the cytosolic surveillance pathway and mediates innate resistance to tuberculosis. *Nat Med* 2015; **21**: 401–406.
130 Via LE, Deretic D, Ulmer RJ, Hibler NS, Huber LA, Deretic V. Arrest of mycobacterial phagosome maturation is caused by a block in vesicle fusion between stages controlled by rab5 and rab7. *J Biol Chem* 1997; **272**: 13326–13331.
131 Roberts EA, Chua J, Kyei GB, Deretic V. Higher order Rab programming in phagolysosome biogenesis. *J Cell Biol* 2006; **174**: 923–929.
132 Fratti RA, Chua J, Deretic V. Induction of p38 mitogen-activated protein kinase reduces early endosome autoantigen 1 (EEA1) recruitment to phagosomal membranes. *J Biol Chem* 2003; **278**: 46961–46967.
133 Cardoso CM, Jordao L, Vieira OV. Rab10 regulates phagosome maturation and its overexpression rescues Mycobacterium-containing phagosomes maturation. *Traffic* 2010; **11**: 221–235.
134 Kim KH, An DR, Song J, Yoon JY, Kim HS, Yoon HJ *et al.* Mycobacterium tuberculosis Eis protein initiates suppression of host immune responses by acetylation of DUSP16/MKP-7. *Proc Natl Acad Sci USA* 2012; **109**: 7729–7734.
135 Duan L, Yi M, Chen J, Li S, Chen W. Mycobacterium tuberculosis EIS gene inhibits macrophage autophagy through up-regulation of IL-10 by increasing the acetylation of histone H3. *Biochem Biophys Res Commun* 2016; **473**: 1229–1234.
136 Puri RV, Reddy PV, Tyagi AK. Secreted acid phosphatase (SapM) of Mycobacterium tuberculosis is indispensable for arresting phagosomal maturation and growth of the pathogen in guinea pig tissues. *PLoS ONE* 2013; **8**: e70514.
137 Vazquez CL, Bianco MV, Blanco FC, Forrellad MA, Gutierrez MG, Bigi F. Mycobacterium bovis requires P27 (LprG) to arrest phagosome maturation and replicate within bovine macrophages. *Infect Immun* 2017; **85**: 3.
138 Quigley J, Hughitt VK, Velikovsky CA, Mariuzza RA, El-Sayed NM, Briken V. The cell wall lipid PDIM contributes to phagosomal escape and host cell exit of Mycobacterium tuberculosis. *MBio* 2017; **8**: 2.

139 Liu M, Li W, Xiang X, Xie J. Mycobacterium tuberculosis effectors interfering host apoptosis signaling. *Apoptosis* 2015; **20**: 883–891.
140 Winau F, Weber S, Sad S, de Diego J, Hoops SL, Breiden B *et al.* Apoptotic vesicles crossprime CD8 T cells and protect against tuberculosis. *Immunity* 2006; **24**: 105–117.
141 Poirier V, Bach H, Av-Gay Y. Mycobacterium tuberculosis promotes anti-apoptotic activity of the macrophage by PtpA protein-dependent dephosphorylation of host GSK3alpha. *J Biol Chem* 2014; **289**: 29376–29385.
142 Velmurugan K, Chen B, Miller JL, Azogue S, Gurses S, Hsu T *et al.* Mycobacterium tuberculosis nuoG is a virulence gene that inhibits apoptosis of infected host cells. *PLoS Pathog* 2007; **3**: e110.
143 Molle V, Girard-Blanc C, Kremer L, Doublet P, Cozzone AJ, Prost JF. Protein PknE, a novel transmembrane eukaryotic-like serine/threonine kinase from Mycobacterium tuberculosis. *Biochem Biophys Res Commun* 2003; **308**: 820–825.
144 Hinchey J, Lee S, Jeon BY, Basaraba RJ, Venkataswamy MM, Chen B *et al.* Enhanced priming of adaptive immunity by a proapoptotic mutant of Mycobacterium tuberculosis. *J Clin Invest* 2007; **117**: 2279–2288.
145 Jain R, Dey B, Khera A, Srivastav P, Gupta UD, Katoch VM *et al.* Over-expression of superoxide dismutase obliterates the protective effect of BCG against tuberculosis by modulating innate and adaptive immune responses. *Vaccine* 2011; **29**: 8118–8125.
146 Dutta NK, Mehra S, Martinez AN, Alvarez X, Renner NA, Morici LA *et al.* The stress-response factor SigH modulates the interaction between Mycobacterium tuberculosis and host phagocytes. *PLoS One* 2012; **7**: e28958.
147 Wang Q, Liu S, Tang Y, Liu Q, Yao Y. MPT64 protein from Mycobacterium tuberculosis inhibits apoptosis of macrophages through NF-kB-miRNA21-Bcl-2 pathway. *PLoS One* 2014; **9**: e100949.
148 Danelishvili L, Babrak L, Rose SJ, Everman J, Bermudez LE. Mycobacterium tuberculosis alters the metalloprotease activity of the COP9 signalosome. *MBio* 2014; **5**: 4.
149 Zhang L, Zhong Q, Bao L, Zhang Y, Gao L, Huang B *et al.* Rv0901 from Mycobacterium tuberculosis, a possible novel virulent gene proved through the recombinant Mycobacterium smegmatis. *Jpn J Infect Dis* 2009; **62**: 26–31.
150 Xu G, Jia H, Li Y, Liu X, Li M, Wang Y. Hemolytic phospholipase Rv0183 of Mycobacterium tuberculosis induces inflammatory response and apoptosis in alveolar macrophage RAW264.7 cells. *Can J Microbiol* 2010; **56**: 916–924.
151 Sanchez A, Espinosa P, Esparza MA, Colon M, Bernal G, Mancilla R. Mycobacterium tuberculosis 38-kDa lipoprotein is apoptogenic for human monocyte-derived macrophages. *Scand J Immunol* 2009; **69**: 20–28.
152 Dasgupta A, Sureka K, Mitra D, Saha B, Sanyal S, Das AK *et al.* An oligopeptide transporter of Mycobacterium tuberculosis regulates cytokine release and apoptosis of infected macrophages. *PLoS One* 2010; **5**: e12225.
153 Samten B, Wang X, Barnes PF. Mycobacterium tuberculosis ESX-1 system-secreted protein ESAT-6 but not CFP10 inhibits human T-cell immune responses. *Tuberculosis* 2009; **89** (Suppl 1): S74–S76.
154 Balaji KN, Goyal G, Narayana Y, Srinivas M, Chaturvedi R, Mohammad S. Apoptosis triggered by Rv1818c, a PE family gene from Mycobacterium tuberculosis is regulated by mitochondrial intermediates in T cells. *Microbes Infect* 2007; **9**: 271–281.
155 Lopez M, Sly LM, Luu Y, Young D, Cooper H, Reiner NE. The 19-kDa Mycobacterium tuberculosis protein induces macrophage apoptosis through Toll-like receptor-2. *J Immunol* 2003; **170**: 2409–2416.
156 Tiwari B, Ramakrishnan UM, Raghunand TR. The Mycobacterium tuberculosis protein pair PE9 (Rv1088)-PE10 (Rv1089) forms heterodimers and induces macrophage apoptosis through Toll-like receptor 4. *Cell Microbiol* 2015; **17**: 1653–1669.
157 Saini NK, Sinha R, Singh P, Sharma M, Pathak R, Rathor N *et al.* Mce4A protein of Mycobacterium tuberculosis induces pro inflammatory cytokine response leading to macrophage apoptosis in a TNF-alpha dependent manner. *Microb Pathog* 2016; **100**: 43–50.
158 Ciaramella A, Martino A, Cicconi R, Colizzi V, Fraziano M. Mycobacterial 19-kDa lipoprotein mediates Mycobacterium tuberculosis-induced apoptosis in monocytes/macrophages at early stages of infection. *Cell Death Differ* 2000; **7**: 1270–1272.
159 Sanchez A, Espinosa P, Garcia T, Mancilla R. The 19 kDa Mycobacterium tuberculosis lipoprotein (LpqH) induces macrophage apoptosis through extrinsic and intrinsic pathways: a role for the mitochondrial apoptosis-inducing factor. *Clin Dev Immunol* 2012; **2012**: 950503.
160 Wang J, Teng JL, Zhao D, Ge P, Li B, Woo PC *et al.* The ubiquitin ligase TRIM27 functions as a host restriction factor antagonized by Mycobacterium tuberculosis PtpA during mycobacterial infection. *Sci Rep* 2016; **6**: 34827.
161 Man SM, Karki R, Kanneganti TD. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. *Immunol Rev* 2017; **277**: 61–75.
162 Ablasser A, Dorhoi A. Inflammasome activation and function during infection with Mycobacterium tuberculosis. *Curr Top Microbiol Immunol* 2016; **397**: 183–197.
163 Eklund D, Welin A, Andersson H, Verma D, Soderkvist P, Stendahl O *et al.* Human gene variants linked to enhanced NLRP3 activity limit intramacrophage growth of Mycobacterium tuberculosis. *J Infect Dis* 2014; **209**: 749–753.
164 He Y, Zeng MY, Yang D, Motro B, Nunez G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. *Nature* 2016; **530**: 354–357.
165 Shi H, Wang Y, Li X, Zhan X, Tang M, Fina M *et al.* NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component. *Nat Immunol* 2016; **17**: 250–258.
166 Master SS, Rampini SK, Davis AS, Keller C, Ehlers S, Springer B *et al.* Mycobacterium tuberculosis prevents inflammasome activation. *Cell Host Microbe* 2008; **3**: 224–232.
167 Shah S, Bohsali A, Ahlbrand SE, Srinivasan L, Rathinam VA, Vogel SN *et al.* Cutting edge: Mycobacterium tuberculosis but not nonvirulent mycobacteria inhibits IFN-beta and AIM2 inflammasome-dependent IL-1beta production via its ESX-1 secretion system. *J Immunol* 2013; **191**: 3514–3518.