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The Innate Immune Response to *Mycobacterium tuberculosis* Infection

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Abstract

Infection with *Mycobacterium tuberculosis* causes >1.5 million deaths worldwide annually. Innate immune cells are the first to encounter *M. tuberculosis*, and their response dictates the course of infection. Dendritic cells (DCs) activate the adaptive response and determine its characteristics. Macrophages are responsible both for exerting cell-intrinsic antimicrobial control and for initiating and maintaining inflammation. The inflammatory response to *M. tuberculosis* infection is a double-edged sword. While cytokines such as TNF-α and IL-1 are important for protection, either excessive or insufficient cytokine production results in progressive disease. Furthermore, neutrophils—cells normally associated with control of bacterial infection—are emerging as key drivers of a hyperinflammatory response that results in host mortality. The roles of other innate cells, including natural killer cells and innate-like T cells, remain enigmatic. Understanding the nuances of both cell-intrinsic control of infection and regulation of inflammation will be crucial for the successful development of host-targeted therapeutics and vaccines.

RECOGNITION OF *M. TUBERCULOSIS* BY PATTERN RECOGNITION RECEPTORS OF THE INNATE IMMUNE SYSTEM

The first step in initiating an immune response to *Mycobacterium tuberculosis* is detection by pattern recognition receptors (PRRs). Several classes of PRRs, including Toll-like receptors (TLRs), nucleotide-binding domain and leucine-rich repeat–containing receptors (NLRs), C-type lectin receptors (CLRs), and cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING), have been proposed to contribute to recognition of *M. tuberculosis* (**Figure 1**). Studies of mouse models have identified TLR2, which recognizes lipoproteins and lipoglycans from *M. tuberculosis*, and TLR9, which recognizes unmethylated CpG DNA, as the most important TLRs for control of *M. tuberculosis* infection (1–4). Mice lacking both TLR2 and TLR9 are more

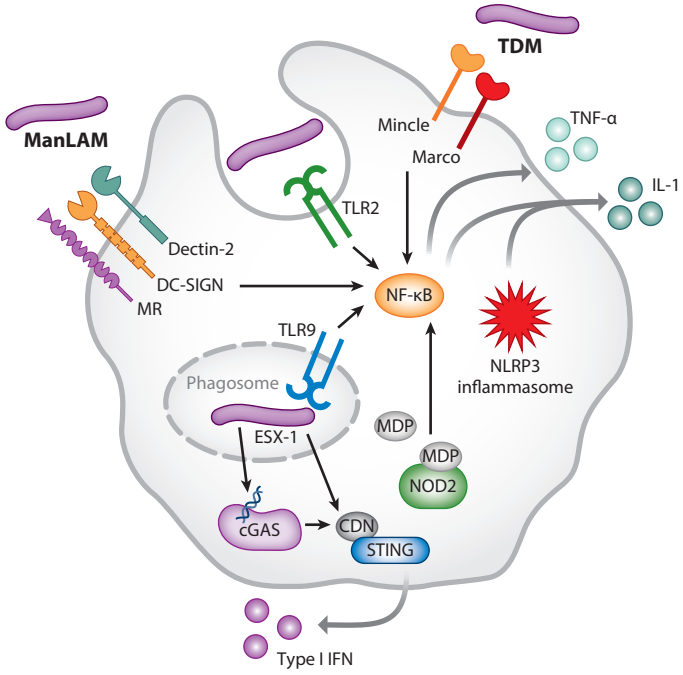

Figure 1

PRRs implicated in detecting *M. tuberculosis* infection and initiating the production of important innate cytokines. *M. tuberculosis* is detected by multiple classes of PRRs. The CLRs MR, DC-SIGN, and Dectin-2 have been proposed to recognize the glycolipid ManLAM, whereas Mincle and Marco recognize TDM on the surface of bacteria. TLR2 recognizes lipoproteins and/or lipoglycans on the surface, whereas TLR9 recognizes DNA released in the phagolysosome. The NLR NOD2 recognizes MDP released from bacterial peptidoglycan. NLRP3 triggers inflammasome activation upon *M. tuberculosis* infection. The ESX-1 secretion system promotes detection by cytosolic sensors by perforating the phagosomal membrane and allowing bacterial pathogen-associated molecular patterns to enter the cytosol, resulting in activation of cGAS/STING. CLRs, TLRs, and NOD2 signal through NF-κB to activate transcription of inflammatory cytokines including IL-1 and TNF-α. Processing and activation of IL-1β are promoted by the NLRP3 inflammasome. The cGAS-STING pathway leads to the expression of type I interferon, which is detrimental to the host. Abbreviations: CDN, cyclic dinucleotide; cGAS, cyclic GMP-AMP synthase; CLR, C-type lectin receptor; ManLAM, mannose-capped lipoarabinomannan; MDP, muramyl dipeptide; MR, mannose receptor; NLR, nucleotide-binding domain and leucine-rich repeat–containing receptor; PRR, pattern recognition receptor; STING, stimulator of interferon genes; TDM, trehalose dimycolate; TLR, Toll-like receptor.

susceptible than TLR2$^{-/-}$ or TLR9$^{-/-}$ single knockout mutants, suggesting that each TLR makes a nonredundant contribution to the immune response (4). The importance of TLR sensing stems from production of inflammatory cytokines, in particular IL-12, which is necessary for priming IFN-γ-producing T cells that mediate control of *M. tuberculosis* infection (4–6). In addition to TLRs, several CLRs have been proposed to play a role in immune recognition of *M. tuberculosis*. The cell wall glycolipid mannose-capped lipoarabinomannan can be recognized by DC-SIGN, mannose receptor, or Dectin-2 (7–10), and trehalose dimycolate can be recognized by Mincle or Marco (10, 11). However, experiments using mutant mice have suggested a limited role for individual CLRs (10, 12–14), which may be partially explained by redundancy in function. Finally, the NLR NOD2, which senses small muramyl peptides derived from bacterial cell wall peptidoglycan, contributes to cytokine responses to *M. tuberculosis* in myeloid cells cultured in vitro (15–21). However, mice lacking NOD2 are largely resistant to infection, exhibiting modest susceptibility only six months after infection (19, 22). The NLR NLRP3, a component of the inflammasome, is reviewed in the section titled IL-1.

cGAS is a cytosolic DNA sensor that produces cyclic GMP-AMP (cGAMP) upon DNA binding (23, 24). STING signaling is initiated by binding of cGAMP or other cyclic dinucleotides exported by pathogenic bacteria (25–27). STING induces expression of type I interferons, a family of cytokines that are detrimental to host control of *M. tuberculosis* infection (28–31). Activation of STING by *M. tuberculosis* and production of type I interferons require perforation of the vacuolar membrane by the ESX-1 type VII secretion system (32). Three independent reports demonstrated that cGAS is required for type I interferon induction, suggesting that DNA is the pathogen-associated molecular pattern (PAMP) that leads to STING activation (33–35). However, it was also reported that *M. tuberculosis* induces type I interferons by direct STING recognition of cyclic-di-AMP produced by the bacterium (36). Whereas TLRs, CLRs, and NLRs have been proposed to benefit the immune response to *M. tuberculosis* by promoting the production of proinflammatory cytokines and chemokines, the cGAS-STING pathway may be an example in which a bacterial pathogen engages an antiviral pathway to promote pathogenesis.

INNATE CYTOKINES

TNF-α

TNF-α was one of the first cytokines associated with tuberculosis and is crucial for control of infection. Macrophages and dendritic cells (DCs) are the primary producers of TNF-α during infection; however, TNF-α is also produced abundantly by CD4 T cells (37). Mice lacking TNF-α or the TNF receptor are highly susceptible to infection and exhibit poor activation of myeloid cells, a defect in chemokine production, and diffuse inflammation that lacks organized structure (38–41). Evidence for the importance of TNF-α in human tuberculosis infection comes primarily from patients treated with anti-TNF agents for inflammatory disorders, who have a high propensity for reactivation of tuberculosis disease (42–44). Nonhuman primate and mouse models support the idea that TNF-α is important for granuloma formation, structure, and integrity (45–47). However, studies using the zebrafish model of infection with *Mycobacterium marinum*, which is particularly well-suited to studying granuloma formation (48), have suggested that TNF-α maintains granuloma structure indirectly by restricting mycobacterial growth (49, 50); this has also been suggested by mouse studies (51). Furthermore, the zebrafish model has demonstrated that excess TNF-α can lead to increased macrophage cell death, which promotes hyperinflammation and death of the host. This finding illustrates the concept that in innate immunity to tuberculosis, excessive production of protective factors can be detrimental (52, 53) (**Figure 2**).

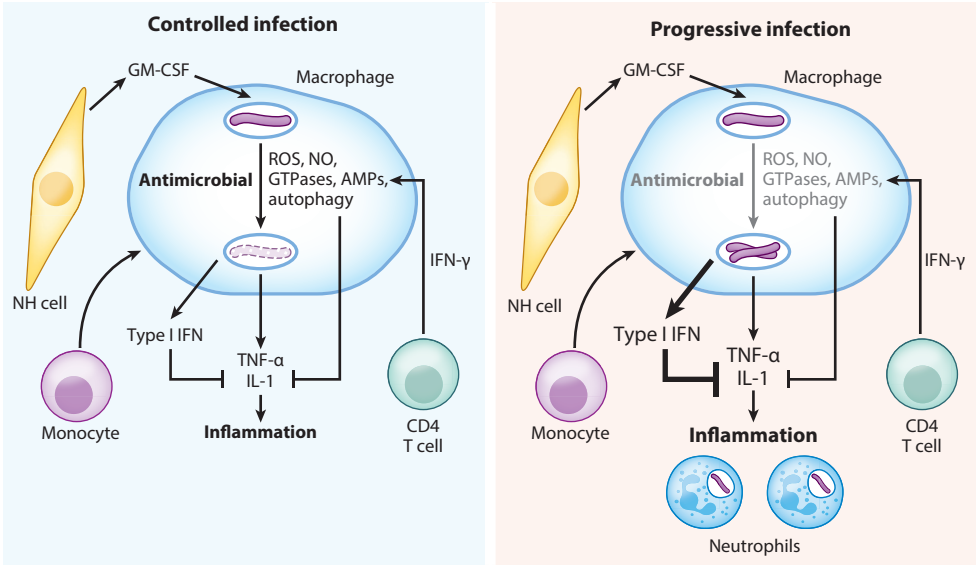

Figure 2

A combination of antimicrobial function and regulation of inflammation is required for successful control of *M. tuberculosis* infection. Successful control of *M. tuberculosis* infection is associated with robust macrophage-based control of bacterial replication by antimicrobial mechanisms. Mechanisms that have been proposed to contribute to cell-intrinsic control of infection include autophagy, interferon-inducible GTPases, ROS, NO, and antimicrobial peptides. Cytokines such as GM-CSF produced by nonhematopoietic cells and IFN-γ produced by CD4 T cells promote the microbicidal functions of macrophages. In controlled infection, there is appropriate production of inflammatory cytokines including TNF-α and IL-1; type I interferons, which block IL-1 function, are produced at low levels. Indeed, some of the susceptibility of mice lacking factors formerly assumed to be directly antimicrobial may be attributed to inflammatory imbalances. In contrast, uncontrolled infection may result from either a failure of antimicrobial control or imbalanced cytokine production. If antimicrobial mechanisms fail, the increased bacterial burden can drive the excessive production of inflammatory cytokines, leading to the recruitment of neutrophils that contribute to excessive inflammation. Alternatively, increased type I interferon production can functionally block IL-1 signaling, leading to immune failure. In most cases in mice, susceptible strains can be rescued by depletion of neutrophils, suggesting that in the mouse model diverse failures of immunity converge on a single neutrophil-driven mechanism of mortality. Abbreviations: AMP, antimicrobial peptide; GM-CSF, granulocyte-macrophage colony-stimulating factor; NH, nonhematopoietic; NO, nitric oxide; ROS, reactive oxygen species.

GM-CSF

The cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) was originally implicated in myeloid cell and granulocyte differentiation. However, mice lacking the GM-CSF gene, *Csf2*, have normal steady-state myelopoiesis but lack alveolar macrophages (AMs) (54). Lungs of *Csf2*$^{-/-}$ mice exhibit a buildup of pulmonary surfactant due to impaired catabolism by AMs, as well as pulmonary lymphoid hyperplasia at baseline (55). GM-CSF levels rise in the lungs of wild-type mice for at least 60 days after *M. tuberculosis* infection, and *Csf2*$^{-/-}$ mice are highly susceptible to *M. tuberculosis*, succumbing rapidly after infection (56). While nonhematopoietic cells are the primary producers of GM-CSF, *Csf2*$^{-/-}$ mice are partially rescued by adoptive transfer of wild-type but not *Csf2*$^{-/-}$ CD4 T cells, implying a minor role for T cell–derived GM-CSF (57). *Csf2*$^{-/-}$ mice have a defect in their production of inflammatory cytokines and chemokines in response to infection, resulting in impaired recruitment of both myeloid cells and T cells to the lungs (56). *Csf2*$^{-/-}$

infected mice also exhibit a significant increase in bacterial burden in the lungs compared with wild-type mice, suggesting a potential antibacterial role for GM-CSF (56). Indeed, addition of exogenous GM-CSF to *M. tuberculosis*–infected murine bone marrow–derived macrophages and human monocytes results in enhanced control of infection (57, 58). However, whereas treatment of wild-type mice with anti-GM-CSF neutralizing antibodies results in significant weight loss and larger granulomas in the lungs, it induces no change in lung colony-forming units, suggesting a role for GM-CSF in immune regulation rather than control of *M. tuberculosis* growth (59). A clear role for GM-CSF in activating the microbicidal capabilities of macrophages in vivo has yet to be demonstrated. Furthermore, the fact that *Csf2*$^{-/-}$ mice have baseline alterations in lung function complicates the interpretation of results from these mice (58, 60, 61).

IL-1

The first interleukin to be described was IL-1, discovered as a potent modulator of innate immunity. The IL-1 family members IL-1α and IL-1β are produced during infection with *M. tuberculosis* by inflammatory monocyte-macrophages, inflammatory DCs, and neutrophils (30, 62). They play critical and nonredundant protective roles early during infection, despite signaling through the same receptor. Neutralization of both IL-1α and IL-1β has a more significant impact on morbidity after infection than neutralization of either protein individually (63). Similarly, mice doubly deficient for IL-1α and IL-1β (*Il1a*$^{-/-}$/*Il1b*$^{-/-}$) are more susceptible to *M. tuberculosis* infection and show higher bacterial burdens in the lungs compared to mice lacking the individual cytokines (30, 51, 64). The protective function of IL-1 is further confirmed by blocking receptor signaling with anti-IL-1R antibodies or in an *Il1r*$^{-/-}$ mouse model; the mice become highly susceptible to *M. tuberculosis* infection and show increased bacterial burden in the lungs (30, 31, 62, 63, 65). Interestingly, loss of IL-1 signaling does not result in diminished TNF-α, IL-12p40, inducible nitric oxide synthase (iNOS), or IFN-γ responses (30). In other bacterial infections, the protective function of IL-1 is often ascribed to recruitment of neutrophils; however, neutrophils are not known to be protective in the context of tuberculosis, and it remains unclear why IL-1 signaling is critical for resistance. IL-1R signaling in *trans* by infected bystander cells is sufficient to induce restriction of intracellular bacterial growth in infected myeloid cells that lack IL-1R (66), suggesting that IL-1 promotes production of a soluble protective factor. Finally, a protective role of IL-1 during human tuberculosis infection has been suggested based on case studies in which rheumatoid arthritis patients treated with IL-1R antagonist anakinra occasionally showed reactivation of tuberculosis (67, 68).

IL-1β is produced as a precursor protein and is cleaved into a mature form by inflammasome and caspase-1 activation and then released to act systemically. Unlike the case of IL-1β, IL-1α activity does not require proteolytic processing by caspase-1. The main inflammasome that becomes activated upon in vitro infection with *M. tuberculosis* appears to be NLRP3. This requires the ESX-1 secretion system (69–73), although the exact mechanism remains controversial. Despite detection of *M. tuberculosis* by the inflammasome, *Nlrp3*$^{-/-}$, *Asc*$^{-/-}$, and *Casp1*$^{-/-}$ mice are not nearly as susceptible to infection as mice deficient in IL-1α and/or IL-1β or IL-1R (65, 72, 74–77). Furthermore, IL-1β production is still present in *Nlrp3*$^{-/-}$ or *Casp1*$^{-/-}$ mice (65, 72), indicating that pro-IL-1β can be processed and released through an inflammasome-independent mechanism (78–81). An excess of IL-1 has been linked to an increased influx of neutrophils and lung inflammation, which results in high bacterial burden and mortality (82) (**Figure 2**). However, IL-1α and IL-1β regulation is complex, and postsecretion, their activity is controlled further by the presence of IL-1R antagonist (IL-1Ra), complicating the interpretation of IL-1 protein levels. For example, *Sst1*^{S} mice, which are highly susceptible to *M. tuberculosis* infection, have elevated levels of

IL-1 protein in the lungs during infection. However, they also have high levels of IL-1Ra, which limit IL-1 activity, causing a functional deficiency in IL-1 signaling and increased *M. tuberculosis* susceptibility (31).

Type I Interferons

Type I interferons comprise a family of cytokines that signal through the interferon receptor to induce interferon-stimulated genes. Most cell types produce type I interferon upon stimulation of cytosolic DNA or RNA sensors that normally sense cytosolic viruses or through signaling via specific TLRs. In the case of *M. tuberculosis* infection, type I interferon is induced when the ESX-1 secretion system perforates the vacuolar membrane, leading to activation of the cGAS/STING pathway (28, 32, 83). Although type I interferon is critical for resistance to viral infections, the effect of type I interferon during *M. tuberculosis* infection is primarily detrimental. Tuberculosis patients with active disease show a distinct upregulation of type I interferon–inducible transcripts in blood neutrophils and monocytes. This gene expression profile correlates with disease severity and may predict the transition from active to latent disease (84–89). In mice, type I interferon is detrimental to *M. tuberculosis* infection; however, the severity of the phenotype appears to be background dependent. In C57BL/6 wild-type mice, loss of the type I IFN receptor or other signaling components results in only modest enhancement of control of infection (28, 31, 90–93). However, if these mice are stimulated to produce higher levels of type I interferon than are naturally produced during *M. tuberculosis* infection by administration of intranasal TLR3 ligand poly-ICLC, increased lung pathology and mortality during *M. tuberculosis* infection are observed, demonstrating that increasing type I interferon levels in the C57BL/6 background results in highly impaired immunity (94). Furthermore, the susceptibility of B6.*Sst1*^{S} congenic mice, which carry the tuberculosis susceptibility allele of the *Sst1* locus derived from the highly susceptible C3H/HeBFeJ strain, was recently shown to be primarily driven by type I interferon, as crossing these mice with *Ifnar*$^{-/-}$ mice alleviated the exacerbated disease (31). Type I interferons inhibit IL-1 signaling indirectly through strong upregulation of IL-1Ra expression during *M. tuberculosis* infection (31). Blocking IL-1Ra in B6.*Sst1*^{S} mice restores IL-1 protective signaling and rescues the type I interferon–induced susceptibility to infection, suggesting that the type I interferon–based susceptibility observed in these mice is almost entirely explained by inhibition of IL-1 signaling (31). Although several mechanisms by which type I interferons inhibit host defenses have been proposed, including modulating eicosanoids, iNOS production, and IL-10 (30, 31, 95–97), it is likely that the primary impact of type I interferon on *M. tuberculosis* immunity is to impair the production of IL-1, which is critical for protection against infection. Despite deleterious effects of high levels of type I interferon on the host immune response, it is possible that type I interferon is protective in some contexts, particularly in the absence of IFN-γ. The balance of deleterious and protective responses of type I interferon is further reviewed by Moreira-Teixeira et al. (98).

IL-10

IL-10 is an anti-inflammatory cytokine that downregulates both innate and adaptive immune responses. Pulmonary tuberculosis patients have elevated levels of plasma IL-10, and their T cells exhibit both enhanced *Il10* expression and evidence of IL-10 stimulation (99, 100). Studies of the role of IL-10 in mice have yielded mixed results, likely reflecting the complex role of IL-10 and other immunosuppressive cytokines in infection. One study showed that *Il10*$^{-/-}$ C57BL/6 mice experience a significant increase in bacterial numbers in the lungs and increased mortality starting late in infection (101), while another study found that *Il10*$^{-/-}$ mice on the C57BL/6 and BALB/C

backgrounds have reduced bacterial burdens in the lungs during the late stage of infection (102). CBA/J mice, which are highly susceptible to *M. tuberculosis*, are clearly impacted by IL-10 deficiency, as *Il10*$^{-/-}$ mice on this background exhibit lower bacterial numbers in the lungs and spleen throughout the course of infection when compared with wild type (103). Furthermore, treatment of CBA/J mice with an anti-IL-10R blocking antibody during the chronic stage of *M. tuberculosis* infection lowers bacterial numbers in the lungs and improves survival compared to untreated CBA/J mice (104). The seemingly contradictory results in the mouse model likely reflect the fact that IL-10 has a context-dependent role in infection; while it can contribute to restraining detrimental inflammation in the context of a potential hyperinflammatory response (such as CBA/J mice), it can also harm the host by suppressing effective responses.

TGF-β

Transforming growth factor beta (TGF-β) is an immunosuppressive cytokine that plays a crucial role in immune homeostasis and peripheral tolerance. TGF-β has a suppressive effect on cells that play a key role in regulating *M. tuberculosis* infection, including macrophages, DCs, neutrophils, and T cells (reviewed in 105). High levels of TGF-β are found in the lungs of patients with active pulmonary tuberculosis (106, 107), and serum levels of TGF-β correlate with disease severity (108). Similarly, high TGF-β levels are associated with active disease in murine and in nonhuman primate models, where successful antibiotic therapy results in diminished TGF-β levels (109, 110). Although production of TGF-β is crucial to prevent hyperinflammation and autoimmunity (105), several lines of evidence suggest that TGF-β suppresses effective immune responses to *M. tuberculosis* to the detriment of the host. In mice, blocking TGF-β signaling using neutralizing antibody, recombinant TGF-β receptor, or small-molecule inhibitors results in increased control of disease as measured by bacterial burden in the lungs (111, 112). One study suggests that the specific mechanism by which TGF-β suppresses host immunity is prevention of CD4 T cells from producing IFN-γ in granuloma cores, which limits effective macrophage activation (113). Thus, pharmacological inhibition of TGF-β may be an attractive strategy for managing patients with active tuberculosis disease.

MACROPHAGE-BASED MECHANISMS OF INNATE CONTROL

Macrophages are programmed to detect invading pathogens, activate microbicidal mechanisms, and coordinate the subsequent immune response. However, in the absence of adaptive immunity, macrophages are not capable of controlling *M. tuberculosis* infection. Although for many years it was speculated that *M. tuberculosis* resisters (individuals whose purified protein derivative (PPD) and IFN-γ release assay (IGRA) results never convert despite considerable exposure to *M. tuberculosis*) were able to clear infection via innate immunity, deeper immunological analysis of these individuals revealed the existence of class-switched antibodies, solid evidence of an adaptive response to infection (114). Indeed, in both mouse and nonhuman primate models, growth of *M. tuberculosis* is unrestricted in macrophages until the arrival of CD4 T cells in the lungs (115, 116). The primary role of CD4 T cells in macrophage activation is understood to be the production of IFN-γ, which can directly activate macrophages to control infection (6). In addition, there appear to be IFN-γ-independent mechanisms that have yet to be identified (117). Although several decades of research have focused on understanding the cell-intrinsic mechanisms of bacterial killing downstream of macrophage activation, recent revisions in our understanding of the functions of antimicrobial responses have left holes in our knowledge of effectors that have direct antimicrobial activity (**Figure 2**).

Autophagy

Autophagy (self-eating) is a conserved cellular process with important roles in homeostasis, development, and metabolism. In addition, it is well-established that a form of selective autophagy known as xenophagy is a major contributor to innate immune defense against microbial infections (reviewed in 118). The first evidence for an antimycobacterial effect of autophagy was the observation that starvation or rapamycin treatment leads to restriction of *M. tuberculosis* growth in RAW macrophages (119). Subsequently it was found that autophagic targeting of *M. tuberculosis* occurs as a response to perforation of the phagosome by the bacterial ESX-1 secretion system and stimulation of cGAS-STING (33, 35, 36, 83). TBK1 activation downstream of STING leads to ubiquitin-mediated autophagic targeting of the *M. tuberculosis*–containing phagosome. The E3 ubiquitin ligases Parkin and Smurf promote autophagic targeting of *M. tuberculosis*, and mice deficient in these factors are susceptible to *M. tuberculosis* (120, 121). In addition, *Atg5*$^{fl/fl}$*Lyz2Cre* mice, which lack the core autophagy effector ATG5 in myeloid cells, are hypersusceptible to *M. tuberculosis* (83, 122). However, subsequent detailed analyses of autophagy-deficient mice have shown the role of autophagy to be complex. While *Atg5*$^{fl/fl}$*Lyz2Cre* mice succumb rapidly to *M. tuberculosis*, mice deficient in other core autophagy effectors have no significant weight loss or inability to restrict bacterial replication through several months of infection (123). The susceptibility of *Atg5*$^{fl/fl}$*Lyz2Cre* mice is rescued by depletion of neutrophils, and much of the susceptibility is recapitulated in *Atg5*$^{fl/fl}$*Mrp8Cre* mice, which lack ATG5 specifically in neutrophils (123). This suggests there is a unique role for ATG5 in the regulation of inflammation and neutrophil recruitment, discrete from its role in autophagic targeting of bacteria. Taken together, these findings provide significant evidence that autophagy plays a role in *M. tuberculosis* infection but not all effects are intrinsic to the macrophage.

Vitamin D and Cathelicidin

Vitamin D has been used to treat tuberculosis since the mid-1800s. Multiple cohort studies show an association between low serum vitamin D levels and tuberculosis disease risk (124, 125). However, clinical trials have not clearly demonstrated that vitamin D treatment of tuberculosis patients already receiving antibiotics improves outcomes (126, 127). In vitro treatment of *M. tuberculosis*–infected cells with vitamin D restricts growth of the bacteria, indicating that vitamin D leads to cell-intrinsic control of *M. tuberculosis* (128, 129). A major effect of vitamin D treatment in *M. tuberculosis*–infected human monocytes is expression of the cathelicidin antimicrobial peptide LL-37 (128, 130). LL-37 has antibacterial activity against *M. tuberculosis* in liquid culture (131), and administration of LL-37 to *M. tuberculosis*–infected mice starting 60 days postinfection significantly reduced the bacterial load in the lungs (131). *Cramp*$^{-/-}$ mice, which lack the gene for murine cathelicidin, have enhanced mortality and a defect in controlling bacterial growth after *M. tuberculosis* infection compared to wild-type mice (132). Importantly, in other studies researchers have observed no effect of exogenous vitamin D on *M. tuberculosis* growth in human monocytes (133, 134). Thus, although low vitamin D levels may correlate with tuberculosis disease, whether the main function of vitamin D is to activate microbicidal mechanisms remains unclear.

Reactive Oxygen Species

The production of reactive oxygen species (ROS) is a crucial defense against phagocytosed pathogens. The production of ROS is initiated by the NADPH oxidase complex, which catalyzes the production of superoxide. Through a series of reactions, multiple other ROSs are then produced, including hydrogen peroxide, hypochlorous acid, and hydroxyl radicals. Data suggest that

NADPH oxidase is required for control of tuberculosis in humans. Patients with chronic granulomatous disease (CGD), who have inherited defects in NADPH oxidase, have presented with active tuberculosis or disseminated bacillus Calmette-Guérin (BCG) disease upon vaccination (135). Macrophages isolated from a CGD patient were unable to control growth of *M. tuberculosis*, suggesting that ROSs are important for cell-intrinsic control of *M. tuberculosis* infection in humans (136). However, studies on the role of ROSs in control of *M. tuberculosis* in the mouse model are inconclusive. Mice lacking components of NADPH oxidase display no increase in bacterial burden in the lungs or, at most, a mild and transient increase (137, 138). A recent study in the mouse model revealed a potential immunoregulatory role for ROSs, independent of bactericidal potential. While *Cybb*$^{-/-}$ mice, which lack the NADPH oxidase component gp91, are able to control *M. tuberculosis* growth similarly to wild-type mice, they experience greater weight loss and have a significant increase in mortality associated with excessive neutrophil recruitment (138). Blocking IL-1 signaling in *Cybb*$^{-/-}$ mice reduces neutrophil infiltration and rescues susceptibility, demonstrating that ROSs may limit harmful inflammation (138).

iNOS

The importance of IFN-γ during *M. tuberculosis* infection has been attributed to its ability to activate microbicidal mechanisms of macrophages, most importantly expression of the enzyme iNOS, encoded by the gene *Nos2* (139). iNOS catalyzes the production of the bactericidal/static radical nitric oxide (NO). Human tuberculosis patients exhibit iNOS expression in the lungs and are known to exhale NO, confirming that this molecule is produced during human *M. tuberculosis* infection (140–142). The importance of NO for control of *M. tuberculosis* infection is clear, as *Nos2*$^{-/-}$ mice are extremely susceptible to infection (143). However, studies of mixed bone marrow chimeras that examined different genotypes in the same inflammatory environment have demonstrated no difference in *M. tuberculosis* burden in wild-type and *Nos2*$^{-/-}$ cells, raising the possibility that NO does not function in a cell-intrinsic manner for control of bacterial numbers. Indeed, it has been proposed that NO limits IL-1β production by two mechanisms. First, by nitrosylation and inhibition of the NLRP3 inflammasome, NO may limit neutrophil recruitment and subsequent destruction of host tissue (82, 144). Depleting neutrophils in *Nos2*$^{-/-}$ mice rescues the increase in bacterial burden in the lungs at 24 days after infection (82). Second, NO may also limit IL-1β transcription by inhibiting NF-κB signaling (145). However, the facts that the ability to resist NO is an important virulence trait for *M. tuberculosis* (146) and that iNOS-deficient macrophages suffer from increased bacterial burdens in vitro make it clear that NO can impact cell-intrinsic antimicrobial activity of macrophages, independent of the inflammatory context. Thus, a role for NO in cell-intrinsic control of infection in vivo cannot be ruled out, and there is likely more to learn about the contribution of NO to control of infection in vivo.

Interferon-Inducible GTPases

Interferon-inducible GTPases are a family of proteins that encompass myxovirus resistance proteins (Mxs), guanylate-binding proteins (GBPs), immunity-related guanosine triphosphatases (IRGs), and very large inducible GTPase proteins (VLIGs). Both GBPs and IRGs are IFN-γ-inducible proteins that have been implicated in mycobacterial infections. Almost a decade ago, it was demonstrated that Gbp1 is required for control of *Mycobacterium bovis* BCG infection in vivo (147). However, mice with a chromosomal deletion that removes six GBPs, including Gbp1, are only mildly susceptible to *M. tuberculosis*, with a modest increase in bacterial burden emerging at 100 days after infection (148). A gene expression signature associated with the transition from latent to active disease contains *Gbp1*, providing some relevance to human disease (88, 149).

Although the IRG family member Irgm1 was shown to mediate host resistance to *M. tuberculosis* in mice (150), the significance of this finding is difficult to interpret in light of the emerging understanding that these knockout mice exhibit baseline alterations in immunity (151). Nonetheless, results from human studies suggest a role for IRGM1 in resistance to *M. tuberculosis* (reviewed in 152). Therefore, more research is needed into a potential role for these proteins in antituberculosis immunity.

Aerobic Glycolysis and Metabolic Regulation of Infection

The metabolic program of aerobic glycolysis is associated with differentiation of macrophages into the M1 phenotype. It is now understood that changes in levels of metabolites during aerobic glycolysis impact specific programs of gene expression and cellular differentiation. *M. tuberculosis*–infected macrophages transition to aerobic glycolysis, and this transition is required for effective control of bacterial growth (153, 154). During *M. tuberculosis* infection, aerobic glycolysis impacts gene expression by promoting the activity of the transcription factor hypoxia-inducible factor 1α (HIF-1α) (155). HIF-1α is a crucial mediator of IFN-γ-dependent immunity required for host defense against *M. tuberculosis* and is essential for expression of inflammatory cytokines, production of host-protective eicosanoids, and cell-intrinsic control of bacterial replication (154). How HIF-1α and/or aerobic glycolysis promote cell-intrinsic control of infection is yet unknown.

CELL DEATH AND EICOSANOIDS

There are multiple mechanisms by which the host cell can undergo cell death during *M. tuberculosis* infection, and the field has coalesced around a paradigm in which apoptotic death benefits the host whereas necrotic death benefits the bacterium. However, this paradigm is based largely on in vitro experiments and is difficult to establish conclusively, as there is no experimental means to selectively eliminate either form of death in vivo without also affecting other parameters of the immune response. In general, several attenuated strains and mutants of *M. tuberculosis* have been found to induce apoptotic cell death in macrophages (156–158). Apoptotic cells can be phagocytosed by DCs and subsequently stimulate T cell priming and activation (159–163). Efferocytosis of apoptotic cells by uninfected macrophages is thought to result in killing of bacteria through fusion of the efferocytic phagosome with lysosomes, and macrophage apoptosis is therefore considered beneficial for host survival (163, 164). In contrast, macrophages infected with virulent *M. tuberculosis* undergo necrosis (158, 165). Recent findings with a zebrafish model of *Mycobacterium marinum* infection showed that excess TNF-α can induce necrosis through interaction of multiple signaling pathways, including activation of RIP kinases, production of mitochondrial ROSs, and subsequent activation of cyclophilin D (52). TNF-α was also implicated in apoptosis induced by eicosanoid synthesis (166). Production of the eicosanoid PGE_2 promotes apoptosis in macrophages infected with avirulent *M. tuberculosis* (167). In contrast, PGE_2 production is inhibited by LXA_4, which is induced during infection with virulent strains and leads to necrosis. Mice lacking prostaglandin E synthase (*Ptges*$^{-/-}$) show a higher bacterial burden in the lungs, whereas *Alox5*$^{-/-}$ mice, which are unable to synthesize certain eicosanoids (including LXA_4 and LTB_4), are more resistant to *M. tuberculosis* infection (165). This suggests that PGE_2 has a protective effect against virulent *M. tuberculosis*. However, whether this effect is mediated through regulation of cell death or regulation of inflammation is unclear. PGE_2 has both pro- and anti-inflammatory functions, including the regulation of cytokine expression in DCs and T cell differentiation (168). In addition, lipoxins have been described as negative regulators of acute inflammatory processes and together with PGE_2 regulate neutrophil recruitment (144, 169). Interestingly, polymorphisms in the promoter region of leukotriene A4 hydrolase (*lta4h*), which catalyzes the production of the eicosanoid LTB_4,

have been associated with mortality and response to anti-inflammatory treatment in patients with tuberculosis meningitis, further supporting the notion that eicosanoids are important for regulating inflammatory processes (170, 171).

OTHER INNATE CELLS

Neutrophils in Host Defense

Polymorphonuclear neutrophils are short-lived cells of the innate immune response that are highly abundant during bacterial infections. Neutrophils possess a potent antimicrobial arsenal effective against many bacterial and fungal pathogens (172). In the case of *M. tuberculosis*, while there is some evidence that neutrophils participate in protective immunity, a clear role in host defense has yet to be defined. In some settings, they may promote *M. tuberculosis* infection. Recruitment of neutrophils to the lungs after *M. tuberculosis* infection is rapid and is mediated through multiple chemokines, including IL-17, CXCL5, and KC, and by eicosanoids produced by 12/15-lipoxygenase (144, 173, 174). Neutrophils take up bacteria in vivo (144, 163, 175). However, studies examining whether neutrophils are able to effectively kill phagocytosed *M. tuberculosis* are inconclusive and contradictory (176), in part because of the difficulty of working with primary neutrophils ex vivo and the paucity of appropriate cells lines for neutrophil research. Studies of neutrophil function in vivo are also inconclusive. Neutrophils harboring bacteria may die by apoptosis, which is followed by efferocytosis by resident macrophages, possibly facilitating control of infection (164). Alternatively, it has also been proposed that neutrophils are a permissive niche for growth and persistence in vivo (177, 178). Separate from their ability to kill bacteria, neutrophils may have an influence on priming of adaptive immunity. Depletion of neutrophils at early stages of infection in resistant mouse strains has yielded differing results, with some studies finding no impact and other studies finding that depletion of neutrophils compromises host defense (175, 179).

Destructive Inflammation Mediated by Neutrophils

In human tuberculosis, neutrophils are generally associated with active disease, caseous necrosis, and exacerbated pathogenesis (180), and neutrophils may be drivers of the pathology associated with active disease. Indeed, animal models established that excessive accumulation of neutrophils in the lungs drives destructive inflammation and susceptibility to infection. Furthermore, the phenotypes of many mice known to be susceptible to *M. tuberculosis* infection, including *Nos2*$^{-/-}$, *Atg5*$^{-/-}$, *Irg1*$^{-/-}$, and *Card9*$^{-/-}$ mice, can be at least partially rescued by depletion of neutrophils (123, 144, 181, 182). These data suggest that defects in immunity resulting from disparate perturbations lead to a common pathway of neutrophil-driven susceptibility (**Figure 2**). However, many questions remain. First, it is unclear whether neutrophils are a common driver of susceptibility in humans. Second, the mechanisms by which neutrophils are recruited to excess under specific conditions, and how they drive destructive inflammation, are unclear. Finally, it is possible that neutrophils are in fact more heterogeneous in tuberculosis disease than is currently appreciated and that specific subsets of neutrophils participate in host defense, whereas others contribute to pathology.

Alveolar Macrophages and Innate Cells During Early Infection

AMs are a subset of tissue-resident macrophages that reside within the lung airspace and play crucial roles in lung homeostasis, surfactant metabolism, and tissue repair (183). AMs are the first cell

type to encounter *M. tuberculosis*. Studies of human AM infections are difficult, as the AM phenotype is programmed and maintained in the tissue niche and is rapidly lost in cell culture (184). In mice, a productive *M. tuberculosis* infection starts with infection of AMs that reside in the lung alveoli (185, 186). Depletion of AMs with liposome-encapsulated dichloromethylene diphosphanate prior to infection reduces the bacterial burden in the lungs and increases survival, suggesting that AMs form a replicative niche early after infection (187, 188). Indeed, infected AMs initially exhibit an anti-inflammatory NRF2-dependent antioxidant response (186, 188, 189). Approximately 10 days after infection is initiated, AMs exhibit a more proinflammatory transcriptional state that precedes their transition from the airway into the pulmonary interstitium at approximately 14 days postinfection (185, 186). AMs in the interstitium localize in infectious foci, a process that is mediated by IL-1R signaling in nonhematopoietic cells (185). At two weeks, AMs appear to be the predominant infected cell type in the lungs (190, 191). Shortly thereafter, however, *M. tuberculosis* disseminates to monocyte-derived cells and neutrophils (188, 192). Interstitial macrophages show a glycolytic transcriptional profile, express iNOS and IL-1, and restrict intracellular growth of *M. tuberculosis* more efficiently than AMs (188). In addition, mycobacterial growth in the lungs appears to be sustained by a constant influx of new monocytes into the lungs (193). Thus, although airway AMs are a more permissive niche for growth early after infection, *M. tuberculosis* replication in the lungs can be sustained through dynamic infection of new monocytes that provide *M. tuberculosis* with new cellular niches that become rapidly infected.

Dendritic Cells

DCs bridge innate and adaptive immunity, traveling from sites of infection and inflammation to secondary lymphoid tissues for activation of T cells. Both classical/resident and monocyte-derived DCs are present in the lungs during *M. tuberculosis* infection (194). Antibody-based depletion of $CD11c^{+}$ cells, which transiently eliminates both classical and monocyte-derived DCs, results in defective CD4 T cell priming and increased susceptibility to *M. tuberculosis* infection, demonstrating the importance of DCs for host defense (195). Several studies using $CCR2^{-/-}$ mice have suggested that inflammatory monocytes, and not DCs, may be responsible for trafficking *M. tuberculosis* to the draining lymph nodes for activation of T cell responses (196, 197). However, a more recent study using diphtheria toxin to selectively ablate CCR2 at different stages of infection found that while interstitial macrophages traffic bacteria to the draining lymph nodes, classical DCs are largely responsible for priming CD4 T cell responses (198). Human data have suggested that the onset of adaptive immunity to *M. tuberculosis* is significantly delayed (199–201). Indeed, data from both mice and nonhuman primates have clearly demonstrated that the priming of T cells in draining lymph nodes is delayed during *M. tuberculosis* infection relative to other infections (163, 194, 202–204), although limited antigen availability due to *M. tuberculosis*'s slow replication rate and low infectious dose may be a confounding factor. Importantly, experimental perturbations that result in more rapid priming of effector T cells, through BCG vaccination, dendritic cell vaccination, or adoptive transfer, result in more effective control of *M. tuberculosis* infection (205–207).

Natural Killer Cells

Natural killer (NK) cells are innate lymphocytes present in both lymphoid and nonlymphoid tissues that play a major role in defense against viral infection. In human tuberculosis, a reduction in the number of NK cells or in their expression of activation markers correlates with loss of control and the transition to active disease (208, 209). Furthermore, changes in peripheral blood NK cell levels correlate with disease progression and treatment response, and they inversely correlate with

lung inflammation in tuberculosis patients across multiple independent cohorts (209). However, whether these studies indicate a functional role for NK cells in the immune response is unclear. Although the exact ligands are unknown, NK cells are capable of detecting *M. tuberculosis*–infected macrophages through activating receptors (e.g., NKp46, NKG2D) (210). Human and mouse NK cells produce perforin and granulysin, are capable of killing *M. tuberculosis*–infected cells through a contact-dependent mechanism (211–214), and produce IFN-γ during infection. *M. tuberculosis*–infected mice show an increase in NK cell numbers in the lungs within 21 days (92, 214). NK cell depletion does not result in an increase in bacterial growth in the lungs in C57BL/6 mice (214), indicating that these cells are not critical for restricting the bacterial burden. However, depletion of NK cells or IFN-γ in RAG$^{-/-}$ mice further increases the susceptibility of these mice to *M. tuberculosis* infection (215).

Nonclassical T Cells

Nonclassical T cells, including mucosal-associated invariant T (MAIT) cells and γδ T cells, span innate and adaptive immunity. Their T cell receptor repertoire is highly limited, often recognizing PAMPs, and they participate in rapid innate-like effector responses. MAIT and γδ T cells have been frequently associated with tuberculosis; however, their role during infection remains unclear. MAIT cells are activated by intermediates of bacterial riboflavin biosynthesis that bind to the highly conserved major histocompatibility complex–related 1 (MR1) molecule (216). Most bacterial species, including *M. tuberculosis*, synthesize riboflavin and therefore activate MAIT cells. Once activated, individual MAIT cell subsets can produce different combinations of inflammatory/T helper 1 (Th1) cytokines and can kill infected cells through the release of cytotoxic granules (216). In nonhuman primates, tetramer-restricted MAIT cells accumulate in the airways but not inside granulomas and only show minimal expression of granzyme B or the proliferation marker Ki76, suggesting that MAIT cells are not essential contributors to *M. tuberculosis* restriction in macaques (217, 218). Mice lacking MR1 are susceptible to infection with BCG and *M. tuberculosis* (219). BCG induces MAIT cell formation in BCG-vaccinated humans and nonhuman primates (220, 221). Furthermore, MAIT cells have activity against BCG-infected macrophages (222). However, it is unclear whether induction of MAIT cells contributes to the efficacy of BCG and what role MAIT cells play in human *M. tuberculosis* infection.

γδ T cells expand early during *M. tuberculosis* infection (223, 224). Furthermore, tuberculosis patients have a higher proportion of IL-17-producing γδ T cells compared to healthy controls (225). Human γδ T cell clones derived from peripheral blood mononuclear cells respond to live *M. tuberculosis* and to *M. tuberculosis* lysate in vitro (226). Both AMs and monocytes activate and induce expansion of γδ T cells (227). Activated γδ T cells can produce IFN-γ in response to *M. tuberculosis* and are cytotoxic to infected monocytes, macrophages, and extracellular bacteria due to release of perforin and granulysin (228, 229). C57BL/6 mice deficient for T cell receptor (TCR) δ chain lack γδ T cells and show a transient higher bacterial burden early in infection compared to control mice. Interestingly, TcR-δ$^{-/-}$ mice show control of low-dose infection at later time points but eventually succumb to high-dose infections (230). The most abundant population of γδ T cells in humans are Vγ9Vδ2 T cells that recognize HMBPP, an intermediate of the nonmevalonate pathway of isoprenoid biosynthesis (231–233). Vγ9Vδ2 T cells activated by BCG are able to protect against *M. tuberculosis* infection in a macaque model (234). Furthermore, using *Listeria monocytogenes* as a vaccine platform to stimulate Vγ9Vδ2 T cells effectively protects against *M. tuberculosis* infection in primates (235), demonstrating the potential of γδ T cells for vaccine-elicited control of infection. However, whether they play an important role in containing natural human infection remains unclear.

HARNESSING THE INNATE IMMUNE RESPONSE

Innate Immunity and Adjuvant Development for Protein Subunit Vaccines

One of the most important practical applications of understanding innate immunity to *M. tuberculosis* is the rational design of novel vaccines. The current vaccine strain BCG is widely administered due to its efficacy in preventing severe manifestations of childhood tuberculosis; however, it has limited efficacy against adult pulmonary tuberculosis. Recently, the M72/AS01$_E$ protein subunit vaccine demonstrated 50% efficacy in preventing reactivation disease in previously BCG-vaccinated adults, providing some of the first concrete evidence that vaccines other than BCG can enhance naturally acquired immunity to tuberculosis (236). Formulating novel vaccines with optimized adjuvant and antigen combinations could improve upon this efficacy, raising the exciting possibility of a truly effective vaccine for tuberculosis. Recent years have witnessed a major leap forward in the development of novel adjuvant systems, including alum and emulsions, TLR agonists, STING agonists, and several lipids derived from *M. tuberculosis* (237, 238). Although these adjuvants all elicit inflammatory responses, the balance of specific cytokines produced can be adjuvant specific, suggesting that adjuvant selection may be important for fine-tuning the innate, and therefore adaptive, response to vaccination. In the context of *M. tuberculosis*, adjuvants under development that have shown efficacy in preclinical animal studies include agonists of TLR2, TLR3, TLR4, TLR7/8, Mincle, and the inflammasome (reviewed in 238). Thus far, the development of vaccines and selection of specific adjuvants have been largely empirical, due to the lack of immune correlates of protection to guide tuberculosis vaccine design. However, several key lessons have emerged from vaccine development. First, whereas traditional vaccination strategies have sought to maximize the development of IFN-γ-producing Th1 and polyfunctional T cells, it is now appreciated that excessive Th1 development may inhibit the development of other (as yet unidentified) protective T cell subsets (239, 240). Furthermore, mucosal delivery of vaccines for tuberculosis can promote enhanced protective immunity relative to parenteral immunization, promoting the development of antigen-specific Th17 cells (241, 242). Therefore, it is crucial that adjuvants for tuberculosis vaccines be selected not purely for their ability to elicit strong inflammatory responses but also for their capacity to elicit balanced Th1/Th17 immunity and for mucosal efficacy. Finally, because the effect of adjuvants can differ based on genetic and epigenetic factors, care must be taken in the selection of the appropriate adjuvant for tuberculosis vaccination in the target population (e.g., infant versus adult) (237).

Trained Immunity

Soon after the introduction of the BCG vaccine in Europe in the early twentieth century, it was noted that BCG reduces childhood mortality in a manner that could not be explained by a reduction in tuberculosis incidence. Subsequent studies have confirmed this phenomenon and have attributed the efficacy to a reduction in mortality from childhood respiratory diseases (reviewed in 243). The ability of BCG to protect against nonmycobacterial infections is attributed to trained immunity—the long-term functional reprogramming of innate immune cells resulting in enhanced responses to other pathogens. BCG vaccination protects mice from viral infections including influenza and herpes simplex virus 2 via nonspecific trained immunity (244, 245). Intriguingly, the observation that coronavirus disease 2019 (COVID-19) cases and fatalities are fewer in regions of the world with universal BCG vaccination has prompted speculation that BCG vaccination may be protective against COVID-19 (246). However, this has not been established through rigorous clinical trials. Intravenously injected BCG elicits an expansion and reprogramming of hematopoietic stem cells in the bone marrow that promote the production of macrophages primed

to respond to *M. tuberculosis* infection. This trained immunity is induced via epigenetic changes that result in enhanced responsiveness of innate immunity genes in macrophages and other innate cells. In the mouse model this results in a modest reduction in bacterial titers after infection with *M. tuberculosis* of ~0.5–1 log—comparable to standard vaccination with BCG (247). BCG infection of bone marrow results in changes that persist for many weeks after eradication of BCG using antibiotics. However, as the timing of infection in the mouse model is necessarily compressed due to a short life span, it is unclear how long-lived trained immunity can be in humans. Importantly, intravenous BCG results in almost complete protection against *M. tuberculosis* infection in macaques (248, 249); however, there is no evidence of a contribution of trained immunity to this remarkable protective efficacy (248). Although early exposure to *M. tuberculosis* in humans induced a protective state in circulating monocytes that limited *M. tuberculosis* outgrowth, this effect was modest in BCG-vaccinated individuals (250). Although it is unclear whether innate immunity alone, even when trained, can ever completely protect against *M. tuberculosis* infection, future vaccination strategies should consider eliciting trained immunity as a contributor to other mechanisms.

CONCLUSIONS AND PERSPECTIVES

The original view of innate immunity to tuberculosis primarily focused on resistance—the ability of the cells and cytokines of the immune system to prevent infection or eliminate infectious microbes. Thus, much of the first few decades of tuberculosis research focused on identifying mechanisms by which activated macrophages kill or prevent the proliferation of *M. tuberculosis* bacilli in a cell-intrinsic manner and inflammatory cytokines that are important for control of disease. However, there are still major gaps in our understanding of resistance mechanisms. It remains unclear exactly how macrophages control infection with *M. tuberculosis* at the cell-intrinsic level. Furthermore, we lack an understanding of how cytokines like IL-1 contribute to control of infection. The roles of many innate cells, including NK cells and nonclassical T cells, remain enigmatic. The idea that tolerance—limiting the collateral damage caused by the immune response to infection—determines the outcome of infection has more recently become a major focus of research. In the mouse model of infection, it appears that disturbing tolerance may be a major pathway to host susceptibility. This corresponds with our understanding that death from human tuberculosis results from inflammatory destruction of host lung tissue. However, in most susceptible strains of mice rescued by neutrophil depletion, there is an increase in bacterial burden in the lungs, leaving open the question of whether a failure of resistance drives the excessive inflammation that results in death. Furthermore, simply suppressing the immune response using nonspecific anti-inflammatory drugs does not clearly benefit patients with active pulmonary tuberculosis (251). Human tuberculosis is a remarkably heterogeneous disease, both during different stages of disease within an individual patient and from patient to patient. The design of novel therapeutics that modulate inflammation appropriately for individual patients, or that enhance resistance mechanisms, will require a deeper understanding of the innate pathways that contribute to progression of disease.

DISCLOSURE STATEMENT

E.V.D. and S.A.S. are authors on a patent broadly related to the topic of this review entitled "Intranasal delivery of a cyclic-di-nucleotide adjuvanted vaccine for tuberculosis" (United States Patent Application 20200338182).

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