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Immunology of *Mycobacterium tuberculosis* Infections

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ABSTRACT Tuberculosis (TB) is a serious global public health challenge that results in significant morbidity and mortality worldwide. TB is caused by infection with the bacilli *Mycobacterium tuberculosis* (*M. tuberculosis*), which has evolved a wide variety of strategies in order to thrive within its host. Understanding the complex interactions between *M. tuberculosis* and host immunity can inform the rational design of better TB vaccines and therapeutics. This chapter covers innate and adaptive immunity against *M. tuberculosis* infection, including insights on bacterial immune evasion and subversion garnered from animal models of infection and human studies. In addition, this chapter discusses the immunology of the TB granuloma, TB diagnostics, and TB comorbidities. Finally, this chapter provides a broad overview of the current TB vaccine pipeline.

INTRODUCTION

Mycobacterium tuberculosis, the etiologic agent of tuberculosis (TB), remains a significant global public health burden (1). In 2016, there were 10.4 million new TB cases reported globally and nearly 1.7 million TB-related deaths (1). Understanding the host response to *M. tuberculosis* infection is a key aspect of efforts to eradicate TB through the development of effective vaccines and immune therapeutics. *M. tuberculosis* is an intracellular pathogen transmitted via inhalation of aerosolized, bacteria-containing droplets. Innate immune cells in the lungs, primarily macrophages, dendritic cells, monocytes, and neutrophils, readily phagocytose *M. tuberculosis* and are the earliest defenders against the pathogen. The transformation of bacteria-containing phagosomes into acidified, antimicrobial compartments is a central tenet of defense against *M. tuberculosis*. In this regard, the production of interferon-γ (IFN-γ), which can activate infected myeloid cells and inhibit bacterial replication, is a well-known antimycobacterial contribution by adaptive immune cells such as CD4 and CD8 T cells. Despite pressures from host immunity, *M. tuberculosis* is able to persist in the host. *M. tuberculosis* infection results in hallmark lesions called granulomas, which are initially aggregates of infected and uninfected myeloid cells circumscribed by a lymphocytic cuff. The granuloma is thought to prevent bacterial dissemination to extrapulmonary sites but can also become a niche for long-term bacterial persistence. *M. tuberculosis* has evolved myriad strategies to evade and subvert immune responses to persist within a host, and it is becoming increasingly clear that the immune response to *M. tuberculosis* infection involves contributions from a wide variety of innate and adaptive immune cells. A clearer understanding of the complex cross talk between *M. tuberculosis* and host immunity is essential for the development of efficacious TB vaccines. Despite being

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developed nearly a century ago, *Mycobacterium bovis* bacillus Calmette-Guérin (BCG), an attenuated strain of *M. bovis*, remains the only licensed vaccine against TB. Vaccination with BCG provides protection against severe forms of disseminated TB in children but has variable efficacy in preventing pulmonary disease in children and adults (2–4). However, the immunological basis for the poor efficacy of BCG remains unclear. Moreover, long-held concepts regarding the nature of desired immune responses in an ideal TB vaccine, namely, the induction of antigen-specific CD4 T cells producing IFN-γ, are being updated to reflect the expanding knowledge of host immunity to *M. tuberculosis* infection gathered from animal models and human cohort studies. Advances in imaging and single-cell technologies combined with high-throughput approaches and systems-based analyses are providing more information on the immune response to *M. tuberculosis* infection at increasingly higher resolutions. As our understanding of the host response to *M. tuberculosis* infection grows, opportunities to leverage knowledge of the immunology of *M. tuberculosis* infection toward improving therapeutics and vaccines for TB are increasing.

This article will cover integral features of the innate and adaptive immune response to *M. tuberculosis* infection. Additionally, it will highlight recent findings on the hallmark granuloma and novel cellular players contributing to the host response to *M. tuberculosis* infection. Finally, it will provide an overview of the state of TB vaccine research, including a summary of BCG-based vaccines and the TB vaccine pipeline.

IMMUNOPATHOGENESIS OF TB IN HUMANS AND ANIMAL MODELS

Overview of Human TB Disease and Comorbidities

Transmission of *M. tuberculosis* occurs after inhalation of aerosolized droplets containing live bacteria into the lungs. Successful transmission is influenced by a variety of conditions, including proximity and duration of contact with an individual with active TB (ATB) disease and the immune-competency of the individual infected with *M. tuberculosis* (5–7). We now appreciate that in a clinical setting, *M. tuberculosis* infection presents as a continuum of diseased/infected states ranging from asymptomatic latent TB infection (LTBI) to ATB disease. This complexity, combined with remarkable heterogeneity in lesions within a single patient, has presented unique challenges to the eradication of TB (8). While the majority of individuals exposed to *M. tuberculosis* are able to control infection in the form of LTBI, an estimated 5 to 10% of people exposed to *M. tuberculosis* develop ATB, which is characterized by a persistent cough accompanied by sputum production, weight loss, weakness, and night sweats (9). Clinical diagnosis and treatment of *M. tuberculosis* infection is complicated by a variety of coinfections and comorbidities.

Comorbidities that modulate immune function can exacerbate TB disease or contribute to progression of individuals with LTBI to ATB. HIV coinfection in latently infected individuals increases the risk of developing TB from a 5 to 10% lifetime risk to a 10% annual risk, and HIV infection is the single greatest risk factor for the development of TB (10–14). The relevance of HIV coinfection to global TB mortality is highlighted by the fact that more than a fifth of all TB-related deaths in 2016 were in HIV-positive individuals (1). Progressive depletion and dysfunction of CD4 T cells following HIV infection leads to immune suppression and negatively impacts immunity to *M. tuberculosis*. Specific depletion of *M. tuberculosis*-specific CD4 T cells has been reported in the peripheral blood (15, 16) and broncheoalveolar lavage (BAL) samples (17, 18) of HIV-infected individuals with LTBI. Several studies indicate that specific depletion may be a consequence of enhanced HIV coreceptor expression in CD4 T cells, particularly CCR5, in TB patients (15, 19–24). Alternative hypotheses to explain specific depletion of *M. tuberculosis*-specific CD4 T cells include differential functionality of specific T cells. In HIV coinfected LTBI, *M. tuberculosis*-specific CD4 T cells are reported to secrete interleukin 2 (IL-2) in contrast to MIP-1β (macrophage inflammatory protein 1 beta) secreted by cytomegalovirus-specific CD4 T cells (16). Analysis of viral loads in HIV coinfected LTBI showed an inverse correlation between viral load and the frequency of *M. tuberculosis*-specific CD4 T cells secreting IL-2 (25), suggesting that IL-2 producing *M. tuberculosis*-specific CD4 T cells may be specifically depleted in the context of HIV coinfection. Relatedly, HIV-coinfected individuals have lower frequencies of cytokine-producing *M. tuberculosis*-specific CD4 T cells with impaired proliferative capacity compared to HIV-uninfected individuals with LTBI (26–28), suggesting *M. tuberculosis*-specific CD4 T-cell dysfunction during HIV-infection. The relative contributions of depletion versus dysfunction of *M. tuberculosis*-specific CD4 T cells to enhanced TB risk following HIV infection remains unclear. Further, HIV infection may perturb protective immunity to *M. tuberculosis* in other immune compartments, such as CD8 T cells. For instance, *M. tuberculosis*-specific CD8 T cells from individuals with LTBI are

reported to have impaired proliferation and degranulation in HIV-infected compared to HIV-uninfected individuals (29). Studies have also described associations between TB and many other conditions or activities, including smoking, malnutrition, diabetes, helminth infections, chronic lung diseases, and cancer (30, 31). Further investigations will be required to fully understand the basis of identified associations with other infections and morbidities.

Animal Models of Infection

Knowledge of the host response to *M. tuberculosis* infection has benefited greatly from the development of animal models of infection. The variable outcomes of *M. tuberculosis* infection in humans are challenging to model in a single animal model. Many experimental animals are susceptible to *M. tuberculosis* infection and can inform us about aspects of human disease. The mouse model for TB benefits from many advantages: ease of manipulation and housing, availability of well-characterized inbred strains, sophisticated techniques for the generation of mutant strains, availability of immunological and other reagents, and relatively low cost. Mice have been utilized to model host responses to *M. tuberculosis* infection, to evaluate drug and vaccine candidates, and to study the immune response to mutant strains of mycobacteria. Experimental infection can be delivered through multiple routes: intravenously, intraperitoneally, intratracheally, or via aerosolized particles. The latter method, especially low-dose aerosol infection, is the most physiologically relevant and has become the preferred method. Different mouse strains have well-characterized lung pathologies and levels of susceptibility (32–36). Typically, following bacterial deposition into the lungs, it takes approximately 2 weeks to begin priming adaptive immune responses in the lung-draining lymph nodes and a further 1 to 2 weeks for robust participation in the lungs by adaptive immune cells, but bacterial burdens continue to be maintained at a high level in the lungs of *M. tuberculosis*-infected mice. There are limitations to what can be gleaned from mouse models of *M. tuberculosis* infection due to the differences in lung pathology between mice and humans. Further, true latent infection and significant immune control of infection are difficult to establish in the mouse model, though chemotherapeutically induced models of paucibacillary disease in mice exist (37, 38). The development of humanized mice that can recapitulate the heterogeneity of human lung pathology may extend the advantages of the mouse model, but humanized mice are also reported to display aberrant T-cell responses and be unable to control bacterial burden (39, 40).

Other animal models of *M. tuberculosis* infection include guinea pigs, rabbits, fish, and non-human primates (NHP). Each has distinct advantages and disadvantages that make their use particularly suitable for different types of research questions. Following infection, guinea pigs exhibit pathological features, such as the organization and development of caseous necrotic granulomas, that more accurately recapitulate the human granulomatous response compared to mice (41). Further, guinea pigs are very susceptible to *M. tuberculosis* infection and, thus, are a good choice for testing candidate drugs and vaccines and studying dissemination dynamics. Similarly, rabbits develop a well-organized granuloma that can become necrotic following mycobacterial infection. However, rabbits are resistant to *M. tuberculosis*, and high numbers of bacteria during inoculation or use of more virulent strains are needed (42–45). Nevertheless, the rabbit model has been leveraged to study relatively rarer forms of TB, such as cutaneous and meningeal TB (46, 47). The usefulness of both the guinea pig and rabbit models is hampered by the scarcity of immunologic reagents relative to mice. The zebrafish model has provided novel insights into the establishment of the mycobacterial granuloma. Infection of transparent zebrafish larvae with the natural fish pathogen *Mycobacterium marinum* leads to the establishment of well-organized granulomas that become necrotic and can be visually monitored (48). The primary advantage of the zebrafish model is the transparency of the zebrafish larvae, which, alongside facile manipulation of host and bacterial genetics, has been leveraged for insight into early innate immune events leading to the formation of the granuloma as well as insights into human disease. Adaptive immunity is present in adult zebrafish, and different populations of CD4 T cells have recently been described (49, 50), but these animals are no longer transparent, and relevance of the adult zebrafish immune response to human TB have yet to be established.

The NHP model of *M. tuberculosis* infection reflects much of the heterogeneity observed in human TB. Infection of NHPs is typically performed by aerosol or direct bronchoscopic deposition into the lungs of rhesus or cynomolgus macaques and, depending on the dose of the inoculation and the strain of bacteria utilized, leads to symptomatic ATB disease or asymptomatic infection in which bacteria persist at low levels akin to LTBI. The NHP model accurately recapitulates many of the hallmark granulomas seen in humans, including the heterogeneity of granulomas that can be present in the same animal (51), and presents clinical symptoms similar to

those seen in humans (52–57). The NHP model is regarded as an important preclinical model for TB research and is an excellent model for studying immunity to *M. tuberculosis* and assessing candidate drug and vaccine efficacies (58–63). Further, the NHP model can be used to study reactivation in the setting of simian immunodeficiency virus coinfection or other types of immune modulation, such as anti-tumor necrosis-α (anti-TNF-α) treatment, CD4 depletion, or inhibition of indoleamine 2,3-dioxygenase (IDO) (64–71).

INNATE IMMUNITY TO *M. TUBERCULOSIS* INFECTION

The earliest encounter between host and pathogen in TB occurs at the interface between innate immune cells and *M. tuberculosis*. While innate immunity is critical for early antimycobacterial responses, it is also important for the progression of infection and long-term control of *M. tuberculosis* by continually priming and educating adaptive immune responses and by regulating inflammation. However, innate immune cells are often niches for bacterial replication, and *M. tuberculosis* utilizes a variety of strategies that subvert innate immune responses to establish a chronic infection. Here, we will detail key features of the innate immune response to *M. tuberculosis* infection, starting from recognition of the bacterium and phagosomal defenses within infected macrophages to priming of adaptive immune responses by professional antigen-presenting cells. In between, we will highlight how neutrophils and monocytes are mobilized after *M. tuberculosis* infection, the role that natural killer (NK) cells play during infection, how the balance of inflammation is regulated by the innate immune system, and how cell death affects the immune response. In each section, we will also highlight some of the myriad strategies that *M. tuberculosis* utilizes to subvert or evade the host innate immune response.

Recognition of *M. tuberculosis* by Pattern Recognition Receptors

Pathogen-associated molecular patterns on *M. tuberculosis* are recognized via a variety of receptors to mediate opsonic and nonopsonic bacterial uptake: C-type lectins (e.g., mannose receptors, DC-SIGN, Dectin-1, Dectin-2, Mincle), complement receptors (e.g., complement receptor 3), collectins (e.g., surfactant proteins A and D, mannose-binding lectin), scavenger receptors (e.g., MARCO, SR-A1, CD36, SR-B1), Fc receptors (e.g., FcgR), glycophosphatidylinositol-anchored membrane receptors (e.g., CD14), and Toll-like receptors (TLRs) (e.g., TLR-2, TLR-4, TLR-9) (72–74). Mannosylated lipoarabinomannan, phosphatidyl-inositol mannosides, phthiocerol dimycocerosates, phenolic glycolipids (PGLs), trehalose dimycolate, peptidoglycan, and other mycobacterial components are recognized by an array of cell surface and intracellular receptors that mediate phagocytosis and/or antimicrobial defenses. *M. tuberculosis* DNA (75, 76) or bacterial second messengers (77) can be recognized by cytosolic pattern recognition receptors (PRRs), such as cGAS and STING (78, 79), to induce downstream cytokine production and autophagy. Further, nucleotide oligomerization domain-like receptors (NLRs) are cytosolic PRRs that recognize *M. tuberculosis* pathogen-associated molecular patterns, such as muramyl dipeptide, to activate a multiprotein complex termed the inflammasome. Functional redundancies for many of the receptors are likely to exist due to promiscuous ligand binding by different receptors and the wide array of available ligands on *M. tuberculosis*. Indeed, single or double knockouts for canonical scavenger receptors and C-type lectin receptors did not modulate susceptibility or attenuate immune responses following *M. tuberculosis* infection (80). However, increased susceptibility to *M. tuberculosis* infection in a variety of knockout mice demonstrate that a number of PRRs and their associated signaling pathways also play important, nonredundant roles in host defense against *M. tuberculosis* infection.

M. tuberculosis expresses a variety of known or putative TLR ligands, and TLR-2, TLR-4, and TLR-9 have been implicated in host recognition of *M. tuberculosis* (reviewed in 73, 74). Polymorphisms in specific TLRs or TLR signaling proteins have also been strongly associated with pulmonary TB in humans and have been shown to influence immunity against *M. tuberculosis* (81–84). The contribution of individual TLRs to immunity against *M. tuberculosis* infection is variable, but the importance of the TLR signaling pathway to antimycobacterial immunity is evident in studies showing that mice lacking the common TLR adaptor protein, myeloid differentiation factor 88 (MyD88), quickly succumb to *M. tuberculosis* infection (85, 86). Susceptibility of *MyD88*$^{-/-}$ mice to *M. tuberculosis* infection has been attributed to deficient expression of NOS2 (86), impaired ability to activate the IL-1β or IL-1 receptor (IL1R) pathway (87, 88), impaired receptivity of macrophages to IFN-γ signaling (89), and impaired IL-12 and TNF-α responses in macrophages and dendritic cells (DCs) (85). Gene-deletion studies in single TLRs have revealed that innate immune responses to *M. tuberculosis* are likely the result of the complex activation of multiple signaling pathways. For instance,

mice lacking both TLR-2 and TLR-9 are more susceptible to *M. tuberculosis* infection than mice lacking the ability to signal through either TLR by itself (90). The susceptibility of *MyD88*$^{-/-}$ mice to *M. tuberculosis* infection is an example of the importance of common adaptor molecules that integrate signals from multiple PRRs and other innate immune pathways for the induction of antimycobacterial immunity. Further evidence for this concept is demonstrated by the increased susceptibility of *M. tuberculosis*-infected mice lacking CARD9, an adapter molecule integrating signals from C-type lectin receptors, or PYCARD/ASC, an adapter molecule integrating signals from nucleotide oligomerization domain-like receptors for the induction of the inflammasome (91, 92).

MyD88 signaling in innate immunity integrates signaling from TLR and IL-1 receptor families by bridging ligand-receptor binding to IL-1-receptor-associated kinases and the activation of multiple downstream pathways, including NF-κB, mitogen-activated protein kinases, and activator protein 1. The IL-1 signaling pathway is clearly required for resistance to *M. tuberculosis* infection in mouse models and is supported by human immunogenetics studies (93–96). In mice, the absence of IL-1 signaling led to severe susceptibility to *M. tuberculosis* infection. Both IL-1α and IL-1β, as well as their common receptor, IL-1R1, have been implicated in immunity to *M. tuberculosis* (87, 88, 97–101). Secretion of the mature form of IL-1β requires cleavage by the terminal inflammasome effector, caspase-1, but *M. tuberculosis*-infected mice lacking MyD88, ASC, or caspase-1 signaling do not display impaired IL-1β levels (87). Further, mice deficient in IL-1β are considerably more susceptible to *M. tuberculosis* infection than mice lacking ASC or caspase-1 (87). These findings suggest that IL-1β is a key mediator of resistance to *M. tuberculosis* infection but also indicate that the basis for resistance conferred by MyD88, CARD9, and PYCARD/ASC likely depend on additional factors beyond IL-1β.

While host recognition of *M. tuberculosis* leads to the activation of innate immunity, *M. tuberculosis* has also evolved strategies that evade innate immune responses mediated by PRRs. Strain-specific expression of cell envelope components may be associated with differential immune responses. For example, the W-Beijing lineage strain, HN878, has been found to express polyketide synthase-derived phenolic glycolipids that are missing in lab-adapted H37Rv or other clinical isolates (i.e., CDC1551) (102). Expression of PGL by HN878 has been found to diminish production of multiple innate immune cytokines and chemokines (102, 103), though its role in the increased virulence of HN878 remains controversial. Modulation of innate immune responses by *M. tuberculosis* is also accomplished through the presence of immune-inhibitory lipid components that compete with immune-activating mycobacterial components for the same receptors. For example, expression of tetraacylated sulfoglycolipids by the W-Beijing strain GC1237 can competitively bind TLR-2 to attenuate responses to canonical TLR-2 agonists, including mycobacterial lipomannans (104). Lastly, *M. tuberculosis* can also impair innate immune responses to cell-envelope components through enzymatic means. For instance, an *M. tuberculosis* serine-hydrolase, Hip1, was found to cleave multimeric, cell wall-associated GroEL2 to a secreted monomeric form to mediate attenuated macrophage and DC responses (105–109). Additionally, *M. tuberculosis* mutants lacking *hip1* or a putative mycobacterial metalloprotease, *zmp1*, display enhanced inflammasome activation (106, 110), suggesting that *M. tuberculosis* has multiple strategies for dampening activation of the inflammasome.

Thus, in addition to the array of host receptors that mediate recognition of *M. tuberculosis*, innate immune responses to infection likely depend on the strain of *M. tuberculosis*, the presence of cell wall components that can competitively inhibit the activation of PRRs, and the presence of *M. tuberculosis* enzymes that modify the immunogenicity of cell envelope components.

Phagosomal Defense in Macrophages

Macrophages are the first immune cells to encounter *M. tuberculosis* during infection and also represent the primary replicative niche for *M. tuberculosis*. Recognition of *M. tuberculosis* by macrophages leads to phagocytosis and sequestration of the bacterium in phagosomes, which typically eradicate pathogens via fusion with lysosomes and consequent acidification of the pathogen-containing phagolysosome. However, *M. tuberculosis* is able to survive and replicate in the phagosome by inhibiting phagosomal maturation and phagolysosomal generation through a variety of mechanisms (reviewed in 72, 111). Further, transcriptional profiling of intraphagosomal bacteria indicated that *M. tuberculosis* readily counters the nitrosative, oxidative, hypoxic, and nutrient-poor phagosomal environment through the expression of stress-adaptive genes (112), though a genome-wide transposon site hybridization screen for *M. tuberculosis* survival in macrophages suggested that *M. tuberculosis* constitutively expresses genes required for its survival (113). Nevertheless, it is clear that *M. tuberculosis* has adapted for a lifestyle inside the macrophage and employs many strategies to survive within these cells.

M. tuberculosis glycolipids can prevent accumulation of phosphatidylinositol 3-phosphate on phagosomal membranes and prevent phagolysosome biosynthesis (114). *M. tuberculosis* also secretes phosphatases (SapM and PtpA) and serine/threonine kinases (PknG) that are proposed to interfere with phagosomal maturation (115–121). There is also evidence that *M. tuberculosis* lipids, in particular, phthiocerol dimycocerosates, can mediate escape from the phagosome and host cell death (122). An *M. tuberculosis* secretion system, ESX-1, is also known for mediating disruptions in phagosomal integrity and preventing phagosome maturation. Promotion of aberrant phagosomal integrity and bacterial replication by *M. tuberculosis* ESX-1 is countered by IFN-γ-induced, Rab20-mediated phagosomal maturation (123). ESX-1-mediated phagosomal escape of bacteria is hypothesized to work through disruption of the phagosome by the 6-kDa early secretory antigenic target (ESAT-6) (124–127), though recent evidence proposes a contact-dependent, ESAT-6-independent mechanism for ESX-1-mediated phagosomal permeabilization (128). Nevertheless, ESX-1-mediated permeabilization of the phagosome exposes *M. tuberculosis* pathogen-associated molecular patterns, such as *N*-glycolyl-muramyl dipeptide, to cytoplasmic nucleotide oligomerization domain 2 receptors to induce type I IFNs (129, 130). ESX-1-mediated permeabilization of the phagosome also exposes extracellular bacterial DNA to the cytosolic DNA-sensing pathway, which leads to targeting of *M. tuberculosis* to autophagosomes for subsequent killing (75). *M. tuberculosis* ESX-3 has also been implicated in modulating intracellular trafficking of bacteria to avoid phagosomal maturation through inhibition of the host endosomal sorting complex required for transport (131–133). Thus, studies of the *M. tuberculosis* ESX secretion system have provided evidence for its role in both bacterial evasion of phagosomal pressures and host sensing of bacterial components. In addition to the ESX system, *M. tuberculosis* also expresses two SecA ATPase protein homologues (SecA1 and SecA2) involved in protein export (134). SecA2, in particular, has been implicated in virulence and intracellular growth (135, 136). Interestingly, both *M. tuberculosis* and BCG Δ*secA2* mutants are enriched in acidified phagosomes, indicating that mycobacterial SecA2 is required for arrest of phagosome maturation (137).

M. tuberculosis entry into macrophages through different receptors can lead to distinct activation of pathways that can inhibit or promote bacterial replication. The overall effect of multiple receptors engaging distinct or overlapping *M. tuberculosis* ligands is a complex and dynamic issue. For example, *M. tuberculosis* uptake by complement receptor 3 depended on host cholesterol, which mediated phagosomal association with coronin-1 and consequent inhibition of phagolysosome formation through activation of host calcineurin (138, 139). Alternatively, TLR-2 recognition of mycobacterial mannosylated lipoarabinomannan activates NF-κB and *NOS2* gene transcription that leads to antimycobacterial nitric oxide (NO) production (140). NO production is strongly associated with resistance to *M. tuberculosis*, though evidence for the antimycobacterial effects of NO is stronger in the mouse model. In mice, reactive nitrogen intermediates are toxic to mycobacteria *in vitro* (141–143), and infection can be exacerbated by the inhibition of NOS *in vitro* (144, 145) or *in vivo* (146–148). NO production following IFN-γ signaling has also been reported to limit overt inflammation by inhibiting processing of IL-1β by the inflammasome (149). Relatedly, mice with disrupted NOS2 alleles display exacerbated disease following *M. tuberculosis* infection (146, 150). Although *in vitro* studies using human alveolar macrophages and primary monocytes did not find an antimycobacterial role for NO (151–153), specific staining for NOS2 in the BAL of TB patients reveals upregulation in infected individuals compared to healthy controls (154). Nevertheless, *M. tuberculosis* has several strategies to cope with otherwise damaging reactive nitrogen and oxygen intermediates: *M. tuberculosis* KatG, a catalase-peroxidase, can inactivate phagosomal reactive oxygen (155), and the *M. tuberculosis* proteasome can mediate resistance to nitrosative stresses (156). Promiscuous recognition of mycobacterial antigens by the same receptor may also have convergent outcomes as in the case for TLR-2-mediated recognition of *M. tuberculosis* cell wall fractions leading to TNF-α production in murine macrophages (157). TLR-mediated recognition of *M. tuberculosis* is also reported to synergize with the vitamin D pathway to induce the antimicrobial peptide (AMP), cathelicidin, in human macrophages (158, 159). The biologically active vitamin D metabolite, calcitriol, induces hCAP-18, a gene encoding the proform of cathelicidin, following TLR ligation of macrophages (158–160). In addition to direct antimicrobial activity, cathelicidin has been shown to exert antimicrobial functions by activating transcription of host autophagy genes *Beclin-1* and *Atg5* (161). The vitamin D pathway also synergizes with IFN-γ secreted by T cells to induce IL-15 autocrine signaling to promote autophagy and phagosomal maturation in *M. tuberculosis*-infected human macrophages (162).

Autophagy is the process whereby cytoplasmic constituents are degraded or recycled. A role for autophagy

in antimycobacterial immunity in macrophages has been extensively characterized. Initial studies utilizing *M. bovis* suggested that autophagy plays a role in promoting phagosomal maturation to enhance bacterial killing (163). Moreover, LRG-47, an IFN-γ inducible p47 GTPase reported to be critical for phagosomal maturation and control of *M. tuberculosis* (164), is also involved in the induction of autophagy in *M. bovis*-infected macrophages (165). Autophagy-related genes were revealed to be involved in regulating the intracellular bacterial load of lab-adapted and clinical isolates of *M. tuberculosis* in a genome-wide small interfering RNA screen in infected human macrophage-like THP-1 cells (166). Accumulating evidence indicates that autophagy is integrated into the host response to *M. tuberculosis* infection by synergizing with pathogen sensing, phagosomal maturation, and IFN-γ inducible pathways to mediate antimycobacterial immunity: STING-dependent cytosolic sensing of *M. tuberculosis* DNA is required to deliver bacteria to autophagosomes and restrict bacterial replication (75); knockdown of cGAS in infected macrophages attenuated the induction of autophagy and survival during chronic *M. tuberculosis* infection (78); detection of cyclic-di-AMP secreted by *M. tuberculosis* in macrophages induced type I IFN production and autophagy to limit bacterial virulence (77); PARKIN, a conserved ubiquitin ligase, was shown to ubiquitinate *M. tuberculosis*-containing phagosomes to facilitate ubiquitin-mediated autophagy and restrict bacterial replication (167); IFN-γ-induced host ubiquilin-1 colocalizes with *M. tuberculosis* and mediates trafficking of bacteria to autophagosomes (168); IFN-γ receptor signaling mediated by the MyD88 adaptor-like (Mal) molecule induced autophagy and killing of intracellular *M. tuberculosis* in macrophages (169). Several studies have also delineated strategies employed by *M. tuberculosis* to evade autophagy. *M. tuberculosis* is reported to induce the expression of microRNA-33 to inhibit autophagy and regulate intracellular lipid metabolism to benefit bacterial replication (170). Further, a screen of *M. tuberculosis* cosmid clones in search of genes that inhibited bone marrow-derived DC antigen presentation revealed *M. tuberculosis* PE_PGRS47 (*Rv2741*) as an inhibitor of autophagy-mediated antigen presentation (171), suggesting that *M. tuberculosis*-mediated impairment of innate immunity can also negatively impact the generation of adaptive immunity. It is also becoming clear that autophagy-related proteins are likely to perform multiple functions, and care must be taken when interpreting specific knockouts or knockdowns of individual genes. For instance, myeloid cell-specific ablation of *Atg5*, but not other autophagy genes, compromised control of *M. tuberculosis* (172, 173). Deletion of the autophagy-related genes *Ulk1*, *Ulk2*, *Atg4B*, or *p62* compromised the ability to induce autophagy, but they were dispensable for the control of *M. tuberculosis* (173). Analysis of lung sections from *M. tuberculosis*-infected *Atg5* knockout mice indicated that Atg5 may be involved in regulation of neutrophil responses during infection, suggesting autophagy-independent roles for Atg5. Further, a recently described role for Atg5 in LC3-associated phagocytosis during *M. tuberculosis* infection supports the notion that specific components of autophagy can also overlap with other phagosomal pathways in immunity against mycobacteria (174).

Taken together, it is clear that macrophage recognition and phagocytosis of *M. tuberculosis* lead to a dynamic tug of war between antimycobacterial defenses and *M. tuberculosis* immune evasion. Macrophage defenses include AMPs, nitrosative stresses, phagolysosomal fusion, and autophagy and may operate independently of or subsequent to IFN-γ signaling. On the other hand, *M. tuberculosis* can subvert macrophage defenses at the level of the bacterial cell wall components that limit phagosomal maturation and the bacterial genes that combat or allow adaptation to intracellular immune pressure.

Recruitment and Function of Neutrophils and Monocytes Following *M. tuberculosis* Infection

Secretion of cytokines and chemokines early during infection recruits additional phagocytes to the site of infection. Early secretion of chemoattractants may be attributed to infected alveolar macrophages as well as lung epithelial cells (175–177). Moreover, a recent study suggests that cross talk between primary bronchial epithelial cells and infected macrophages may also promote secretion of chemokines (178). Trafficking of additional monocytes and granulocytes to the lung exerts immune pressure on *M. tuberculosis* and is crucial for the initiation of adaptive immune responses, but it may also promote *M. tuberculosis* cell-to-cell transmission and dissemination.

Recruitment of neutrophils serves as an early line of defense against *M. tuberculosis* infection via secretion of antimicrobial molecules and inflammatory mediators, but neutrophils also serve as niches for bacterial replication and can impede immunity against *M. tuberculosis*. In humans with active pulmonary TB, neutrophils have been found to be a significant population of *M. tuberculosis*-infected phagocytes in the BAL and sputum (179). Whole blood transcriptional profiling

also identified a neutrophil signature in ATB patients that is associated with type I and type II IFN-inducible genes (180) and expression of the inhibitory molecule PD-L1 (181), suggesting that neutrophils may play an immunomodulatory role in human TB. In mice, the kinetics and magnitude of neutrophil recruitment following *M. tuberculosis* infection depends on the strain of mouse infected. Evidence for a pathogenic role for neutrophils is shown in studies comparing neutrophil recruitment in resistant versus susceptible mouse strains (182, 183). When comparing resistant C57BL/6 mice to susceptible DBA/2 mice after *M. tuberculosis* infection, a study found that neutrophils were rapidly recruited into the broncheoalveolar space at higher magnitudes in susceptible mice. Depletion of neutrophils at the onset of *M. tuberculosis* infection specifically extended the life spans of DBA/2 mice, suggesting that early neutrophil involvement was pathogenic in genetically susceptible mice (183). Similarly, neutrophil depletion in susceptible I/St mice shortly after *M. tuberculosis* infection reduced lung pathology and bacterial growth and improved survival compared to C57BL/6 mice (184). In a separate study, depletion of neutrophils 5 weeks after aerosol *M. tuberculosis* infection of resistant BALB/c mice enhanced the levels of lung IL-6 and IL-17 without impacting IFN-γ and modestly enhanced control of bacterial burden (185). Neutrophil depletion in the first 4 days following intravenous *M. tuberculosis* infection of BALB/c mice, however, led to enhanced bacterial growth at extrapulmonary sites, suggesting that antimycobacterial immunity conferred by neutrophils may be dependent on the route of infection and the kinetics of neutrophil involvement (186). Utilizing fluorescently labeled bacteria, a recent study demonstrated that bacterial distribution in myeloid cells shifts from CD11b+Ly6G– monocytes and macrophages to CD11b+Ly6G+ neutrophils in *Nos2*$^{-/-}$ animals infected with *M. tuberculosis*, suggesting that neutrophil influx can create a growth-permissive environment for *M. tuberculosis* under NO-deficient conditions (187). Evidence for beneficial roles that neutrophils play in antimycobacterial defense focus on neutrophil secretion of AMPs such as cathelicidin and lipocalin-2 to restrict bacterial replication (188) or via uptake of AMP-containing apoptotic neutrophils by *M. tuberculosis*-infected macrophages (189). Neutrophils can also release chromatin scaffolds that trap extracellular bacteria in an AMP-containing mesh. *M. tuberculosis* has been shown to induce the formation of neutrophil extracellular traps *in vitro* (190), and levels of neutrophil extracellular traps detected in the plasma of ATB patients were associated with disease severity and decreased with antibiotic therapy (191). Further, as discussed later in the chapter, dysregulation of neutrophil recruitment by unrestrained IL-17 responses during *M. tuberculosis* infection can incur pathological consequences by driving lung-damaging inflammation. Thus, the overall effect of neutrophil recruitment to the site of *M. tuberculosis* infection may be determined by host genetics, the context of infection (pulmonary versus extrapulmonary), or timing and duration of neutrophil activity.

In addition to neutrophils, monocytes are recruited to the site of *M. tuberculosis* infection. Similar to neutrophils, monocyte recruitment is important for innate immunity during *M. tuberculosis* infection but may also inadvertently promote *M. tuberculosis* dissemination. C-C chemokine receptor type 2 (CCR2) is a chemokine receptor expressed on monocytes and is responsible for CCL2-mediated recruitment of monocytes to sites of bacterial infection (192). CCR2 was found to mediate immunity against *M. tuberculosis* depending on the dose of infection. CCR2 knockout mice were more susceptible to high-dose intravenous *M. tuberculosis* infection (193), but not after low-dose infection (194). Monocytes have been shown to differentiate into macrophages and DCs following *M. tuberculosis* infection, and monocytes transferred into *M. tuberculosis*-infected mice were shown to be the predominant population of innate immune cells producing iNOS (195). Additionally, monocyte delivery of *M. tuberculosis* to pulmonary lymph nodes can coordinate with DCs to prime CD4 T cells after infection (196). Monocytes may therefore represent a recruited population of innate cells that combat *M. tuberculosis* infection through the production of reactive nitrogen intermediates and priming of adaptive immunity. However, monocyte recruitment following *M. tuberculosis* infection may also be detrimental to the host by providing an environment full of permissive cells. Treatment of *M. tuberculosis*-infected mice with polyinosinic-polycytidylic acid (polyIC) led to CCR2-dependent recruitment of a population of *M. tuberculosis*-permissive monocytes, severe susceptibility, and early mortality (197). Interestingly, susceptibility of polyIC-treated mice to *M. tuberculosis* infection was dependent on type I IFN signaling and was not due to any particular alteration to the T-cell response. The recruitment of neutrophils and monocytes to the site of *M. tuberculosis* infection represents a host strategy to contain bacterial replication that is co-opted by the bacterium to facilitate its growth and dissemination.

NK Cells in *M. tuberculosis* Infection

NK cells are innate lymphocytes with the capacity to secrete IFN-γ and perform cytolytic functions to mediate

control of a variety of pathogens, including *M. tuberculosis*. Various components of the *M. tuberculosis* cell wall can bind directly to NKp44 found on NK cells (198), and NK cells can also recognize stress molecules upregulated on the surface of *M. tuberculosis*-infected cells (199). NK cells can mediate direct killing of *M. tuberculosis*-infected macrophages (199) but can also restrict intracellular bacterial replication via secretion of IL-22 (200) and IFN-γ (201) to increase phagolysosomal fusion of *M. tuberculosis*-containing phagosomes. Additionally, NK cells can enhance immunity against *M. tuberculosis* indirectly by enhancing CD8 T-cell production of IFN-γ (202) by promoting the expansion of γδ T cells (203) and by lysing *M. tuberculosis*-expanded regulatory T cells (204). The cytolytic capacity of NK cells is diminished in ATB patients relative to healthy controls and can be reconstituted following antibiotic therapy (205). Further, NK cell function in TB patients can be attenuated by monocyte-derived IL-10 (201). Interestingly, a population of IL-21-dependent NK cells that appears following BCG vaccination has been shown to expand following *M. tuberculosis* challenge (206), suggesting that NK cells may also display some hallmark characteristics of memory cells.

Inflammation and Cell Death During *M. tuberculosis* Infection

The regulation of inflammation is a critical factor that determines the outcome of *M. tuberculosis* infection. Overexuberant inflammation impairs cellular immunity, damages lung tissue, and can lead to lung cavitation and enhanced transmission. Inversely, too little inflammation can impair control of bacterial burden by delaying the induction of innate and adaptive immunity. While neutrophil recruitment and activity during *M. tuberculosis* infection can help contain bacterial replication, sustained neutrophilic inflammation can mediate damaging inflammation and promote disease. Importantly, whole blood transcriptomics identified a neutrophil-driven type I IFN-inducible signature in human TB that decreased upon treatment (180). Excessive type I IFN signaling has been shown to promote disease in mouse models and human samples. Mice lacking type I IFN signaling are more resistant to *M. tuberculosis* infection (207–210), though signaling through type I IFNs may play a protective role in the absence of IFN-γ (211, 212). Mechanisms underlying the pathogenic role of type I IFNs during *M. tuberculosis* infection include inhibition of IL-1β production (213, 214), induction of IL-10 to impair innate cytokine production (215), and loss of IFN-γ responsiveness in infected macrophages (215). In addition to induction of type I IFNs, neutrophils have also been reported to drive lung destruction through the secretion of matrix metalloproteinase 8 (216). The matrix metalloproteinase family of enzymes has been implicated in lung tissue destruction during *M. tuberculosis* infection (217–220) but has also been shown to promote macrophage recruitment and bacterial dissemination during infection of zebrafish (221).

Eicosanoids are lipid mediators of inflammation derived from the oxidation of arachidonic acid. The balance between proinflammatory prostaglandin E2 (PGE2) and anti-inflammatory lipoxin A4 (LXA4), two members of the eicosanoid family of signaling molecules, can determine the outcome of *M. tuberculosis* infection (222–224). During *M. tuberculosis* infection, mice incapable of synthesizing PGE2 display increased susceptibility (223), and absence of the enzyme 5-lipoxygenase, which metabolizes arachidonic acid to LXA4, confers resistance (222). Importantly, therapeutic correction of low PGE2 levels can confer enhanced survival in highly susceptible mice infected with *M. tuberculosis* (100). Leukotriene A4 hydrolase is an enzyme that catalyzes the production of proinflammatory leukotriene B4 from leukotriene A4, which can also be converted to anti-inflammatory LXA4 as a counterbalance. In zebrafish, *LTA4H* mutants were found to be hypersusceptible to *M. marinum* infection due to dysregulation of the balance between leukotrienes and lipoxins; increased levels of LXA4 in *LTA4H* mutants impaired TNF-α responses and promoted susceptibility (225). The relevance of this finding to humans is highlighted in a TB meningitis cohort in Vietnam where heterozygosity for six *LTA4H* polymorphisms conferred a survival advantage over homozygosity (225). Indeed, anti-inflammatory glucocorticoid treatment efficacy in TB meningitis patients can be differentiated by a single nucleotide polymorphism in the *LTA4H* promoter controlling transcriptional activity, which suggests that the balance of inflammation is critical to disease progression and treatment outcomes in TB meningitis (226).

TNF-α is a critical proinflammatory cytokine in immunity against *M. tuberculosis* infection and can be secreted by a number of innate and adaptive immune cells. The importance of TNF-α in antimycobacterial immunity is clearly demonstrated by heightened susceptibility of TNF-α antibody-depleted animals or in animals lacking TNF receptor signaling following *M. tuberculosis* infection (227). TNF-α is also a critical mediator of immunity against TB in humans. This is demonstrated by increased rates of progression to ATB in LTBI patients receiving anti-TNF treatment for inflammatory

disorders (228), which can be recapitulated in the NHP model of infection (70). The effects of anti-TNF treatment in humans and NHPs, as well as in mice (229–231), suggests that TNF-α is critical for maintaining sequestration of *M. tuberculosis* in the granuloma. Histopathological evidence from gene-disrupted or antibody-depleted mice infected with *M. tuberculosis* also suggests that TNF-α signaling may be playing a role in modulating apoptotic or necrotic cell death following infection (229, 231).

Cell death can be a means of restricting bacterial replication by the host or a way to disseminate to secondary loci of infection for *M. tuberculosis*. Apoptosis of *M. tuberculosis*-infected cells leads to fewer viable bacteria and effective cross-presentation of bacterial antigens (224, 232, 233), whereas necrosis of *M. tuberculosis*-infected cells allows viable bacteria to exit and disseminate (223, 234, 235). Proapoptotic *M. tuberculosis* mutants lacking *secA2* (236) and *nuoG* (237) were attenuated *in vivo*, and mice infected with these strains displayed enhanced priming of adaptive immunity compared to infection with wild-type *M. tuberculosis*, suggesting that prevention of host cell apoptosis is an *M. tuberculosis* virulence strategy. Relatedly, *M. tuberculosis*-infected murine neutrophils can aid in DC trafficking to the draining lymph nodes to initiate antigen-specific CD4 T-cell responses (238), but *M. tuberculosis* delays CD4 T-cell priming by inhibiting neutrophil apoptosis (239). Infection with the proapoptotic *nuoG* mutant *M. tuberculosis* resulted in earlier DC trafficking to lung-draining lymph nodes and earlier priming of antigen-specific CD4 T cells, but enhanced priming was abrogated upon neutrophil depletion (239). Additionally, uninfected macrophages performing a constitutive housekeeping function called efferocytosis can uptake *M. tuberculosis*-containing apoptotic bodies, which leads to delivery and killing of bacteria in lysosomes (240). This suggests that apoptosis may be a host strategy to limit bacterial replication by sequestering bacteria in vesicles that can be safely degraded by nearby innate immune cells. Inhibition of apoptosis by *M. tuberculosis* is driven by host intrinsic factors following infection with virulent strains. The proinflammatory eicosanoid PGE2 has been demonstrated to regulate synaptotagmin-7, a calcium sensor that maintains plasma membrane integrity (241). Human macrophages infected with virulent *M. tuberculosis* H37Rv, but not avirulent H37Ra, promote LXA4 production and inhibition of PGE2 biosynthesis, which impairs resealing of plasma membrane disruptions to preferentially induce host cell necrosis instead of apoptosis (241). Mice lacking PGE2 also suffered from increased lung bacterial burden following low-dose aerosol infection with virulent *M. tuberculosis* (223). Host cell necrosis following *M. tuberculosis* infection can be induced through activation of the cytosolic receptor interacting protein kinase 3 pathway, which inhibits apoptosis of infected macrophages through Bcl-xL and promotes necrosis through upregulation of ROS (242). Additionally, macrophages infected with virulent H37Rv, but not avirulent H37Ra, undergo proteolysis at the N-terminal of annexin-1, which prevents the completion of the apoptotic envelope and drives macrophage necrosis (235). Taken together, apoptosis represents a strategy by the host to limit infection through the combination of bacterial sequestration in apoptotic vesicles and the induction of adaptive immune responses, but *M. tuberculosis* may delay apoptosis or promote necrosis to facilitate replication and dissemination.

Initiation of Adaptive Immunity to *M. tuberculosis* by DCs

An important function of innate immunity during *M. tuberculosis* infection is the priming of adaptive immune responses. DCs are professional antigen-presenting cells that initiate adaptive immunity by presenting *M. tuberculosis* antigens in the context of major histocompatibility complex (MHC), costimulatory molecules, and cytokines. Depletion of cells expressing the pan-DC marker, CD11c, following *M. tuberculosis* infection impaired control of bacterial burden and delayed the initiation of adaptive immunity, illustrating the importance of DCs in mobilizing adaptive immune responses that can control bacterial replication (243). There is abundant evidence that *M. tuberculosis* is able to infect murine (244–246) and human DCs (247–249). In mice infected with green fluorescent protein GFP-expressing *M. tuberculosis*, DCs were found to be the major population of phagocytes infected by bacteria after 4 weeks (246). Upon *M. tuberculosis* infection, DCs mature and migrate to the lung-draining lymph nodes to initiate antigen-specific T-cell responses, which depended on the chemokine receptor CCR7 and its corresponding chemokines CCL19 and CCL21 (250–252). Further, IL-12, a cytokine secreted by myeloid cells and important for the induction of IFN-γ responses, is required for DC migration during *M. tuberculosis* infection (253). Priming of adaptive immune responses requires the transport of live bacteria to the lung-draining lymph nodes (246, 250), but antigen-specific T cells can be primed by both the infected migratory DC and uninfected lymph node resident DC. A study demonstrated that infected DCs migrate to the lung-draining lymph nodes, where they secrete soluble, unprocessed *M. tuberculosis* antigens that are summarily

phagocytosed by uninfected lymph node resident DCs (254). The exportation of *M. tuberculosis* antigens was initially proposed to benefit the host by circumventing inefficient antigen presentation by infected DCs. However, secretion of *M. tuberculosis* antigens by infected DCs may also benefit the pathogen by diverting antigen away from MHC class II antigen presentation (255).

Effective interaction between DCs and T cells is dependent on appropriate function of antigen presentation machinery, including expression of MHC, costimulatory molecules, and cytokines following *M. tuberculosis* infection. However, there is abundant evidence that *M. tuberculosis* infection impairs antigen presentation to evade antigen-specific T-cell responses. It is well recognized that *M. tuberculosis* infection leads to impaired MHC class II antigen presentation by macrophages (reviewed in 256). *M. tuberculosis*-mediated inhibition of phagosomal maturation has been implicated in attenuating processing of *M. tuberculosis* antigen 85 (Ag85) and the MHC class II-associated invariant chain (257). Multiple studies have also reported that *M. tuberculosis* infection impairs MHC class II expression in macrophages through inhibition of class II transactivator, a master transcriptional regulator controlling expression of MHC class II molecules (258–261), although there is little evidence of similar inhibition of MHC class II in DCs. Nevertheless, *M. tuberculosis* infection of DCs leads to functional impairment of antigen presentation. *M. tuberculosis* infection has been shown to impair DC maturation of human (reviewed in 262) and murine DC functions (reviewed in 263, 264). Studies examining proliferation of T-cell receptor transgenic CD4 T cells specific for *M. tuberculosis* Ag85 as a proxy for functional antigen presentation have demonstrated that *M. tuberculosis* EsxH can impair antigen processing through inhibition of the host endosomal sorting complex required for transport (ESCRT) (265). Additionally, *M. tuberculosis* promotes suboptimal antigen presentation *in vitro* and *in vivo* without detectable differences in the expression levels of costimulatory molecules when compared to BCG-infected DCs (266). Interestingly, studies using a mutant *M. tuberculosis* strain lacking *hip1* (discussed above) indicate that *M. tuberculosis* readily impairs DC costimulation and cytokine production to evade antigen-specific CD4 T-cell responses (107, 109), and a recent study demonstrated that BCG *hip1* retains similar immune evasion functions (267). Taken together, the initiation of the adaptive immune response requires the participation of DCs, which themselves are readily infected and subverted by *M. tuberculosis* infection. *M. tuberculosis* subversion of DC functions can interfere with antigen presentation and delay or impair the initiation of the adaptive immune response. Improving DC functions during *M. tuberculosis* infection may improve innate and adaptive immunity and enhance immune control of bacterial burden. A study that exogenously engaged the CD40 costimulation pathway in *M. tuberculosis*-infected DCs improved DC functions and promoted antigen-specific CD4 T-cell responses that augmented control of lung bacterial burden (268). Further, mucosal transfer of Ag85B-loaded DCs following challenge with *M. tuberculosis* augmented the efficacy of BCG vaccination (269), suggesting that early antigen presentation by DCs is an important component that determines the efficacy of vaccine-induced immunity. DCs are critical players that initiate adaptive immune responses to *M. tuberculosis* and determine the outcome of infection. Interventions or therapies that improve DC functions may provide benefits by augmenting cross talk between DCs and antigen-specific T cells.

ADAPTIVE IMMUNITY AGAINST *M. TUBERCULOSIS*

Protective immunity to *M. tuberculosis* and control of bacterial replication requires adaptive immune responses. This is best exemplified by the extreme susceptibility to mycobacterial infections of lymphopenic HIV patients and gene-deleted mice lacking MHC class II or T cells in general. Cytokine secretion and direct antimicrobial actions of antigen-specific T cells are key features of the adaptive immune response against *M. tuberculosis* infection. Further, the long-lived nature of antigen-specific memory T cells provides the basis for developing vaccines that induce antimycobacterial immunity. There are also expanding roles for B cells, γδ T cells, and CD1-restricted T cells that provide specific responses to a diverse set of *M. tuberculosis* antigens that complement antigens classically presented through MHC class I and II. However, adaptive immune responses can also become malignant by promoting excessive inflammation or be rendered ineffective from chronic antigen exposure. Here, we cover the importance of timing, location, and quality of CD4 T-cell responses during *M. tuberculosis* infection, how CD8 T cells contribute to immunity against *M. tuberculosis*, the roles that inhibitory receptors play during infection, the phenotypes and functions of memory T cells, and the roles that B cells, γδ T cells, CD1-restricted lymphocytes, and mucosal associated invariant T (MAIT) cells play in immunity against *M. tuberculosis*.

Kinetics and Homing of CD4 T Cells after *M. tuberculosis* Infection

In the mouse model of infection, CD4 T-cell responses are absolutely required to control bacterial replication, and animals lacking such responses succumb rapidly (270, 271). MHC class II knockout mice or CD4 depletion led to abrupt mortality following *M. tuberculosis* infection (270, 271). CD8 T cells play a key role in immunity against *M. tuberculosis* but cannot compensate for CD4 deficiency (270). Similarly, antibody depletion of CD4 in cynomolgus macaques severely compromised control of *M. tuberculosis* and led to reactivation in latently infected animals (69). Thus, the initiation of the CD4 T-cell response is a key feature defining the outcome of *M. tuberculosis* infection. There is a widely recognized delay in the initiation of antigen-specific CD4 T-cell responses following low-dose aerosol infection of mice (250, 272–275) and NHPs (276). *M. tuberculosis*-infected cynomolgus macaques had detectable antigen-specific responses 4 weeks postinfection (276). In mouse models of infection, antigen-specific CD4 T-cell responses are first detected in the lung-draining lymph nodes 2 weeks after infection. Significant antigen-specific lung CD4 T-cell responses are subsequently detected in the lungs 3 weeks after infection. This is in stark contrast to antigen-specific responses to other bacterial (277) or viral (278) pathogens, which are detected swiftly after infection. Adoptive transfer of ESAT-6-specific CD4 T cells prior to aerosol *M. tuberculosis* infection have demonstrated an apparent kinetic bottleneck whereby lung antigen-specific activation occurs only 7 days after infection despite the presence of antigen-specific T cells (279), suggesting that antigen-specific responses are delayed by mechanisms other than trafficking of CD4 T cells from the mediastinal lymph nodes to the lungs. Delay in the initiation of adaptive immune responses to *M. tuberculosis* infection may be due to a variety of factors, including slow growth of the bacterium, inhibited apoptosis of infected macrophages and neutrophils, and delayed activation and migration of DCs, which cumulatively allow *M. tuberculosis* to establish a persistent infection in the lung.

CD4 T cells interact with infected macrophages to restrict intracellular *M. tuberculosis* replication. Thus, the effectiveness of the CD4 T-cell response depends on proper homing of antigen-specific CD4 T cells from lymphoid tissues to *M. tuberculosis*-infected cells in the lung. In *M. tuberculosis*-infected mice, antigen-specific CD4 T cells expressing CXCR3 localized to the lung parenchyma and were more efficient at controlling bacteria following *M. tuberculosis* infection when compared to vasculature-restricted CD4 T cells that expressed CX3CR1 (280). Interestingly, cells retained in the lung vasculature secreted the highest amount of IFN-γ during infection (280). Adoptive transfer studies demonstrated that IFN-γ accounted for greater control of bacterial burden in the spleen over the lung and drove immunopathology when overexpressed (281), suggesting that the function of IFN-γ may be to mediate control of bacterial dissemination to extrapulmonary sites and that IFN-γ may be detrimental when unrestrained. The distinction between vasculature-restricted and parenchyma-localizing CD4 T cells seems less important in rhesus macaques (282), where the majority of antigen-specific CD4 T cells can be found in the lung parenchyma but are restricted to the outer lymphocytic cuff of granulomas. Notably, studies have demonstrated that expression of IDO by cells in the granulomas of *M. tuberculosis*-infected rhesus macaques can mediate inhibition of T cell entrance into granuloma, and biochemical inhibition of IDO led to reorganization of the granuloma to include T cells localizing into the macrophage core (66, 283). Taken together, there is strong evidence that localization of antigen-specific CD4 T cells into the lung tissues where *M. tuberculosis*-infected myeloid cells reside is an important feature of protective immunity to *M. tuberculosis*.

Quality and Specificity of the CD4 T-Cell Response to *M. tuberculosis*

The quality of the T-cell response is an important feature determining the outcome of *M. tuberculosis* infection. Canonically, the production of IFN-γ by Th1 cells, CD8 T cells, and other lymphocytes is considered essential for protection against mycobacterial infections. In human immunogenetics studies, Mendelian susceptibility to mycobacterial disease (MSMD) is a spectrum of genetic mutations in five autosomal genes (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB*) and an X-linked gene that confer susceptibility to avirulent environmental mycobacteria and BCG (284). Deficiencies related to IFN-γ signaling in young patients with mutations in *IFNGR1* and *IFNGR2* confer fatal susceptibility to mycobacterial infections (285–288). STAT1 is an intracellular molecule important for IFN-γ signaling, and individuals with heterozygous germline *STAT1* mutations lose gamma-interferon activating factor (GAF) expression (289). GAF is an important transcription factor that facilitates IFN-γ-induced gene expression. Individuals with heterozygous *STAT1* mutations have impaired nuclear accumulation of GAF and suffer from recurrent mycobacterial infections (289). Additionally, mutations affecting IL-12 expression levels and signaling

also confer susceptibility to mycobacterial infections. Two mutations in the leucine zipper domain of NEMO, an intracellular protein involved in NF-κB activation, impairs CD40-mediated IL-12 production in monocytes and DCs (290) and leads to recurrent mycobacterial infections. Similarly, defects that impair IL-12p40 lead to decreased IFN-γ levels and confer susceptibility to mycobacterial infections (291–294). Mutations in *IL12RB* are the most frequent genetic factors associated with Mendelian susceptibility to mycobacterial disease, but recurrent mycobacterial susceptibility in individuals with *IL12RB* mutations can be mitigated with BCG vaccination or primary BCG disease (291, 292, 295–298), suggesting that IL-12/IL-23 signaling may not be completely required for secondary immunity. IFN-γ is readily detected in human BAL in patients with TB disease and decreases following therapy (299), which is likely a consequence of decreasing bacterial loads. In contrast, studies of human peripheral blood mononuclear cells show a decrease in IFN-γ responses in ATB patients compared to controls (300–305). Lower frequencies of *M. tuberculosis*-specific IFN-γ responses in ATB patients may reflect trafficking of these cells to the lungs, resulting in specific depletion from the periphery. IFN-γ secretion is also an important tool leveraged for the detection of *M. tuberculosis*-specific CD4 T-cell responses in humans and in animal models. Genome-wide analysis of *M. tuberculosis*-specific CD4 T-cell epitopes in LTBI individuals revealed three broadly immunodominant antigenic islands related to bacterial secretion systems recognized by IFN-γ secreting CD4 T cells (306). Animal models of TB also demonstrate a key role for IFN-γ in immunity against *M. tuberculosis* infection. Mice deficient in IFN-γ succumb to low-dose *M. tuberculosis* infection (307, 308). Correspondingly, mice lacking IL-12 are also unable to control *M. tuberculosis* infection (253, 309, 310). The antimycobacterial effects of IFN-γ in mouse models are broadly related to the induction of AMPs, iNOS, and cytokines that activate infected macrophages to restrict intracellular bacterial replication, though other mechanisms underlying IFN-γ-mediated immunity to *M. tuberculosis* infection are still being elucidated. IL-10-deficient mice are less susceptible to *M. tuberculosis* infection due to an enhanced Th1 response (311), suggesting that IL-10 limits Th1 immunity during *M. tuberculosis* infection. However, Th1 cells secreting IL-10 can also impair host control of *M. tuberculosis* infection (312), and CD4 T cells producing both IFN-γ and IL-10 are detected in the BAL of ATB patients (313). Given that IL-10 secretion by Th1 cells has been shown to be a result of high antigen dose (314), it is possible that adaptive immunity at stages of infection when bacterial burden is high may be compromised by T cell-derived IL-10. T-bet is a member of the T-box family of transcription factors that is encoded by *Tbx21* and is the master transcriptional regulator for lineage commitment to the Th1 subset (315). Interestingly, adoptive transfer of T-bet knockout ESAT-6-specific T-cell receptor-transgenic CD4 T cells skewed toward Th1 *in vitro* retains the capacity for early protection against *M. tuberculosis* infection (316), suggesting that protection conferred by Th1 cells may be independent of T-bet or IFN-γ production. Taken together, these studies demonstrate a clear requirement for the IL-12/IFN-γ axis in immunity against *M. tuberculosis* infection in humans and animal models. Further studies delineating the mechanisms underlying IFN-γ- and Th1-mediated immunity against *M. tuberculosis* are warranted.

Although Th1 responses are important for immunity against TB, studies have also demonstrated that CD4 T-cell subsets secreting IL-17 (Th17) and FoxP3+ regulatory CD4 T cells contribute to the response against *M. tuberculosis* infection. There are context-dependent beneficial or detrimental roles for Th17s during infection with *M. tuberculosis*. Infection with a W-Beijing lineage strain of *M. tuberculosis*, HN878, induce Th17 responses, and mice deficient in IL-17 display increased bacterial burden following infection (317). IL-17 receptor A subunit knockout mice (318) and IL-17A knockout mice (319) also displayed impaired long-term control of high-dose infection with H37Rv. Transfer of BCG-specific, IFN-γ knockout Th17 cells into *M. tuberculosis* infected, T cell-deficient mice conferred enhanced protection and prolonged survival compared to transfer of naive IFN-γ knockout CD4 T cells (320), suggesting that Th17 cells can mediate protection independently of IFN-γ. In humans, significant frequencies of IL-17-producing CD4 T cells were found in the peripheral blood mononuclear cells and BAL of BCG-vaccinated healthy individuals and declined in patients with active disease (321). Further, individuals with bi-allelic *RORC* loss-of-function mutations displayed impaired IL-17 and IFN-γ responses and were susceptible to mycobacterial disease and candidiasis (322). The generation of Th17 responses to *M. tuberculosis in vitro* requires costimulation through the CD40-CD40L pathway since the absence of CD40 on DCs or CD40L on CD4 T cells attenuates antigen-specific IL-17 responses (268). Activation of *M. tuberculosis*-infected DCs through CD40 promoted enhanced antigen-specific Th1 and Th17 responses that contributed to better control of bacterial burden *in vivo* (268), suggesting that a balanced Th1

and Th17 response is desirable for immunity against *M. tuberculosis*. The precise role of Th17 cells in protective immunity to *M. tuberculosis* remains unclear but may be related to their role in the development of less hypoxic granulomas (323), in the recruitment of Th1 cells (324), or in the induction of CXC-chemokines and B-cell follicles (325). However, unrestrained IL-17 responses have also been shown to promote detrimental immunopathology, typically through pathological neutrophilia. IFN-γR1 knockout animals (326) or IFN-γR1 bone marrow chimeric mice selectively lacking the receptor in nonhematopoietic cells (327) display amplified Th17 responses following *M. tuberculosis* infection that lead to a pathogenic accumulation of neutrophils detrimental to the host, suggesting that IFN-γ signaling serves a regulatory role by limiting excessive IL-17-mediated neutrophilia.

FoxP3+ CD4 T cells, or T-regulatory cells (T-regs), can impair antimycobacterial T-cell responses and contribute to disease but can also limit overt inflammation. FoxP3+ T-regs can be found in the peripheral blood and airways of *M. tuberculosis*-infected macaques (328) and humans (329–334). In mice, T-regs accumulate in the lung-draining lymph nodes and the lungs following low-dose aerosol *M. tuberculosis* infection (335). Importantly, FoxP3+ T-regs localized to pulmonary areas adjacent to effector CD4 T cells and depletion of T-regs before and early after infection-enhanced control of bacterial burden (335). Further, *M. tuberculosis*-specific T-regs delay the expansion of antimycobacterial CD4 and CD8 T cells and, consequently, transfer of *M. tuberculosis*-specific T-regs confers increased susceptibility to infection (336). Regulation of T-regs during *M. tuberculosis* infection may be mediated by Th1 responses since *M. tuberculosis*-specific T-regs are selectively eliminated following IL-12 driven T-bet expression (337). The functional properties of T-regs responsible for limiting antimycobacterial CD4 and CD8 responses remains unclear. IL-10 was not found to be secreted by T-regs in mice infected with H37Rv (335). In contrast, T-regs from mice infected with the W-Beijing strain, HN878, were found to secrete IL-10, express inhibitory receptors, and expand to greater degrees compared to infection with H37Rv (209), suggesting that IL-10 secretion by T-regs may be dependent on bacterial strain. Notably, the expansion of T-regs in the lungs of mice and outbred guinea pigs infected with W-Beijing strains occurred concurrently with a loss of Th1 responses and is associated with severe pulmonary pathology (209, 338). However, progressive loss of T-regs in chronically infected TLR-2 knockout mice was associated with increased pulmonary inflammation (339), highlighting a role for TLR-2-mediated recruitment of T-regs in limiting tissue pathology at chronic stages of disease. Taken together, these results suggest that the functional contribution of T-regs to immunity against *M. tuberculosis* infection and outcome of disease may be dependent on multiple factors, including strain of bacteria and stage of infection.

In humans and animal models, *M. tuberculosis* establishes a persistent infection despite the induction of adaptive immune responses. Persistent inflammation and chronic antigen exposure precedes functional exhaustion due to chronic antigenic stimulation. In contrast to the expression of Ag85B, which decreases early following infection, ESAT-6 is expressed by *M. tuberculosis* throughout infection (340, 341). Multiple studies examining CD4 T-cell responses to ESAT-6 and Ag85B have suggested that antigen-specific responses are dictated by bacterial expression of those antigens throughout infection. CD4 T cells specific for ESAT-6 display a terminally differentiated phenotype with evidence for functional exhaustion, which runs in contrast to Ag85B-specific CD4 T cells that appear functional but are quickly diminished (272, 342–347). Indeed, a vaccine that contains ESAT-6, Ag85B, and Rv2660c, which is expressed at late stages of infection, demonstrated enhanced efficacy compared to BCG or to a vaccine containing ESAT-6 and Ag85B (348), suggesting that rational incorporation of antigens present at different stages of infection may improve vaccine efficacy. A clearer understanding of protective CD4 T-cell immunity will require further studies of the spectrum of antigens recognized by CD4 T cells following infection with *M. tuberculosis* in animal models and in humans.

Role of CD8 T Cells in *M. tuberculosis* Infection

Mice with gene deletion of β2 microglobulin, which abrogates MHC class I antigen presentation, or mice depleted of CD8 T cells live longer than corresponding disruptions to the MHC class II pathway or CD4 T-cell responses following *M. tuberculosis* infection (270). Regardless, CD8 T cells contribute significantly to immunity against *M. tuberculosis* infection. Mice lacking TAP-1 (transporter associated with antigen processing 1) antigen presentation molecules have deficient CD8 T-cell responses and succumb more rapidly following *M. tuberculosis* infection compared to wild-type controls (349, 350). Depletion of CD8 T cells in rhesus macaques compromises protective immunity from BCG vaccination or chemotherapeutic interventions (57), suggesting that CD8 T cells are important components of recall responses to *M. tuberculosis* infection. Similarly,

in a mouse model of latency induced by antibiotic treatment, CD8 T-cell responses were found to be important in preventing reactivation (351). The importance of CD8 T cells during *M. tuberculosis* infection is related to their secretion of cytokines and cytolytic effector molecules that can limit bacterial replication. In addition to IFN-γ and TNF-α, CD8 T cells secrete perforin to lyse *M. tuberculosis*-infected macrophages (352). CD8 T cells can also release granulysin in cytotoxic granules to directly kill intracellular *M. tuberculosis* (353, 354). The use of anti-TNF-α therapy in patients with rheumatoid arthritis depletes a subset of effector memory CD8 T cells that secrete granulysin and express cell surface TNF (355), which may partially explain the increased progression from LTBI to ATB in patients undergoing anti-TNF-α therapy. Human CD8 T cells respond to epitopes in CFP10 (356), ESAT-6 (357, 358), and the Ag85 complex (359, 360). A variety of human CD8 T-cell clones tested against a panel of synthetic peptides derived from immunodominant *M. tuberculosis* antigens revealed that CD8 T-cell responses are concentrated toward a limited set of epitopes and are generally restricted by the HLA-B allele (361, 362). *M. tuberculosis* escape from the phagosome and induction of apoptosis by *M. tuberculosis*-infected macrophages can promote cross-presentation of *M. tuberculosis* antigens to CD8 T cells. However, as previously discussed, virulent *M. tuberculosis* has been shown to inhibit host apoptosis and favor necrosis to circumvent efficient induction of CD8 T-cell responses. All considered, CD8 T cells are a critical component of adaptive immunity to *M. tuberculosis* infection and play an important role in different disease contexts by limiting reactivation during latency and by directly participating in antimicrobial functions during active infections.

Inhibitory Receptors During *M. tuberculosis* Infection

Chronic viral infections, such as HIV, induce the expression of coinhibitory receptors on the surface of T cells that can dampen T-cell functionality. Abrogation of coinhibitory receptor ligation has been shown to be a viable strategy to revitalize functionally exhausted virus-specific T-cell responses. The evidence for the importance of coinhibitory receptors during *M. tuberculosis* infection in animal models and in human samples varies between human and small animal models and between the specific inhibitory receptor studied. PD-1, CD160, and 2B4 are inhibitory receptors associated with CD8 T-cell dysfunction in chronic viral infections (363, 364) but are expressed at low levels on *M. tuberculosis*-specific CD8 T cells (365). Expression of inhibitory molecules, including PD-1 and CTLA-4, among *M. tuberculosis*-specific CD4 T cells has been shown to decrease following treatment (366, 367). Importantly, expression of PD-1 on antigen-specific CD4 T cells from LTBI was not associated with decreased effector functions, and these cells proved to be polyfunctional with respect to cytokine production upon antigen restimulation (368), suggesting that PD-1 may be an indicator of bacterial burden and CD4 T-cell activation rather than functional exhaustion. However, there is some *in vitro* evidence from human samples suggesting that blockade of PD-1/PD-L1 interaction can prevent *M. tuberculosis*-specific CD4 T-cell apoptosis (369) and enhance CD8 T-cell degranulation and antigen-specific IFN-γ responses from the peripheral blood mononuclear cells of a subset of high-responding ATB patients (370). There is evidence that T-cell responses during ATB disease are less polyfunctional and have limited proliferative capacity compared to LTBI individuals (371, 372), but whether this functional impairment is mediated by inhibitory receptors such as PD-1 remains unclear. PD-1-deficient mice infected with *M. tuberculosis* have increased bacterial burden, neutrophilic infiltration, overt inflammation, tissue necrosis, and diminished lifespan compared to wild-type mice (373), suggesting that PD-1 is required to prevent aberrant inflammation during *M. tuberculosis* infection. Further, adoptive transfer studies demonstrated that PD-1-expressing CD4 T cells are highly proliferative (342, 346), and CD4 T cells lacking PD-1 can drive pathology and mortality following *M. tuberculosis* infection (374), together suggesting that PD-1 may mark functional CD4 T cells with intrinsic capacity for immunoregulation. T-cell immunoglobulin and mucin domain-containing 3 (Tim-3) is another inhibitory receptor shown to play a role in mediating antimicrobial responses by binding to one of its ligands, galectin-9 (375), and inducing the production of IL-1β by human and murine macrophages infected with *M. tuberculosis* (375, 376). In contrast to PD-1, Tim-3-deficient mice were less susceptible to *M. tuberculosis* infection, and Tim-3 blockade was shown to improve antigen-specific CD4 and CD8 T-cell cytokine expression (377), suggesting that Tim-3 may play a role in limiting T-cell responses by promoting functional exhaustion. However, Tim-3-expressing, *M. tuberculosis*-specific T cells from ATB patients were functionally superior to T cells expressing low levels of Tim-3. Further, small interfering RNA- or antibody-mediated disruption of Tim-3 signaling on the T cells from ATB patients led to attenuated IFN-γ and TNF-α production by Tim-3-expressing T cells, while Tim-3 ligation augmented IFN-γ production (378). The

mechanisms underlying the roles of receptors such as PD-1 and Tim-3 require further study and may deviate from their role in viral immunity. The evidence accumulated thus far suggests that these molecules mark functional T cells that play important roles in antimicrobial activity and prevention of uncontrolled inflammation following *M. tuberculosis* infection.

Memory T-Cell Responses

In humans, antigen-specific memory T-cell responses have been detected in individuals with LTBI and in TB patients following successful treatment and cure. Memory T-cell subsets can be identified according to their cell surface phenotype and functional properties, and distinct populations of antigen-specific memory T cells can be categorized based on their expression of a panel of cell surface activation markers and chemokine receptors (379). Characterization of *M. tuberculosis*-specific memory CD4 T cells in LTBI indicated that these cells did not express activation markers and were largely of a CD45RA-CCR7 phenotype descriptive of T effector memory cells (368, 380). In contrast, analysis of LTBI individuals using MHC class II tetramers revealed a population of tetramer+CD45RA-CCR7+ central memory CD4 T cells that further expressed CXCR3+CCR6+ (306), highlighting the heterogeneity of memory CD4 T-cell phenotypes that can vary based on antigen specificity, disease status, and manner in which specific responses are identified. Human memory CD8 T cells are predominantly terminally differentiated effector memory T cells in individuals with LTBI (365, 381). Memory T-cell responses have also been studied in the context of "memory-immune" mice, which are *M. tuberculosis*-infected mice that subsequently receive antibiotic treatment. In this context, both memory CD4 (382, 383) and CD8 (384, 385) T cells play a role in immunity against *M. tuberculosis* infection. T cells from memory-immune mice expanded rapidly, secreted IFN-γ, and conferred a significant level of protection at early timepoints after infection (383, 386–388) but are ultimately unable to confer long-term protection (389), suggesting that memory T cells generated after primary *M. tuberculosis* infection have limited capacity to protect from reinfection.

B-Cell and Antibody Responses During *M. tuberculosis* Infection

There is a body of evidence suggesting that humoral immunity plays a role in defense against *M. tuberculosis* infection (reviewed in 390). B cells can be found alongside T cells in the lymphocytic cuff in human granulomas (391–393), and whole blood gene expression analysis revealed significant changes in B-cell-associated genes in TB patients after initiation of TB treatment (394). Notably, antibodies to *M. tuberculosis* proteins have been reported in the sera of TB patients (395), and antibodies identified in a subset of health care workers exposed to *M. tuberculosis* provide modest protection *in vitro* and in a mouse model of infection (396). Utilization of a high-throughput approach to identifying antibody targets in the *M. tuberculosis* proteome revealed a set of extracellular antigens recognized by antibodies in the plasma of patients with ATB (397), suggesting that B cells are active participants in immunity to *M. tuberculosis* infection. B-cell-deficient mice have elevated neutrophilic recruitment and exacerbated lung immunopathology following *M. tuberculosis* infection (398), which is mediated through enhanced IL-17 responses in *M. tuberculosis*-infected B-cell-deficient or B-cell-depleted animals (399). These studies suggest that B cells can influence the outcome of *M. tuberculosis* infection by moderating inflammatory responses. Antibody production by B cells can promote divergent outcomes (400). Binding of antibody to the inhibitory Fc gamma receptor II B attenuates macrophage IL-12 production and negatively impacts Th1 responses (401), while passive transfer of monoclonal antibodies specific for *M. tuberculosis* cell wall components can improve the outcome of infection in mice (390). B-cell secretion of cytokines can also influence *M. tuberculosis*-infected macrophages. Type I IFN expression by murine B cells and B cells from pleural effusion of TB patients altered macrophage polarization toward an anti-inflammatory phenotype (402). Taken together, these studies highlight a role for B cells, which constitute a significant population of lymphocytes around lung granulomas in the adaptive immune response to *M. tuberculosis* infection by modulating inflammation through the secretion of antibodies and cytokines.

γδ, CD1-Restricted T Cells, and MAIT Cells in Immunity against *M. tuberculosis*

γδ T cells are a population of T cells that express a restricted repertoire of T-cell receptor genes, recognize nonpeptide antigens such as microbial metabolites and phosphoantigens (403), and can be found at mucosal surfaces including the lung (404). γδ T cells proliferate when exposed to *M. tuberculosis*-infected monocytes (405). Multiple *M. tuberculosis* metabolites, including pyrophosphate, prenyl pyrophosphate derivatives (406, 407), and triphosphorylated thymidine-containing compounds (408), are recognized by human γδ T cells. Human γδ T cells can also respond to mycobacterial

heat shock proteins (409), though this response may be dependent on BCG immunization (410). Vγ9Vδ2-expressing γδ T cells represent a significant proportion of *M. tuberculosis*-reactive T cells in peripheral blood (411–413) and can restrict intracellular *M. tuberculosis* replication in macrophages (414). Interestingly, Vγ9Vδ2 T cells can function as antigen presentation cells via provision of CD40 costimulation to promote the expansion of αβ T cells with enhanced capacity to restrict intracellular BCG replication (415). Additionally, human Vγ2Vδ2 T cells recognize *M. tuberculosis* (416), and in NHPs, Vγ2Vδ2 T cells are expanded by phosphoantigen and IL-2 administration (417). Adoptively transferred Vγ2Vδ2 T cells into naive animals confer protection against *M. tuberculosis* infection (418). γδ T cells have been shown to mediate direct killing of *M. tuberculosis* via secretion of granulysin and perforin (419) or through the induction of TNF-α by monocytes (420). There is also evidence that γδ T cells can influence DC cross talk with T cells by promoting DC maturation and expression of costimulatory molecules (421). In mice, γδ T cells accumulate in the lung-draining lymph nodes, are responsive to *M. tuberculosis* antigen independent of MHC class II (422), and are significant sources of early IL-17 production following *M. tuberculosis* infection (423).

Due to the large repertoire of glycolipids present on the mycobacterial cell wall, a significant T-cell response is directed at glycolipid antigens presented by the CD1 family of molecules. CD1 molecules are a family of MHC class I-like antigen presentation molecules that present glycolipid antigens to T cells. There are five CD1 family members in humans, split into two groups based on sequence homology. Group 1 molecules include CD1a, CD1b, CD1c, and CD1e. CD1d is the sole inclusion in group 2 (424). Mycobacterial lipids are readily presented by CD1 molecules in human cells, but mechanistic studies of this family of molecules is limited because mice only express two orthologs of CD1d and do not express group 1 molecules. Nevertheless, studies in human cells revealed that mycobacterial lipids presented by group 1 CD1 molecules promote T-cell proliferation and cytokine production (425–432). Mycobacterial glycerol monomycolate, glucose monomycolate, sulphoglycolipids, and mycolic acid can be presented through CD1b (426–428, 433). CD1b-restricted T cells expand and secrete IFN-γ and IL-2 upon interaction with cognate antigen and contract following anti-TB therapy (430). Interestingly, use of CD1b tetramers loaded with glucose monomycolate revealed that CD1b-restricted T cells are antigen-specific and also express CD4 (429, 434). *M. tuberculosis* lipids presented through CD1a and CD1c have also been identified. A family of *M. tuberculosis* lipopeptides called didehydroxymycobactins are presented by CD1a (435), and a variety of phospholipid antigens are presented by CD1c (425). The precise role of CD1-restricted T cells in immunity during *M. tuberculosis* infection remains unclear, and further studies of their function in the periphery and especially in BAL would inform their potential as targets for TB vaccines.

MAIT cells are a subset of T cells with innate-like qualities enriched in mucosal tissues, including the intestinal mucosa, lung, and liver (436–438). These cells recognize antigen through a nonpolymorphic MHC class I-related molecule 1 (439) presenting pterin-containing byproducts of riboflavin synthesis in bacteria and fungi (440). In humans, MAIT cells express a semi-invariant Vα7.2 and CD161 and can either be double negative for CD4 and CD8 or CD4-CD8+ (436, 441). MAIT cells have been described in the peripheral blood of healthy individuals and are depleted in ATB patients (442), possibly reflecting migration into the lung. These cells produce IFN-γ and TNF-α upon activation (442, 443), but their contribution to the immune response to *M. tuberculosis* infection requires further study.

INITIATION AND HETEROGENEITY OF THE GRANULOMA

The granuloma is a hallmark histopathological structure in TB. It represents host sequestration of bacteria to limit dissemination as well as a niche for long-term persistence of *M. tuberculosis*. Further, the selectively drug-permeable nature of the TB granuloma can diminish the efficacy of drugs meant to treat persistent bacteria (444). The granuloma is composed of an aggregate of *M. tuberculosis*-infected and -uninfected macrophages in varying stages of maturation and differentiation (445–447). Macrophages in the granuloma can undergo an epithelioid transformation, become lipid-filled foamy macrophages, or merge into multinucleated giant cells. This central core of macrophages is accompanied by neutrophils, DCs, and fibroblasts circumscribed by T and B lymphocytes and progressively becomes a hypoxic environment where many cells undergo necrotic death to form an acellular core termed the caseum (448). The granuloma is a hallmark structure in human TB that is modeled variably among available animal models. C57BL/6 and BALB/C mice do not naturally recapitulate the human granuloma in that lung lesions are rarely necrotic and caseating. The animal models that most closely recapitulate the heterogeneity of human granulomas include certain susceptible inbred mouse strains

that present with necrotizing granulomas (C3HeB/FeJ, DBA/2, CBA/J, I/St), guinea pigs, rabbits, and the NHP model. Additionally, the zebrafish model has also yielded fundamental insights into the initiation and dynamics of the tuberculous granuloma.

The transparency of zebrafish larvae has made direct visualization of the initiation of the granuloma possible following infection with *M. marinum* (48). Studies based on this model have revealed that the innate immune response is sufficient to initiate the granuloma following infection. Recruitment of additional macrophages mediated, in part, by mycobacterial ESX-1 proteins initiates a cascade of events that leads to the establishment of the mycobacterial granuloma (221, 449). Importantly, recruited macrophages can traffic through the initial granuloma to phagocytose apoptotic infected macrophages and egress to form distal secondary granulomas (450). Mycobacterial lipids play a key role in establishing the granuloma by limiting macrophage effector functions and promoting the recruitment of additional macrophages to facilitate dissemination. In particular, mycobacterial phthiocerol dimycocerosate can mask TLR-signaling and prevent induction of nitrosative stresses (451), and mycobacterial PGL can induce macrophage production of CCL2 to recruit CCR2+ monocytes that permit bacterial dissemination (452). These studies collectively indicate that the initiation of the mycobacterial granuloma is dependent on recruitment of bacteria-permissive macrophages and monocytes following initial infection and can be mediated by mycobacterial secreted factors and membrane lipids.

TB granulomas can vary in their cellular composition, oxygenation levels, inflammatory milieu, and bacterial burden. This heterogeneity can exist between and within infected hosts. Infection of cynomolgus macaques with a panel of *M. tuberculosis* isolates that differed by a single nucleotide polymorphism revealed that individual granulomas can be founded by a single bacterium and can vary in their bacterial burden compared to other granulomas within the same host (51). Analysis of T-cell functionality between sterile and nonsterile granulomas revealed a modest association between IL-10 and IL-17 responses and clearance of *M. tuberculosis* in sterile granulomas (453). However, in the context of TNF-α neutralization in latently infected macaques, IL-10 and IL-17 responses were associated with animals at higher risk of reactivation (71). Proteome analysis of laser-capture microdissected human and rabbit lung lesions suggests that inflammatory responses typical of the center of the TB granuloma are physically segregated from anti-inflammatory responses in adjacent lung tissue (454). T-cell functionality in the granuloma may therefore be a function of disease status and proximity to the bacteria-containing, hypoxic, and necrotic core of the TB granuloma. Additionally, T cells near the granuloma can be negatively impacted by the depletion of key amino acids required for proper function. As mentioned previously, IDO, an enzyme that functions in the catabolism of tryptophan, is expressed by cells in the core of the granulomas of rhesus macaques infected with *M. tuberculosis* (283), and inhibition of IDO promoted granuloma reorganization and attenuated disease (66). The functionality of T cells within granulomas may also be regulated by direct cross talk with infected myeloid cells, including macrophages and DCs. Intravital imaging of mycobacteria-induced liver granulomas revealed limited antigen-specific T-cell migration arrest in response to infected myeloid cells (345), suggesting that T cells do not interact meaningfully with infected cells in granulomas. Taken together, these studies highlight the vast complexity and heterogeneity of the TB granuloma.

IMMUNOLOGY OF TB DIAGNOSTICS

TB diagnosis relies on evaluation of clinical symptoms and patient history combined with radiographic examination and detection of bacteria in sputum (9). The presence of acid-fast bacilli in sputum smears by microscopy does not specifically indicate infection with *M. tuberculosis*; microbiological culture and nucleic acid amplification-based tests are required to confirm the presence of *M. tuberculosis* infection. Xpert MTB/RIF, a cartridge-based near-patient diagnostic assay utilizing real-time nucleic acid amplification of *M. tuberculosis* DNA, which also detects drug resistance to the first-line drug rifampicin, is recommended by the World Health Organization for TB diagnosis (455, 456). IFN-γ release assays (IGRAs), which leverage the specificity of the immune response to *M. tuberculosis*, are the basis of the QuantiFERON-TB Gold In-Tube and T-SPOT.TB diagnostic assays. IGRAs measure IFN-γ produced by antigen-specific T cells in blood that recognize *M. tuberculosis* antigens (ESAT-6, CFP-10, TB7.7) (457). IGRAs provide increased specificity over traditional Mantoux skin tests that depend on delayed-type hypersensitivity reactions to purified protein derivative, which is not specific to *M. tuberculosis* infection, and positive results may be due to BCG vaccination or exposure to environmental mycobacteria. However, IGRAs do not differentiate between active and latent TB and cannot be used to diagnose TB disease. While sputum-based smear and culture techniques are established worldwide for

clinical indication of *M. tuberculosis* infection, collection of sputum, especially from children, can be challenging and is not completely reliable. Therefore, there is interest in developing non-sputum-based diagnostic approaches for TB. Detection of urinary lipoarabinomannan in suspected TB cases is being investigated in HIV-infected (458) and -uninfected (459) individuals. Blood-based biomarkers discriminating between LTBI and ATB are being investigated for potential application to TB diagnostics and treatment response (460–462). HLA-DR, CD38, and Ki67 expression on *M. tuberculosis*-specific CD4 T cells from peripheral blood is reported to be a highly specific and sensitive method to discriminate LTBI and ATB and evaluate treatment response (460). A recent study suggests that HLA-DR could function as a robust marker distinguishing LTBI and ATB in HIV-infected populations (461). Further understanding of the spectrum of antigen-specific responses to *M. tuberculosis* infection can be leveraged to develop diagnostics that can monitor infection and treatment response.

TB VACCINES

The only currently licensed vaccine against TB is bacillus Calmette-Guérin (BCG), an attenuated strain of *M. bovis* (463, 464). BCG confers protection against severe forms of TB, including miliary TB and TB meningitis (465), but does not reliably protect against pulmonary TB in children or adults (3, 4, 466). The lack of validated correlates of protection against TB is a severe limitation to TB vaccine development. Despite the importance of IFN-γ responses in resistance against *M. tuberculosis* infection in humans and animal models, accumulating evidence suggests that induction of enhanced IFN-γ responses is not sufficient to obtain a more efficacious TB vaccine. Indeed, the frequency and functional profile of BCG-specific CD4, CD8, and γδ T cells from whole blood, including IFN-γ-producing T cells, did not correlate with protection against TB in newborns (467). As of 2017, there are 14 TB vaccine candidates in varying phases of clinical development representing three broad strategies: subunit vaccines pairing *M. tuberculosis* antigens with adjuvants, viral-vectored vaccines utilizing an attenuated virus for antigen delivery, and whole-cell vaccines utilizing attenuated *M. tuberculosis* or related mycobacterial species. Protein subunit vaccines currently under clinical development include M72/AS01E (468), H4:IC31 (469), H56:IC31 (470), and ID93/GLA-SE (471). Among viral-vectored vaccines, results from the MVA85A phase IIb clinical trial have prompted reevaluation of immune correlates to aim for in a TB vaccine. MVA85A is a modified vaccinia Ankara virus expressing Ag85A from *M. tuberculosis* that was utilized as a booster vaccine in infants previously vaccinated with BCG (472). Notably, vaccination with MVA85A enhanced frequencies of antigen-specific, polyfunctional CD4 T cells co-expressing IFN-γ, IL-2, and TNF-α (472). Although MVA85A vaccination enhanced antigen-specific CD4 T-cell responses, it did not provide added protection against TB disease in infants (472). Other viral-vectored vaccines in various stages of development include Ad5Ag85A (473), ChAdOx1.85A + MVA85A (474), MVA85A-IMX313 (475), and TB/FLU-04L. Additionally, a recent study utilizing a recombinant cytomegalovirus demonstrated protection in rhesus macaques (476). While viral vectors do not require the use of adjuvants, previous exposure to the vector may attenuate vaccine-induced responses and represents a potential complication to the use of viral vectors. Whole-cell vaccines currently under development include killed *Mycobacterium vaccae*, DAR-901 (477), VPM1002, MTBVAC, and RUTI. VPM1002 is an approach to improve BCG immunogenicity and vaccine potential by engineering BCG to express lysteriolysin from *Listeria monocytogenes* to escape the phagosome and carry a urease deletion mutation that facilitates phagosomal acidification, thereby enhancing MHC class I antigen presentation to CD8 T cells (478). MTBVAC is a genetically attenuated *M. tuberculosis* strain lacking *phoP* and *fadD26* that abrogates synthesis of various surface lipids (479). Lastly, the therapeutic vaccine candidate RUTI was developed by growing *M. tuberculosis* under stress prior to fragmentation, detoxification, and delivery in liposomes to individuals with LTBI to prevent progression to ATB (480–482).

There have been substantial advances in our understanding of immunity against *M. tuberculosis* from the days of Drs. Calmette and Guérin. Nevertheless, the absence of suitable alternatives to BCG highlights the challenges before us. *M. tuberculosis* is adept at subverting the cross talk between innate and adaptive immunity, and it will be important to understand that cross talk for the rational development of better vaccines. Even in the absence of protective correlates and in the face of disappointing preliminary results for MVA85A, the state of TB vaccine development is resurgent now more than ever and provides cause for optimism for the development of more efficacious vaccines and therapeutics against TB.

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