Immunopathology in human tuberculosis

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Abstract (150 words)

Mycobacterium tuberculosis (*M.tb*) is a bacterial pathogen that has evolved in humans, and its interactions with the host are complex and best studied in humans. Myriad immune pathways are involved in infection control, granuloma formation, and progression to tuberculosis (TB) disease. Inflammatory cells such as macrophages, neutrophils, conventional and unconventional T cells, B cells, NK cells and innate lymphoid cells, interact via cytokines, cell-cell communication and eicosanoid signaling to contain or eliminate infection but can alternatively mediate pathological changes required for pathogen transmission. Clinical manifestations include pulmonary and extrapulmonary TB, as well as post-tuberculous lung disease. Risk factors for TB progression, in turn, largely relate to immune status and, apart from traditional chemotherapy, interventions primarily target immune mechanisms, highlighting the critical role of immunopathology in TB. Maintaining a balance between effector mechanisms to achieve protective immunity and avoid detrimental inflammation is central to the immunopathogenesis of TB. Many research gaps remain and deserve prioritization to improve our understanding of human TB immunopathogenesis.

Introduction

Mycobacterium tuberculosis (*M.tb*), the major aetiological agent of tuberculosis (TB) in humans, is considered an obligate human pathogen because effective transmission requires a pathologic reaction in the human host. Disease is often confined to the lung, virtually the only portal of entry and transmission for *M.tb.* However*, M.tb* can infect almost any part of the body, and the resulting pathology can vary (**Box 1** and **Figure 1**). Although recent evidence suggests that *M.tb* can be aerosolized by tidal breathing (*12*), it is generally accepted that individuals with high sputum bacillary loads, typically associated with severe lung pathology and cavitary disease, are most infectious (*13, 14*). The host-pathogen interaction is, therefore, a conflict in which the host must mount a sufficiently

protective immune response to contain or eliminate *M.tb* without allowing it to drive the immunopathology it needs to transmit efficiently.

M.tb is responsible for millions of infections yearly that result in a spectrum of possible outcomes, the most common (approximately 90%) being successful long-term control or eradication of the organism. Progression to clinical disease, however, occurs in at least 10 million individuals annually and resulted in an estimated 1.3 million deaths in 2022 (*15*). In addition, millions of individuals harbor manifestations of *M.tb*-associated pathology that are asymptomatic or return a negative sputum test for *M.tb* (*16*), the significance of which is incompletely understood.

In this review, we discuss the main manifestations, immunological players, and risk factors of TB immunopathology and highlight opportunities for medical intervention. We acknowledge that *M.tb* genotype and phenotype likely play a crucial role in immunopathology, but this is reviewed elsewhere (*18*). Similarly, several recent reviews have discussed the extensive mechanistic insights gained from different animal models of TB, including mice, guinea pigs, rabbits, cattle and non-human primates (NHP), and their respective shortcomings (*14, 17*). Where possible, we have limited our review on human studies and mentioned whenever data was derived from animal models.

Control of M.tb infection

Aerosolized bacteria inhaled into lung alveoli are typically phagocytosed by alveolar macrophages, which can kill or host *M.tb*, depending on multiple factors, including macrophage activation status (*19*). Preventing *M.tb* dissemination probably requires the formation of cellular aggregates around infected macrophages, creating granulomatous lesions. These lesions typically comprise resident and recruited macrophages, lymphocytes, and other immune and non-immune cell types. Granulomas usually form in the lung parenchyma and interstitial sites where tuberculous pneumonitis has developed. Importantly, control of *M.tb* at this early stage requires antigen-specific T cell responses (*20*), occurring approximately 6–8 weeks after infection (*21, 22*) and commonly manifested by a positive tuberculin skin test (TST) or interferon-gamma (IFN-γ) release

assay (IGRA). It is worth noting that a proportion of highly TB-exposed individuals never appear to become TST- or IGRA-positive (*23*). However, these individuals, often termed resisters, typically do have evidence of *M.tb*-specific antibodies or T cells that do not secrete IFN-γ (*24*). Irrespectively, evidence for immune eradication of *M.tb* comes from autopsy studies in the pre-antibiotic era, which frequently identified old TB lesions containing no culturable bacteria (*25*). Additionally, most *M.tb*-exposed individuals who become immune compromised do not develop active disease (*26, 27*) and the risk of TB disease among TB contacts is highest in the first 1-3 years post-infection and then asymptotically decreases, along with a waning TST response (*27, 28*). However, the same autopsy studies recovered live *M.tb* from lesions and healthy lung tissue in humans without other evidence of TB disease (*25*), and *M.tb* reactivation can occur decades after exposure (*29*). Thus, effective TB immunity can lead to both eradication and long-term stable control, termed latent infection. Understanding the mechanisms behind successful pathogen control or clearance remains a priority for TB research but is challenging to address in humans because the timing of infection is often unknown and access to infected and diseased tissues is limited.

Disease manifestations and progression

The manifestations of TB, including granulomas, tissue destruction, effusions and scarring, are largely driven by immune-mediated processes. For example, granuloma formation is classically described as a type IV hypersensitivity response **(see Text box 1)** (*30*)**.** The immune mechanisms of functional tissue destruction within affected organs are detailed in the cell death and lung cavitation sections. The section on extrapulmonary TB discusses the production of effusions, which are responsible for clinical pathology in specific sites. Scarring is a consequence of chronic inflammation and can itself lead to organ compromise. The pathogenesis of fibrosis is described together with post-tuberculous lung disease.

Box 1: The role of the granuloma in human TB

Granulomas, cellular aggregates that form around infected macrophages, are a dominant pathological TB feature in human lungs (*1*) and are found in all other organs to which *M.tb* disseminates.

- The study of granulomas in humans, particularly in early and subclinical states, is limited by access to affected tissues. Most studies have been conducted postmortem.
- Human TB granulomas are extremely heterogenous in size and cellular composition (*2, 3*), and can be grouped into non-necrotizing and necrotizing lesions. Combining spatial mapping with detailed cellular analyses shows diverse features, ranging from epitheloid macrophage aggregates to more organized non-necrotizing granulomas with lymphocyte cuffs, to caseum-filled and cavitating necrotizing granulomas (*4, 5*).
- Histological sections of human granulomas often do not detect *M.tb* bacilli by Ziehl-Neelsen (ZN) staining. This can be due to sterilization or a loss of “acid-fastness” and detection by ZN staining, induced by granuloma conditions (*6*). ZN negative lesions can contain *M.tb* DNA and RNA (*7, 8*) and RNA appears more frequently in the outer granuloma and adjacent regions rather than in the necrotic core (*9*).
- *M.tb* is more abundant in the ‘loose inflammatory reaction’ mounted in the HIV immunocompromised compared to the paucibacillary well-formed granulomas in HIV negative individuals (*10, 11*).
- The role of granulomas in protection versus immunopathology in humans remains incompletely understood (*2*).
- Lung granulomas are present in primary and post-primary TB in individuals without overt disease, and likely play a protective role in both settings. However, it is commonly said that a failed immune response in the granuloma leads to uncontrolled bacterial replication, central necrosis and cavitation (*17*). Yet, post-primary TB also develops from an unresolved pneumonia rather than from necrotic granulomata, questioning the central role of this response in the progression of post-primary disease (*2*).

The processes underlying disease progression are not well understood in humans. In *M.tb*-unexposed hosts, usually children, an initial infection focus can lead to rapid disease

progression, termed "primary TB". Animal models typically mirror primary disease phenotypes (*31*) and can lack the spectrum of features of human pathology (*32*).

Most disease, however, develops in previously exposed hosts, occurs after a period of dormant infection or, reinfection, and is consequently referred to as “post-primary TB” (*2, 33*). Computed tomography (CT) imaging of asymptomatic IGRA-positive humans at high risk of disease identified lung parenchymal abnormalities such as infiltrates and/or fibrotic scars consistent with bronchogenic reactivation, or active nodules consistent with hematogenous spread of TB (*34*). A recent positron-emission tomography (PET)-CT study of TB patients undergoing treatment suggested bronchial spread of disease, likely via inflammatory debris, primarily from cavities, but also from consolidations, which appears to be involved in establishing new lesions (*35*). This has also been observed in NHP with a primary *M.tb* infection, which develop pulmonary consolidation and bronchogenic spread of cellular infiltrates early during infection (*31*). Nevertheless, the pathologies of primary and post-primary TB are distinct, implicating an important role for adaptive immunity in driving immunopathology (*2*).

Primary TB usually develops from a single lung lesion in the lower part of the lung, is less likely to cavitate (*36*), and is often paucibacillary (*37*), at least in children. By contrast, post-primary TB typically occurs in the lung apices and more often leads to necrosis and cavitation (*36*)(**Figure 1B**). Post-primary TB is by far the most common manifestation of TB disease globally, and consistent with its features, is more infectious than primary TB (*38*).

Disease progression has been associated with sequential modulation of immunological processes, such as type I/II interferon signaling and complement cascade activation (*39*). These can be detected by blood cell gene expression and serum proteomic profiling more than a year before disease diagnosis, providing the biological basis of correlates of risk (CoR) of TB (*40*). More proximal to TB diagnosis, myeloid inflammation and modulation of lymphoid, monocyte, and neutrophil gene expression, as well as markers of tissue degradation, can be detected (*39*). These peripheral biomarkers are likely to reflect tissue

inflammation, where expression of matrix metalloproteinases (MMPs) and cysteine cathepsins mediate lung cavitation observed in post-primary TB (*41, 42*).

Lung Cavitation

One of the most striking pathological features of post-primary TB is the development of lung cavities, usually in the apices (defined as the lung portion superior to the first rib), which can be very large and may emerge rapidly (*1, 14*). Development of cavities is associated with increased *M.tb* sputum burden and cough frequency, and development of drug resistance, all of which are advantageous to the pathogen as they increase transmission (*14*). For the host, however, cavitation is associated with significant morbidity. It may distort or obliterate airways, causing airflow obstruction and impairing gas exchange by destroying alveoli during the lipoid pneumonia that precedes cavitation. This loss of functional lung tissue can lead to chronic hypoxia (*43*). Additionally, cavity formation is associated with aspergillomas and hemoptysis, a common mechanism of death in TB patients (*14, 43*). Importantly, lung cavities persist in up to 50% of cases following successful TB treatment (*44*), with significant life-long consequences, including post-TB lung disease, discussed below.

The precise order of events that lead to cavitation remains somewhat unclear, but the breakdown of the extracellular matrix (ECM) is an essential step. This requires the activity of matrix metalloproteinases (MMPs) and other proteases capable of degrading ECM proteins such as collagen, which provide the structural framework of the lung (*45, 46*). Evidence from the rabbit model suggests that depletion of the extracellular fibrotic fibrils is tightly coupled with extensive necrosis, which can then be evacuated with little mechanical resistance during the formation of a cavity (*14, 47*). To maintain the structure essential for effective gas exchange, the lung is skewed toward ECM protection and production and activation of proteolytic enzymes like MMPs, and these processes are highly regulated through molecules such as tissue inhibitors of metalloproteases (TIMPs). How this is overcome during post-primary TB is unclear, but requires an immune

competent host and T cells, and it is likely promoted by multiple evolutionary adaptations of *M.tb* (*14, 46, 48*). Several MMPs are implicated in the development of lung cavities in humans, including MMP-1, 3, 7, 8, 9, 12, 13, and the cysteine cathepsin K (*14, 49, 50*). Of these, MMP1 appears to play a crucial role and has been identified through numerous unbiased approaches as being one of the most differently expressed genes in TST skin biopsies during active TB (*51, 52*). Strikingly, gene expression of sarcoidosis lesions, a human granulomatous disease that rarely cavitates, is highly similar to TB, with the notable exception of MMP-1 that is only elevated in TB lesions (*53*). The inhibition of MMPs in animal models has not led to reliable prevention of cavitation, implying that modification of this process may be complex (*51*). However, a recent clinical trial using doxycycline, an inhibitor of MMP-1 (among other effects), observed a significant reduction in cavity size, supporting the potential of MMP inhibition as an adjunct therapy in humans (*54*). Certainly, reducing the formation of lung cavities would have enormous benefit to the host and epidemic control.

Extrapulmonary TB

Although pulmonary involvement is the most common form of TB, extrapulmonary disease also occurs and is significantly more frequent in young children and the immunocompromised (**Figure 1**). The prevalence of extrapulmonary TB varies according to region and comprised 26% of TB in a meta-analysis of sub-Saharan African patients (*55*). Interestingly, patients with extrapulmonary TB may not display lung involvement despite this almost certainly being the route of infection. The most affected sites are the pleura, lymphatics, and the abdomen, especially in children (*55*); however, TB can affect any organ or tissue in the body, and the pathology varies accordingly (**Figure 1**).

Universally, immunopathology leads to tissue destruction and scarring with compromised function. Macroscopic autopsy appearance is of classic caseous necrosis or foci of firm, rubbery tissue. Lymph nodes are enlarged and irregular and adhere to one another without clear tissue planes separating them from surrounding structures. Adhesions are prominent, notably in the pleural spaces and at the base of the brain in TB meningitis. Histologically, patterns include mixed inflammatory cell infiltrates, necrotizing and non-

necrotizing granulomatous inflammation, or, rarely, suppuration. In the most severe cases, usually affecting immunocompromised patients, TB pathology is disseminated throughout the whole body (*56*). Dissemination of *M.tb* from the lungs must be lympho-hematogenous, and some believe it occurs in all active TB disease cases.

Tuberculous effusion is a particular disease manifestation that occurs in potential spaces including the pericardium, pleura, and peritoneum. The pathogenesis is a combination of a type IV hypersensitivity reaction and direct pleural infection (*57*). Rupture of a subpleural caseous focus deposits *M.tb* antigen into the pleural space. In response, the initial neutrophil influx increases capillary permeability with both fluid and protein accumulating (*58*). The protein in turn favors osmotic accumulation of more fluid. Additionally, fluid clearance is impaired by inflammatory obstruction of lymphatic stomata in the parietal pleura (*57*). This neutrophil phase is followed by extravasation of macrophages and then Th1 lymphocytes, which are associated with high levels of IFN-γ and IL-12. In contrast, anti-inflammatory IL-4-producing Th2 cells are reduced in the pleural space compared to peripheral blood (*59*). This lymphocyte compartmentalization is associated with effective bacterial containment. Adenosine deaminase released by lymphocytes is used in TB diagnosis of pleural taps since these effusions are paucibacillary (*60*). A minority of patients have higher rates of culture positivity; these individuals have progressed to a second neutrophil-predominant phase with empyema formation and have a more guarded prognosis (*57, 61*). The clinical pathology of tuberculous effusions varies according to site. For example, tuberculous pericarditis leads to accumulation of an exudate containing lymphocytes and monocytes and is characterized by both pro-inflammatory mediators such as IFN-γ, IL-10, IL-1β, IL-6, IL-8, and TNF, as well as low levels of the anti-fibrotic N-acetylseryl-aspartyl-lysyl proline. Patients present with congestive cardiac failure due to fluid tamponade and even after resolution of the effusion, fibrosis leads to chronic restriction of cardiac filling (*62, 63*).

Drug-resistant tuberculosis

It is estimated that 20% of *M.tb* isolates globally are resistant to at least one agent and these strains are associated with a similar proportion of worldwide TB deaths (*64*). Drug-resistant organisms may act differently to drug-sensitive strains, particularly in the initial host-pathogen interactions (*65*). For example, drug resistant *M.tb* can induce a different host immune response on contact with alveolar lining fluid, possibly due to altered bacillary envelope composition. *M.tb* dissemination may be enhanced by increased adhesion and invasion of alveolar epithelial cells. However, within the granuloma environment, some drug-resistant strains demonstrate a similar phenotype to drug sensitive *M.tb*. Likewise, host-pathogen interactions mirror those in drug-sensitive cases in active disease (*65*). Some mutations, however, may lead to less successful organism survival or reproduction and there is an unclear effect on transmission. Nonetheless, the high mortality of drug-resistant disease is well-established (*64*). Apart from the differential host-pathogen interactions, another reason for this is more advanced disease progression due to diminished treatment effect. It should also be noted that significant morbidity results from treatment efforts, including drug toxicity and surgical complications.

Post-tuberculous lung disease (PTLD)

A historically underappreciated consequence of immunopathology is post-tuberculous lung disease (PTLD), which describes lung damage after curative TB treatment. It is an irreversible and often progressive condition, which affects up to half of survivors and causes considerable morbidity and mortality (*66*). Variability in PTLD is influenced by host-pathogen interactions. Serial PET/CT scans have shown that many patients who complete curative treatment have unresolved lesions or continue to develop new inflammatory lesions (*35, 67*). Some patients who were culture-negative after treatment still had *M.tb* RNA in their respiratory fluids, suggesting persistent bacterial transcription contributes to this sustained response (*67*). TB is a strong risk factor for chronic obstructive pulmonary disease, and a range of obstructive and restrictive ventilatory deficits is possible, with symptoms encompassing dyspnea, chronic bronchitis, and reduced effort tolerance (*66*). Heterogenous lung remodeling includes bronchiectasis, cavitation, and fibrotic scarring. Bronchiectasis is irreversible bronchial dilation and

thickening with loss of the normal elastic and muscular components. It is a major risk factor for subsequent bacterial infection. Ongoing inflammation with airway narrowing obstructs exhalation (*66*). Cavitation and the subsequent discharge of necrotic material also contribute to the obstruction of small airways. Fibrosis replaces functional tissue, leading to reduced gas exchange. In the lungs, this scarring stiffens pulmonary walls and restricts inhalation (*66*).

Fibrosis results from fibroblast deposition of structural extracellular matrix (ECM) including collagen, glycosaminoglycans and proteoglycans. It is the final stage of post-inflammatory tissue repair and is controlled by multiple parenchymal and immune cell inputs. In fibrotic lung, there is an increased proportion of SPP1+ monocyte-derived macrophages, found in 'fibrotic niches' near fibroblasts (*68*). These scar-associated macrophages have conserved transcriptional profiles in fibrosis occurring throughout the body. A profibrotic state is triggered by ligands that include IL-1ß, AREG, PDGF and SPP1 that activate IL-1RA, EGFR, PDGFRA, and CD44 on fibroblasts (*69*). Fibroblasts and macrophages also signal through direct contact, via cadherin-11 and TGFβ (*70*). In addition to those that produce ECM, scRNA-seq has defined inflammatory fibroblasts, which express chemokines and profibrotic cytokines such as IL-6. These fibroblasts transition to the ECM-producing state following interaction with macrophages. In time, fibroblasts can develop autocrine PDGF signaling and produce inflammatory mediators such as CCL2 to self-propagate fibrosis (*71*). In turn, the ECM has an immunomodulatory role as it contains growth factors, cytokines, and chemokines. The reduced mechanical compliance of pathological ECM deposition affects immune cell function through stiffness-sensing mechanisms; for example, some macrophage pathways that regulate collagen synthesis are mechanosensitive (*69*).

TB immunopathology in the CNS

TB of the central nervous system (CNS) has the highest mortality of extrapulmonary disease sites (*72*). The brain is a unique environment that can be described as 'immune privileged'. This site is maintained by the blood-brain barrier (BBB) and blood-

cerebrospinal fluid barrier (BCSFB), which influence the spread of *M.tb* into the brain and its pathological outcomes. Histopathological studies of CNS TB reveal that lesions are centered around blood vessels and demonstrate increasing size and bacillary load as they progress from non-necrotizing to necrotizing granulomas and then to abscesses (*73*). Neutrophils have not been found in the areas of parenchymal encephalitis by Zaharie et al., potentially because the BBB prevents penetration of these highly damaging cells into the brain (*73*). The immune cell complement of the healthy brain is restricted to microglia and mast cells, whereas T and B cells, neutrophils, dendritic cells, macrophages and mast cells are found in the meninges (*74*), and they act as an important neuroimmune interface (reviewed in (*75*)). Microglia can be directly infected by *M.tb* (*76*) and attract, stimulate, and activate other leukocytes, which can lead to CNS barrier dysfunction. Another distinctive aspect of the immunopathology of CNS TB is neurotoxicity, mediated by components of the neurotransmitter system such as glutamate and tryptophan (*72*).

Inflammation and the importance of balance

Successful control of *M.tb* infection is dependent on a complex collaboration between adaptive and myeloid immune subsets and a balance of pro- and anti-inflammatory responses in the local tissue environment (*77, 78*), but the underlying mechanisms are not well understood.

Macrophages, neutrophils, and other infected cells

Infection is initiated after aerosolized *M.tb* is deposited in the lower respiratory tract, where resident alveolar macrophages phagocytose bacilli. Animal models show that other recruited phagocytes, including infiltrating macrophages, dendritic cells (DCs), and neutrophils, also become infected (*17*). Macrophages are crucial for innate defense, maintaining tissue integrity, and regulating inflammation (*79*). In lung lesions of TB patients, mixed macrophage phenotypes co-exist; M1-like/proinflammatory macrophages are thought to promote granuloma formation, while M2-like/anti-inflammatory macrophages appear to inhibit this process (*19*). However, M2-like/anti-inflammatory

macrophages predominate in granulomas (*19*) and macrophage polarization in chronic TB disease appears to favor this state, presumably to regulate inflammation and promote tissue repair. Ironically, *in vitro* studies of THP1 cells show that macrophage polarization might facilitate bacilli persistence and proliferation (*80*). It should be noted that the M1/M2 designation of macrophage differentiation remains incompletely understood in human tissue *in situ*; more research is required to address this.

Neutrophils are also critical components of the innate immune response against *M.tb* and important mediators of immunopathology. Neutrophils are major producers of MMPs, enzymes that degrade collagen, leading to alveolar and lung matrix destruction and, ultimately, cavitary disease (*81, 82*). There is an inverse association between the risk of *M.tb* infection and peripheral blood neutrophil count in household contacts of TB patients (*83*). However, sustained neutrophilia and neutrophil responses in later stages are a main driver of tissue pathology and contribute to *M.tb* spread and increased mortality risk (*84*). Peripheral blood cells, especially neutrophils, display significant upregulation of IFN-stimulated genes (ISGs) during TB (*39, 85*). Neutrophils are also the most heavily infected cell type in human sputum (*84*) and are implicated in TB-related pathologies such as TB immune reconstitution inflammatory syndrome (IRIS, see below) (*86*). Within human TB lesions, bacterial load is generally moderate when macrophages are present and more numerous where neutrophils predominate (*87*). The role of neutrophils as mediators of immunopathology is further supported by the finding that depletion of neutrophils in the murine model of TB was sufficient to reverse pathology (*88*), underlining the central importance of this cell type.

M.tb infects non-myelocytic cells in mice and humans (*10*), including epithelial cells, lymphatic endothelial cells, adipocytes, and progenitor cells in the bone marrow, which can all act as potential niches for *M.tb* persistence. Infection of these cell types, particularly airway epithelial cells, initiates early immune activation and production of cytokines and chemokines that modulate inflammatory processes, influencing infection outcomes (*89*). The diversity of cell types infected by *M.tb* and their distinct microenvironments highlight the complexity of TB immunopathology and *M.tb* survival.

Cytokines and eicosanoids

Cytokines play a critical role in the orchestration and regulation of the complex host response to *M.tb* infection, as well as the pathogenesis of disease. Our knowledge of these host-pathogen interactions is largely derived from experiments in animal models and *in vitro* cellular assays. Many pro-inflammatory, anti-inflammatory and regulatory mediators are implicated in the orchestration of the finely balanced immune response to *M.tb*. While these are reviewed in detail elsewhere (*17, 20, 78*), we focus on the most pertinent here.

IFN-γ and TNF, the primary Th1 cytokines, are arguably the most important cytokines for successful immunity against mycobacteria, as illustrated by the high susceptibility to mycobacterial disease in hosts with a deficiency in the Th1 pathway(*90, 91*), or those who receive TNF inhibitors (*92*). IFN-γ, which is produced primarily by T cells and NK cells, mediates activation of antimicrobial functions and autophagy in macrophages and other phagocytes, restricts bacterial growth and orchestrates granuloma development (*20*). Although often referred to as the hallmark cytokine of protection in TB, IFN-γ can be detrimental as discussed further below.

The pro-inflammatory cytokine, TNF, produced by macrophages, monocytes, DCs and in lesser quantities, T cells, also plays a dual role in TB (*17, 77, 78*). Animal models have shown that TNF is a crucial regulator of granuloma formation and protection against *M.tb* during the initial response to *M.tb* infection (*20, 93*). TNF-neutralizing drugs, used to treat autoimmune conditions, have been found to lead to the reactivation of TB and uncontrolled, disseminated disease (*92*). However, excessive TNF signaling is also associated with macrophage necrosis, severe inflammation, and higher bacterial loads in animal models (*94*). In humans, levels of TNF production, inflammatory state and severity of TB meningitis were found to be associated with *LTAH4* enzyme activity, which is regulated by a single nucleotide polymorphism (*95*). Interestingly, individuals had increased disease severity if they were homozygous for high or low expression *LTAH4*

alleles, whereas heterozygotes, with an intermediate inflammatory state, were the least susceptible to severe meningitis. Cytokines also account for some classic constitutional symptoms of TB. For example, TNF directly acts on myocytes to cause both proteolysis and impaired protein synthesis, possibly contributing to TB-associated weight loss. It is also responsible for the fever and night sweats experienced by TB patients (*96*).

IL-17 is another key cytokine in TB pathogenesis. *M.tb*-specific IL-17-expressing CD4 T cells or Th17 cells are readily detected in blood and lungs of *M.tb*-infected humans (*97-99*) and have been associated with control of *M.tb* (*97, 99*). In NHP, frequencies of lung-resident antigen-specific Th1/17 cells, which share features of Th1 and Th17 cells correlate with protection against *M.tb* afforded by intravenous BCG vaccination (*100*).

Type I IFNs, including multiple isoforms of IFN-α primarily produced by DCs, and IFN-β produced by multiple cell types, including *M.tb*-infected macrophages, also play a dual role. Type I IFNs may promote host-protective responses during early infection (reviewed (*101*)). However, excessive type I IFNs are associated with increased *M.tb* replication, more immunopathology and suppression of protective responses in animal models of TB (*20, 102*). In humans, IFNAR1 (IFN 1 receptor) mutations that impair type I IFN signaling have been associated with a lower risk of TB (*103*). An inherited deficiency in the type I IFN-inducible gene ISG15 resulted in reduced IFNγ production and elevated risk of mycobacterial disease (*104*). In addition, reactivation of TB in patients receiving IFN-α-based therapy for chronic viral hepatitis has been reported (*105-107*).

These studies suggest that type I and type II IFNs counter-regulate each other (*78, 101*) to achieve balanced, effective immune control.

TB IRIS

The importance of a balanced inflammatory response to TB is strikingly demonstrated by the effect of immune cell restoration in TB-associated immune reconstitution inflammatory syndrome (IRIS), which can occur after initiation of antiretroviral therapy in people with advanced HIV disease.

IRIS involves either unmasking of undiagnosed TB or paradoxical symptomatic worsening of those already on TB treatment (*108*). HIV-mediated immune impairment allows unchecked *M.tb* replication in macrophages and other phagocytes. With treatment, drug-mediated suppression of HIV replication enables CD4 T cell count restoration, which can drive activation of infected phagocytes and precipitates an excessive and pathological inflammatory response (*108, 109*). IRIS may involve caspase activation, causing high levels of cell death, while exuberant cytokine signaling can activate neutrophils, which release MMP, further contributing to tissue damage. Immune dysregulation can persist even after CD4 counts have recovered (*109*).

The role of cell death in TB immunopathogenesis

Cell death is fundamental to the interaction between *M.tb* and the human immune system, and is a major factor in tissue destruction and plays a central role in clinical pathology. The death of infected phagocytes as well as bystander (uninfected) cells occurs via a complex and diverse set of processes, historically grouped into programmed/regulated (apoptosis and autophagy) and non-programmed/non-regulated (necrosis) pathways (*110*). However, necrosis may also be regulated, as it can occur via receptor signaling and includes diverse cell death pathways such as necroptosis, pyroptosis, parthanatos, oxytosis, ferroptosis, and NETosis (*111, 112*).

Apoptosis can be induced intrinsically, via cytochrome C, or via extrinsic pathways involving cell death receptor activation (including TNF, FasL, TRAIL), in addition to other mechanisms, including granzyme B and perforin release by cytotoxic lymphocytes (*113*). However, common signaling pathways can also lead to necrotic cell death. In a zebrafish model, excessive TNF induces pathogenic programmed necrosis of infected macrophages through the production of mitochondrial reactive oxygen species (ROS) (*114*). Necrotic death pathways are induced by various cell stressors, including ROS, DNA damage, ion imbalance, and through pattern recognition and cytokine receptors.

Generally, apoptosis and autophagy promote *M.tb* control, limit damaging pathology, and are mostly promoted by the host, whereas necrosis favors bacillary growth and promotes the immunopathology thought to be required for efficient transmission (**Figure 2**). In the rabbit model, necrosis is associated with tissue cavitation and destruction (49,114). Crucially, membrane integrity is largely retained during apoptosis, limiting the release of intracellular inflammatory components and pathogens, while the opposite occurs in necrotic cell death (*115*). In addition, apoptosis enhances antigen presentation and T cell induction, and apoptotic cells express signals facilitating their removal by phagocytes without causing inflammatory responses that recruit additional inflammatory cells, including neutrophils (*116, 117*). Moreover, apoptosis and autophagy generally limit the recruitment of additional inflammatory cells (*116, 117*). In contrast, the uptake of necrotic cells promotes bacterial growth (*118*) and promotes neutrophil recruitment.

The influence of cell death pathways on neutrophil recruitment is also important in immunopathology. This may be partly due to NETosis, a form of neutrophil death that releases decondensed chromatin called neutrophil extracellular traps (NET), containing antimicrobial peptides and enzymes, including proteinases. NETs seem ineffective against *M.tb* (*119*) but are abundant in sputum (*82*) and in necrotic human lung lesions (*120*). NETs induce release of IL-8, driving more neutrophil recruitment and production of MMPs 8 and 9, promoting tissue damage (*82*). NETs also activate surrounding macrophages and pDCs, further fuelling inflammation and neutrophil recruitment (*121*). IFN-α produced by NET-activated pDCs also induce further NETosis, potentially initiating a positive feedback loop of NETosis-induced immunopathology.

M.tb can regulate cell death, which often involves blocking apoptosis and autophagy while promoting necrotic pathways through diverse pathways (**Figure 2**). The *M.tb* protein tuberculosis necrotizing toxin (TNT), for example, activates necrosis by depleting NAD+ levels and the activating necrosome complex (*122*), while protein tyrosine phosphatase A (PtpA) triggers ferroptosis by inhibiting the key regulator glutathione peroxidase-4 (GPX4) (*123*). Additional *M.tb* effectors and their respective mechanistic roles in cell death are portrayed in **Figure 2**. Interestingly, some *M.tb* molecules promote apoptotic cell death and autophagy, implying both outcomes may benefit the pathogen depending

on context. In addition, several *M.tb* proteins interact with multiple cell death pathways. ESAT-6, for example, can inhibit autophagy (*124*), and promote necrosis (*118*), pyroptosis and NETosis (*125*).

Thus, cell death of both infected and bystander cells likely plays a crucial role in immunopathology of TB. It may, therefore, also represent an important opportunity to limit tissue destruction via host directed therapy. However, the highly complex and overlapping modes of cell death and their varying importance at different disease stages makes these pathways challenging to target with precise outcomes.

T cells can protect against or promote pathology

T cells are essential for successful immune control of TB, as discussed in multiple reviews (*20, 77, 78*). The importance of CD4 T cells, particularly Th1 responses expressing IFN-γ and TNF, is clearly illustrated by the high susceptibility to mycobacterial disease in hosts with a Th1 pathway deficiency or who receive TNF inhibitors (discussed above). However, there is growing evidence for multiple immune mechanisms contributing to successful immunity. For example, as discussed above, the non-human primate model shows that lung-resident antigen-specific Th1/Th17 cells are correlates of protection (*100, 126, 127*) and *M.tb*-specific IL-17-expressing CD4 T cells or Th17 cells have been associated with control of *M.tb* (*97, 99*).

There is also evidence that excessive T cell responses drive immunopathology. Although progressive HIV infection dramatically increases the risk of developing TB, these individuals are less likely to develop lung cavities, which correlates with CD4 T cell count (*26*) and is also associated with reduced *M.tb* transmissibility (*128*). More recently, the use of immune checkpoint inhibitors of the PD-1/PD-L1 pathway in cancer therapy has led to numerous case reports of TB reactivation (*129*). PD-1/PD-L1 results in the expansion of *M.tb*-specific T cells and rapid development of lung pathology. Likewise, PD-1 inhibition in *M.tb*-infected mice and NHP caused exacerbated lung pathology and poor outcomes (*130*), suggesting that unrestrained T cell activity drives TB pathology. In further support of this, analysis of antigenic variability in *M.tb* found that T cell epitopes

are hyper-conserved compared to non-antigenic regions (*48*), which makes evolutionary sense if *M.tb* needs T cell-driven pathology to effectively transmit. The dominant hyper-conserved epitopes were subsequently found to induce primarily IFNγ and TNF-expressing Th1 cells, while a small subset of variable *M.tb* epitopes was found to predominantly induce Th1/Th17 responses (*131*), a response phenotype correlated with protection in NHPs and in human lung tissue (*97, 100*). Similarly, there is some evidence that people with active TB target a different set of antigens or epitopes to those with asymptomatic *M.tb* infection (*132*). A recent TCR sequencing-based approach identified certain TCR clusters indicative of T cell clonotypes that associated with control of M.tb infection and other TCR clusters that associated with TB progression (*133*). Together these data imply that T cells driving pathogenesis in TB may target a different set of epitopes or antigens than those associated with protection, although more work is needed to confirm this.

As with many aspects of TB, timing is also likely to be important. T cells play a crucial protective role in early infection, but beyond a certain point, they may serve to exacerbate pathology. Numerous vaccine studies in NHPs, for example, provide strong evidence for a protective role for Th17 cells in early infection (*126, 127*). However, *in vivo* work using the TST to measure immune signaling in humans showed a strong link between Th17 responses and immune pathology, linked to neutrophil recruitment and MMP-1 production (*52*). IL-17 is a potent chemoattractant of neutrophils and is known to induce NETosis in cancer (*134*), further fueling inflammation.

Factors that tip the balance

When *M.tb* persists beyond primary infection and causes disease, the length of incubation and resulting immunopathology are strongly influenced by non-modifiable risk factors, including age and sex, and environmental factors such as nutrition, smoking, substance abuse, and co-infections (*135*). Risks are highest below 4-5 years of age and in the elderly, and, in those over the age of 20, men are at greater risk than women (*135*). Changes in risk pattern appear to occur during puberty, during which the predominant phenotype of TB shifts from the paucibacillary, intrathoracic lymph node disease

commonly observed in children to adult-type post-primary pulmonary TB (*136*). Immunological changes mediated by primary sex hormones are thought to be responsible for these transitions. For example, testosterone inhibits Th1 and promotes Th2 cell differentiation (*137*), while estrogen increases Th1 and Th17 and decreases Th2 cell differentiation (*138*). Adrenal hormones, including cortisol and dehydroepiandrosterone sulfate (DHEAS), may also impact *M.tb* control (*139*).

Undernutrition is a biological factor closely associated with poverty and is a strong risk factor for TB incidence and mortality. In many countries where TB is endemic, TB and undernutrition co-exist (*135*). Low body mass index (BMI) has been associated with up to 12-fold higher risk of TB (*135*) underscored by the results of a recent trial in India demonstrating that the provision of nutritional support was associated with a 48% reduction in TB incidence (*140*). A related risk factor for TB is diabetes mellitus (DM). People with DM are at higher risk of *M.tb* infection, progression from infection to disease, and poor treatment outcomes (*135, 141*). The mechanisms underlying this association are incompletely understood, but microvascular, macrovascular, and diabetic nephropathy diseases associated with DM, which are driven by chronic hyperglycemia and related oxidative stress (*142*) are likely involved. TB with concurrent DM is associated with a higher burden of lung pathology, cavitation, and high levels of systemic inflammation compared to non-diabetic persons (*142, 143*).

Substance abuse, including alcohol, tobacco, and illicit drugs, are all well-known risk factors for TB (*135, 144*). Illicit drug use is commonly associated with other risks for TB (*144*) and may also impair immune function, although more research is required to understand its biological effects.

Several co-infections are known to modulate immune responses and inflammation in ways that increase the risk of TB progression. HIV-associated immunocompromise is among the strongest risk factors for TB. CD4 counts in peripheral blood are inversely associated with the risk of pulmonary and disseminated disease in people living with HIV (*128, 135*). Mechanisms include preferential HIV infection and depletion of *M.tb*-specific CD4 T cells (*145*), increased HIV replication at sites of *M.tb* infection, with increased

pathology (*146*), and reduced macrophage ability to control *M.tb* (*147*). In a systematic review of studies investigating HIV effects on tissue granulomas (*148*), Dietrich et al. reported increased bacillary load within *M.tb*-infected tissue in HIV-infected persons. They also found that lower CD4 counts in HIV-infected persons were associated with both poorer granuloma formation and higher *M.tb* load. Likewise, the frequency of lung cavitation in PLWH inversely correlates with CD4 count (*26*) and HIV co-infection is associated with reduced M.tb transmissibility (*128*).

Infection with respiratory viruses, such as influenza, rhinovirus, and seasonal coronavirus, promote type I IFN responses and have been linked with elevated risk of TB and more severe TB disease (*149, 150*). TB patients with nasopharyngeal viral–bacterial coinfection were also likely to have more severe TB disease (*151*). CMV is another viral infection associated with a higher risk of TB (*152, 153*). CMV induces chronic activation and modulation of CD4 and CD8 T cell effector responses (*152, 154*) and such T cell activation has been associated with elevated risk for TB (*39, 154*).

Interventions: chemotherapy

Prompt anti-TB treatment holds major benefits since it arrests pathology and reduces the likelihood of transmission. The current standard regimen for drug-susceptible TB is effective, but patients with uncomplicated disease have to take multiple drugs for 6 months, and a small percentage are at risk of recurrent disease (*155*). However, even in those with clinical cure, a large proportion suffer long-lasting morbidity due to post-TB lung disease. These serious sequalae of TB pathology could also be averted by earlier treatment, requiring active community screening, including those who are asymptomatic.

Interventions: Host directed therapies

Host response modulators, termed host-directed therapies (HDTs), given alongside anti-TB therapy, could shorten treatment times, reduce lung pathology and post-TB lung disease, and lower the risk of recurrent disease. Corticosteroids are routinely used as adjunctive therapy to prevent inflammatory immunopathology and improve survival, particularly in cases of meningitis, immune TB-IRIS, and pericarditis (*156-158*). The

mechanisms of steroid agents, which have pleiotropic effects, are incompletely understood, and many individuals still have poor outcomes (*156, 159*).

Similarly, a range of recombinant cytokines, toll-like receptor (TLR) agonists, tyrosine kinase inhibitors, and other immunomodulators have been assessed as HDTs to augment adaptive or innate immune responses (*159, 160*). Very few novel HDT agents, however, have shown clear beneficial effects in clinical trials.

For example, adjunctive IFNγ therapy has been assessed in a number of small trials. Several have shown some clinical benefit of IFNγ, such as more rapid clearance of Mtb from the sputum than observed with TB drugs alone (*161, 162*), primarily in individuals with drug resistant TB or MDSM, or those with non-tuberculous mycobacterial infection (discussed by Wallis (*163*) and Casanova et al., (*164*)). However, other trials reported no efficacy (*163*) and one trial was halted prematurely by the data safety monitoring board due to safety concerns (trial not published, but results reported in the supplement protocol of the trial by Dawson et al. (*162*)). Ultimately, larger, well-designed and controlled trials are needed to definitively address the efficacy and best indication of IFNγ as an adjunct therapy for TB.

When used as an adjunctive therapy, the phosphodiesterase-4 inhibitor (PDE-4i), CC-11050, demonstrated safety and reasonable tolerability and significantly improved obstructive deficits compared to the control group (*165*). Similarly, the mucolytic agent, N-acetylcysteine (NAC), was safe and significantly reduced oxidative stress in patients with HIV-TB co-infection in a recent phase II trial (*166*), suggesting a potential benefit by managing TB-related inflammation and lung pathology. As discussed above, administration of MMP inhibitor doxycycline for 14 days was found to reduce the volume of lung cavities, and effect that persistent for the 6 week follow up period (*54*). These promising results demonstrate that HDTs may indeed play an important role.

The main HDT targets and approaches are summarized in **Figure 3,** and the current status of HDTs in preclinical and clinical development has been reviewed in detail (*160, 167*). Ultimately, achieving personalized HDT in TB remains challenging, particularly in

high-burden settings, which are often under-resourced in low- to middle-income countries.

Interventions: vaccines

Vaccine-mediated prevention of *M.tb* infection or pathology associated with TB disease hold obvious benefits (*168*), as does blocking onward transmission. BCG is the only currently licensed TB vaccine and consistently protects children against disseminated disease, TB meningitis and, in certain settings, against pulmonary TB (*169*). However, the duration of this effect is limited, and BCG revaccination does not provide additional benefit. Many recent papers have reviewed the benefits and shortcomings of BCG and the progress and challenges faced with developing novel TB vaccines (*170, 171*). While several vaccine candidates are in late-stage trials, evidence for prevention of TB disease in humans has to date been reported for only one: the adjuvanted recombinant protein-subunit vaccine M72:ASO1$_E$ (*172*).

Vaccine efficacy is measured by the prevention of TB disease, and assessment of beneficial effects on tissue pathology is not routinely practiced because available methods are insensitive (e.g., X-ray), invasive (e.g., biopsy), and costly (PET-CT). Nevertheless, we believe that developing approaches that include pathology data in clinical trials is important. This is underscored by the recent realization that subclinical TB is far more prevalent than previously recognized (*173*), presenting the possibility that a vaccine could attenuate lung pathology in some without necessarily reducing the number of symptomatic TB cases. It would also ensure that potentially pathology-enhancing effects of vaccines could be detected.

Conclusion

M.tb infection is much more common in endemic settings than generally realized, with far-reaching personal and societal implications. The clinical manifestations are as much a result of host immune responses to infection as they are to *M.tb* itself. Future research should utilize modern technologies and methods to study the immunology of *M.tb*

infection and disease with a strong focus on human studies to inform impactful interventions for the individuals affected.

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Figure Legends

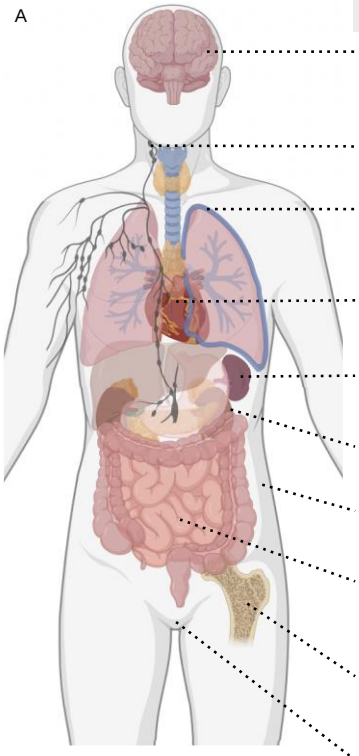
Figure 1. Clinical manifestations of and organ-specific pathologies of TB in humans. (A) Extrapulmonary TB (B) Primary and post-primary pulmonary TB.

Figure 2: Cell death pathways and *M.tb* immunopathology. *M.tb* virulence factors (i.e., ESAT-6) in light red bacillus (rod) shapes and host cellular factors that are altered by *M.tb* (i.e., TNF, plasma membrane) in dark red boxes. Factors that inhibit protective autophagy and apoptotic cell death are shown on the left and those that promote pathological necrotic pathways on the right. Blue shapes represent protective cell death pathways, while green shapes represent pathological necrotic cell death pathways. Abbreviations: ESAT-6 secretion systems-1 (ESX-1); B-cell lymphoma-extra-large (BCL-xL); Protein phosphatase 1A (PPM1A); mitochondrial permeability transition (mPT); BTB domain and CNC homologue 1 (BACH1); phosphatidylserine (PS), danger associated molecular patterns (DAMPs).

Figure 3. Candidate host-directed therapies for TB are at various stages of preclinical or clinical development, arranged into those that aim to augment protective immune responses and those that seek to dampen inflammation. Corticosteroids have been in use for decades.

Figure 1

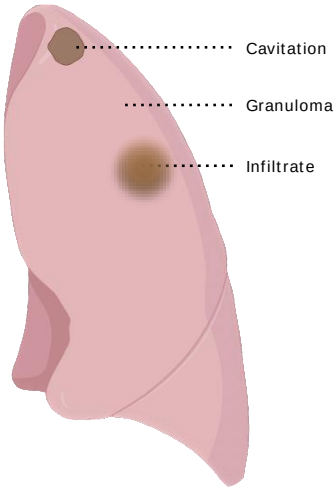
A



Pathology	Clinical Manifestation/s
CNS	
Brain oedema	*Herniation
Meningitis; ventriculitis	*Foraminal obstruction & hydrocephalus
Vasculitis; endarteritis obliterans	*Brainstem/basal ganglia infarcts
Lymph nodes	
Lymphadenitis	*Chronic draining cutaneous fistula
Pleura	
Pleuritis	*Effusions & *adhesions
Heart	
Pericardial effusion/adhesions	Right heart failure
Myocarditis	Arrythmias
Coronary obstruction	*Myocardial infarction
Aortitis	*Aneurysm
Spleen	
Splenomegaly	Cytopaenias
Abscesses	
Kidney / urinary tract	
Renal interstitial nephritis	Dysuria; haematuria
Ureteral fibrosis	*Hydronephrosis; post-renal failure
Abdomen	
Peritonitis	*Ascites
Mesenteric adenopathy	Abdominal pain
Intestine	
Ileotyphlitis	Bloody diarrhoea
Intestinal strictures	Bowel obstruction
Perianal abscess	
Bone and joints	
Pott's disease	*Spinal cord compression & paraplegia
	*Kyphosis
	*'Cold' psoas abscess
Genital tract	
Ascherman's syndrome (uterus)	Infertility
Epididymo-orchitis (testes/ epididymis)	*Discharging scrotal sinus

*asterisk indicates clinical manifestation also observable at autopsy

B



Key

Primary TB

Post-primary TB

Figure 2

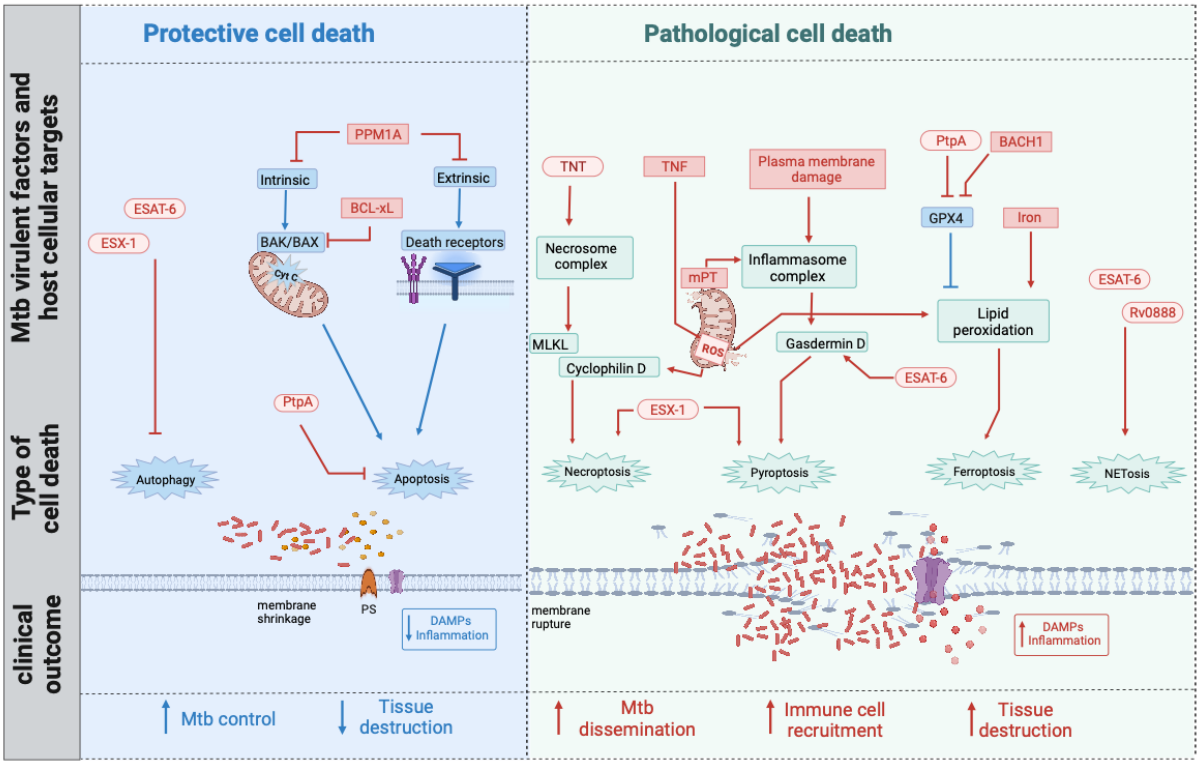
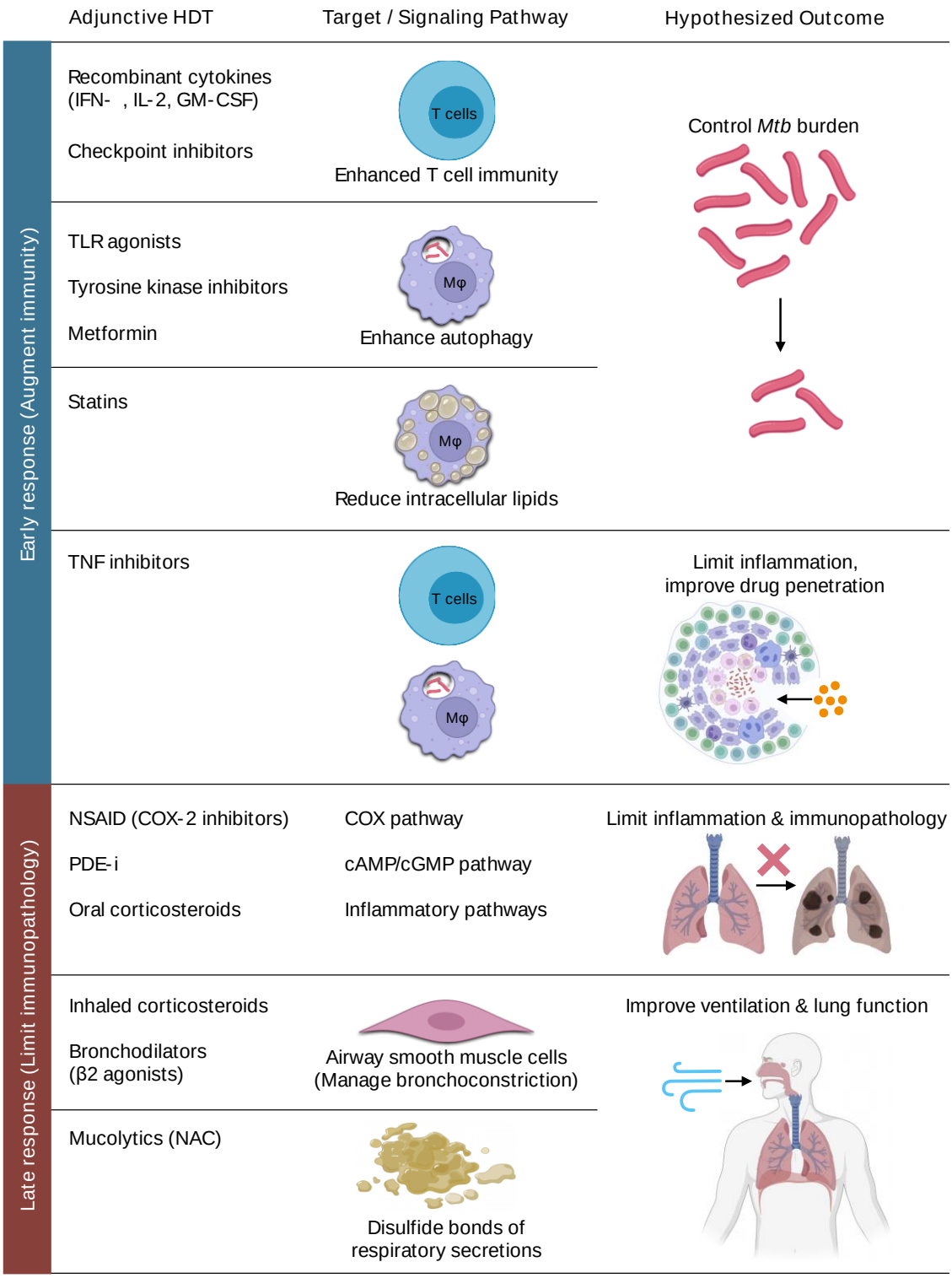

Protective cell death
Pathological cell death
Mtb virulent factors and host cellular targets
Type of cell death
clinical outcome
PPM1A
Intrinsic
Extrinsic
ESAT-6
ESX-1
BCL-xL
BAK/BAX
Death receptors
Cyt c
PtpA
Autophagy
Apoptosis
membrane shrinkage
PS
DAMPs Inflammation
Mtb control
Tissue destruction
TNT
TNF
Plasma membrane damage
PtpA
BACH1
GPX4
Iron
Necrosome complex
mPT
Inflammasome complex
ESAT-6
Rv0888
Lipid peroxidation
MLKL
ROS
Gasdermin D
Cyclophilin D
ESAT-6
ESX-1
Necroptosis
Pyroptosis
Ferroptosis
NETosis
membrane rupture
DAMPs Inflammation
Mtb dissemination
Immune cell recruitment
Tissue destruction

Figure 3


Adjunctive HDT
Target / Signaling Pathway
Hypothesized Outcome
Early response (Augment immunity)
Late response (Limit immunopathology)
Recombinant cytokines (IFN- , IL-2, GM-CSF)
Checkpoint inhibitors
T cells
Enhanced T cell immunity
Control Mtb burden
TLR agonists
Tyrosine kinase inhibitors
Metformin
Mφ
Enhance autophagy
Statins
Mφ
Reduce intracellular lipids
TNF inhibitors
T cells
Mφ
Limit inflammation, improve drug penetration
NSAID (COX-2 inhibitors)
PDE-i
Oral corticosteroids
COX pathway
cAMP/cGMP pathway
Inflammatory pathways
Limit inflammation & immunopathology
Inhaled corticosteroids
Bronchodilators (β2 agonists)
Airway smooth muscle cells (Manage bronchoconstriction)
Improve ventilation & lung function
Mucolytics (NAC)
Disulfide bonds of respiratory secretions