

MINI-REVIEW

Immune responses in pulmonary tuberculosis: A concise review

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Abstract

Pulmonary tuberculosis (PTB) caused by *Mycobacterium tuberculosis* (MTB), remains a major global health concern due to its high morbidity and mortality rates, especially in resource-limited settings. The pathophysiology of tuberculosis (TB) is characterized by complex interactions between the human host immune system and the pathogen. Alveolar macrophages are especially vulnerable targets of MTB, triggering a cascade of pro-inflammatory and anti-inflammatory responses that either contain the infection or facilitate progression to active disease. In addition, recent advances in immunopathology have highlighted the roles of cytokine networks, T-cell responses, and immune checkpoints in disease progression. A deeper understanding of TB pathophysiology has significant implications for clinical management and research. It aids in the development of novel diagnostic biomarkers, host-directed therapies, and more effective vaccine strategies. Emerging therapeutic approaches focus on modulating the immune response to enhance MTB clearance while minimizing tissue damage. Moreover, drug-resistant TB strains pose a growing challenge, necessitating research into host-pathogen interactions that could lead to more effective treatment strategies. This review provides a concise examination of the key mechanisms underlying PTB, emphasizing recent scientific advancements and their relevance for clinicians and researchers. By bridging the gap between basic science and clinical application, this work aims to contribute to the ongoing efforts to improve TB control and patient outcomes.

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1. Introduction

Tuberculosis (TB) remains the leading cause of morbidity and mortality worldwide, with *Mycobacterium tuberculosis* (MTB) as the infectious agent. Despite global efforts, TB continues to pose a significant public health challenge, particularly in low- and middle-income countries.¹ The pathophysiology of TB remains complex, involving intricate interactions between the human host and MTB, immune evasion mechanisms, and granuloma formation.² Understanding these processes is critical for developing effective diagnostic, therapeutic, and preventive strategies. This review provides a concise overview of the underlying mechanisms driving pulmonary TB (PTB), emphasizing

recent advances in immunopathology and potential targets for intervention.

2. Description of MTB

MTB is a facultative anaerobic, non-spore-forming bacillus measuring 0.5 – 3 μm and exhibiting acid-fast staining properties.³ The mycobacterial cell wall is composed of mycolic acid attached to the polysaccharide arabinogalactan, which is bound to a peptidoglycan.⁴ The carbohydrate antigen lipoarabinomannan (LAM) is an outer component of the cell wall and is partly responsible for ensuring the survival of the mycobacteria within the host's macrophages.⁵ Sputum containing MTB bacilli expectorated by individuals results in droplets that remain suspended in the air for several hours and, once inhaled, settle in the airways.^{3,6} Active pulmonary disease results when the human host's pathophysiological processes are overwhelmed by MTB.⁷

3. Immune response to MTB

The host's innate immune response commences when most of the bacilli are trapped in the mucus secreted by the goblet cells of the respiratory tract and cleared by the cilia.⁸ The cell-mediated immune response commences when neutrophils are mobilized at the implantation sites.⁶ Those bacilli that evade the first physical defense of the host, spread to the alveoli and are phagocytosed by macrophages, a process facilitated by LAM and complement C3.⁹ Bacterial replication in the macrophages is slow, as these cells divide every 25 – 32 h.³ Inflammasomes, which are intracellular protein complexes released by macrophages to destroy the bacilli.¹⁰ The NLR family pyrin domain containing 3 inflammasomes typifies this mechanism by facilitating the activation of caspase-1 and promoting the secretion of proinflammatory cytokines, interleukin (IL)-8 and IL-18, in response to MTB infection.¹¹ However, phagosome maturation, the transfer of lysosomes, and autophagy are blocked by the MTB, thus allowing active replication of the bacilli.¹² Several regulatory pathways that govern macrophage metabolism become disrupted during MTB infection. These include the mechanistic target of rapamycin (mTOR), sirtuins, and AMP-activated protein kinase (AMPK).¹³ The mTOR comprises two distinct complexes, mTORC1 and mTORC2. In macrophages, the PI3K/AKT signaling pathway regulates mTORC1 activity, resulting in the suppression of autophagy. However, pharmacological inhibition of mTOR by rapamycin can induce autophagy, thereby enhancing antimicrobial responses.¹⁴ Sirtuins, a family of NAD⁺-dependent histone deacetylases, play a critical role in the host defense against MTB by promoting autophagic processes, maintaining mitochondrial integrity, and mitigating the accumulation

of reactive oxygen species in macrophages.¹⁵ AMPK has been implicated in the differentiation of M2 macrophages, contributing to a reduction in proinflammatory cytokine production while preserving anti-inflammatory cytokine expression, thereby supporting tissue repair processes.¹⁶

In mycobacteria, mycothiol, a low molecular mass thiol, plays a role similar to that of glutathione.¹⁷ When the mycothiol pathway is disrupted, it interferes with the activation of WhiB3, which in turn affects signal transduction, as well as nucleic acid and protein synthesis in MTB.^{18,19} In murine models infected with MTB, genetic disruption of the enzyme thioredoxin reductase resulted in the elimination of the pathogen during both the acute and chronic phases of infection.²⁰ The DosS/T/R signal transduction system in MTB detects host-derived nitric oxide,²¹ oxygen,²¹ carbon monoxide,²² and hydrogen sulfide, triggering the activation of the DosR dormancy regulon, which comprises 48 genes.²³ SenX3-RegX3 was one of the earliest two-component regulatory systems identified in MTB,²⁴ and its operon has been shown to be essential for bacterial persistence during infection in mouse models.²⁵ Collectively, these defense mechanisms of MTB, namely mycothiol, thioredoxin, WhiB proteins, the DosS/T/R system, and the SenX3-RegX3 system, among others, help counteract oxidative stress imposed by the host immune response.¹² Heme oxygenase-1, an enzyme activated in response to oxidative stress, is significantly upregulated during MTB infection. This elevated expression results in an abundance of free iron and reactive oxygen species, triggering lipid peroxidation and ferroptosis, an iron-dependent cell death pathway that promotes the spread of MTB.²⁶ The released cytokines attract T lymphocytes to the infection sites, where they are presented with mycobacterial antigens by macrophages in the lung lymph nodes.²⁷ The activated T lymphocytes produce interferon-gamma (IFN- γ), tumor necrosis alpha (TNF- α), and macrophage colony-stimulating factor to inhibit intracellular growth of the bacilli.²⁸ This process continues for 2 – 12 weeks, during which time the mycobacteria continue to replicate.³ Neonates and young children (<2 years of age) are at the highest risk of TB infection as the T cell antigen response is poor due to the immature immune system.²⁷ In the elderly, immunosenescence leads to reduced responsiveness of both the cellular and humoral immune systems to antigen stimulation.²⁸

If the host's cell-mediated immune system is intact, activated CD4⁺ and CD8⁺ T lymphocytes, B cells, neutrophils, and macrophages form the nodular-type granulomas to contain the infection by limiting bacterial replication and spread.²⁹ The aggregation of several granulomas forms a primary lesion known as the "Ghon focus."³⁰ Ironically, it is the macrophages that are destroyed,

whereas the mycobacteria can survive by changing certain protein regulations such as natural-resistance-associated macrophage protein-1 (NRAMP1).^{31,32} High expression of NRAMP1 resulted in elevated levels of TNF- α , IL-6, transforming growth factor- β , and C-C Motif Chemokine Ligand 2 (CCL2) in MTB-infected macrophages. Moreover, single nucleotide polymorphisms were found to modulate macrophage functional responses to MTB.³² Although the main purpose of granulomas is to contain the infection by preventing the proliferation of MTB, failure to do so, even in a single granuloma, can result in disease progression.³³ After 2–3 weeks, caseous necrosis occurs in the granulomas due to decreased oxygen, pH, and nutrient levels. Mural fibrosis and calcification of the lesions then follow, allowing containment of the mycobacteria; further growth is restricted, and latency is established.³ Complete eradication of MTB occurs in about 10% of individuals whereas containment occurs in the rest, resulting in MTB remaining in a dormant or non-replicating state. This is known as latent TB infection (LTBI).³⁴ It is important that cases of LTBI are identified, as these may progress to active disease in about 10% of individuals.³⁵ Therefore, LTBI individuals, especially children, constitute the most significant reservoir of possible transmission.^{36,37}

If the cell-mediated immune response of the host is defective, the infection progresses to active primary disease.³¹ The granulomas undergo liquefaction and lose the structural integrity of their walls.³ The necrotic material drains into a bronchus, lymph node, or the nearest blood vessel.^{3,6} Drainage into a bronchus facilitates the development of PTB, whereas drainage into a blood vessel facilitates extrapulmonary TB (EPTB). Drainage into a lymph node facilitates both PTB (through collection in the tracheobronchial lymphatic system) and EPTB.³⁶ Tuberculous empyema results from peripheral expansion of the infectious lesion and rupture of the pleural space.³⁷ Infants, children older than 10 years of age, and immunosuppressed individuals are at the highest risk of developing pulmonary disease. In children under 5 years of age, erosion of the airways by enlarged lymph nodes can result in the aspiration of bacteria, whereas adult-type cavitary disease, more common in children older than 10, is another cause of primary disease in children.³⁸

4. Reactivation of MTB

Reactivation of TB disease, which can occur months or years after infection, usually involves the upper lung zones because of higher oxygen levels in these regions and can spread through the lymphatic and hematogenous systems, leading to EPTB.³⁹ Evidence suggests that host-MTB interaction continues after completion of anti-tuberculosis treatment.²⁴ Reactivation of latent MTB infection may

occur spontaneously or be triggered by exposure to immunosuppressive therapies, including glucocorticoids.² In murine models, reactivation has been associated with the production of reactive nitrogen intermediates through induction of nitric oxide synthase in macrophages,⁴⁰ neutralization of TNF- α ,⁴¹ and sustained macrophage activation through CD8 T-cell-derived IFN- γ .² New inflammatory lesions have been observed by positron emission tomography and computed tomography following 6 months of anti-tuberculosis treatment and 1-year post-treatment completion.⁴² Reactivation is likely to occur in adolescents and HIV-infected individuals, thus contributing to the disease burden in high TB-endemic areas.³⁸

5. The clinical and research significance of the TB pathophysiology

Given the complex host-pathogen interactions characteristic of MTB disease, such as granuloma formation, immune evasion, and latency, the efficacy and limitations of existing treatment regimens warrant critical evaluation.⁷ MTB manipulates host immune responses, particularly within macrophages, to evade destruction, leading to chronic infection and disease progression.¹¹ An example of how improvements in the understanding of the pathophysiology of TB would lead to the development of newer treatment approaches is the identification of thioredoxin reductase B2 (TrxB2) in MTB as a potentially druggable target. However, its functional characterization remains limited, with current evidence primarily based on predictions of its essential role in bacterial growth under standard *in vitro* conditions.^{20,43} According to the World Health Organization's 2025 guidelines, TB treatment strategies have shifted toward shorter, more efficacious regimens. For drug-susceptible TB, a 4-month treatment course is now recommended, while drug-resistant cases incorporate newer therapeutic agents such as bedaquiline, pretomanid, and delamanid. The shorter treatment duration aims to reduce poor treatment adherence, reactivation of TB, and the emergence of drug-resistant strains.⁴⁴ Understanding these mechanisms aids in developing targeted therapies, vaccine strategies, and diagnostic tools. Therefore, advancing research into TB pathophysiology is essential to improve global TB control efforts.

6. Conclusion

Understanding the immune response in PTB is critical for advancing diagnostics, therapies, and vaccines. This mini-review highlights key host-pathogen interactions and emerging molecular targets. Continued research into immunological mechanisms will support innovative,

host-directed strategies, ultimately improving TB control, especially in the face of drug resistance and latent infection challenges.

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Conflict of interest

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