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REVIEW ARTICLE

Role of Th2 Cytokines in the Course of Tuberculosis Infection: Immunological Insights and Clinical Implications

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ABSTRACT

Background: Tuberculosis (TB), caused by Mycobacterium tuberculosis, is a major global infectious disease killer. The imbalance between Th1 and Th2 immune responses plays a key role in disease progression, tissue damage, and treatment outcomes. Th1 cells drive cell-mediated immunity, while Th2 cells promote humoral immunity. Th2 cytokines like IL-4 and IL-13 can worsen control of intracellular M. tuberculosis infection. Specifically, IL-4 can induce the development of regulatory T cells (CD25+ Tregs) from naive CD4+ T cells, which become anergic and suppress the proliferation of other T cells, similar to natural Tregs. This study aimed to investigate the role of Th2 cytokines, specifically IL-4 and IL-10, in the pathogenesis of tuberculosis. It focused on how these cytokines contribute to disease progression, modulate the host immune response, and affect bacterial load. The study examined differences in cytokine impact on pulmonary versus extrapulmonary TB and explored how alternatively activated macrophages influence the immune environment during infection.

Methods: A thorough literature search was performed using Scopus, PubMed, Web of Science, and Google Scholar. Included studies addressed TB immunopathogenesis, clinical presentation, diagnostic approaches, and management, with particular emphasis on Th2 cytokine activity. The collected evidence was organized into thematic areas encompassing epidemiology, etiology, host immune response, clinical features, diagnostics, and therapeutic strategies.

Conclusions: TB continues to pose a major worldwide health burden, where the immune balance determines disease outcome. Th2 cytokines, particularly IL-4 and IL-10, had a dual function: moderating inflammation but also weakening protective Th1 responses, allowing bacillary persistence and contributing to fibrosis and cavitation.

Keywords: Tuberculosis, Mycobacterium Tuberculosis, Cytokines, Immune Response, Pathogenesis.

INTRODUCTION

Tuberculosis (TB) continues to pose a formidable global health challenge. According to the World Health Organization (WHO), data indicate that around one-third of the world's population, close to 2 billion people, are latently infected with Mycobacterium tuberculosis (MTB) infection. Despite advances in therapy, TB treatment remains lengthy, relying on multiple antibiotics, which unfortunately increases the risk of drug-resistant strains. The prolonged use of multiple antibiotics in TB therapy heightens the risk of resistance. Consequently, extensively drug-resistant (XDR) and Multidrug-resistant (MDR). MTB strains have become a serious global concern across all regions, independent of economic development. MTB now

represents a global concern, affecting countries regardless of economic development [1].

Human TB exemplifies the dual role of the immune system: while it is critical for limiting infection, it can also contribute to tissue injury during active disease. Most people exposed to MTB develop latent infection, with disease progression effectively blocked by host immunity, although the pathogen is rarely fully eradicated. In those who do progress, pulmonary TB is the most frequent manifestation, with a variable degree of lung involvement [2].

The range of pulmonary TB lesions is wide, spanning from limited foci in the upper lobes to extensive necrotic areas. These can coalesce into cavities or erode into blood vessels, causing hemorrhage. T lymphocyte functionality is pivotal for both protective immunity and granuloma formation, and thus the clinical manifestations of TB are closely tied to the type of immune response mounted during infection [3].

Effective immunity against MTB requires a delicate equilibrium between adaptive responses that restrict bacterial replication and mechanisms that prevent excessive tissue damage. T cells can be categorized into subsets according to their cytokine profiles. Th1 cells produce IL-2, interferon-gamma (IFN-γ), and lymphotoxins, mediating cell-mediated immune responses like macrophage activation and delayed-type hypersensitivity. In contrast, Th2 cells secrete IL-4, IL-6, and IL-10, primarily supporting humoral immunity. Th1 and Th2 subsets reciprocally regulate each other via cytokine signaling, shaping the host's overall immune balance [4, 5].

However, excessive Th2 activity, particularly through IL-4 and IL-13, can undermine the host's ability to control intracellular MTB. These cytokines inhibit IFN-γ release and Th1-dependent macrophage activation, impairing bacterial clearance. Elevated Th2 responses are also linked to reduced autophagy, fibrosis, and cavitation in the lungs, further compromising respiratory function. Moreover, IL-4 promotes the differentiation of CD25+ regulatory T cells (Tregs) from naive CD4+CD25– precursors, inducing anergic phenotypes that suppress responder T cell proliferation, similar to naturally occurring Tregs [6].

This review aims to explore the interplay between Th2 cytokines (IL-4 and 10) and TB pathogenesis, emphasizing their influence on disease severity, bacterial burden, pulmonary versus extrapulmonary involvement, and radiologic features.

METHODS

This narrative review was developed through an extensive and systematic literature search conducted on Google Scholar, PubMed, Scopus, and Web of Science, covering publications up to March 2025. The search strategy incorporated keywords like "tuberculosis," "MTB," "cytokines," "Th1," "Th2," "IL-4," "IL-10," "immune response," and "pathogenesis." Studies were included if they addressed TB immunology, clinical manifestations, or diagnostic approaches, particularly emphasizing Th2 cytokines. Both original research articles and review papers, as well as relevant international guidelines, were analyzed. Findings were then organized thematically into categories encompassing epidemiology, etiology, immune mechanisms, clinical presentation, diagnostic approaches, therapeutic strategies, and prognosis, with a focus on the immunological roles of IL-4 and IL-10.

EPIDEMIOLOGY

In 2021, countries such as India, Indonesia, China, and the Philippines together accounted for more than half of all new TB cases. Between 2000 and 2021, TB caused 1.4–2 million deaths each year, including 1.6 million in 2021, affecting both HIV-negative and HIV-positive individuals. Before the COVID-19 pandemic, TB was the leading cause of death from a single infectious disease,

surpassing HIV/AIDS. Worryingly, TB cases rose again in 2021 and 2022, returning to levels seen in 2019, with only a modest decline since 2015, far short of the WHO End TB Strategy goal of a 50% reduction by 2025 [7].

ETIOLOGY

MTB are aerobic, nonmotile, non-spore-forming organisms with a lipid-rich cell wall that confers acid-fastness and contributes to virulence. Humans serve as the primary reservoir, though infection of animals can occur, and genetic variability among isolates may influence pathogenicity [8].

STRUCTURE OF MYCOBACTERIUM TB

The MTB complex (MTBC) includes MTB, M. africanum, M. bovis, M. caprae, M. pinnipedii, and M. microti [9].

MTB is a slow-growing bacillus with a doubling time of approximately 12–24 hours. The cell wall consists of peptidoglycan, arabinogalactan, mycolic acids, glycolipids, and waxy components, which serve as key targets for antimycobacterial agents such as isoniazid and ethambutol. In addition, virulence is influenced by specialized protein secretion systems.

These secretion systems include ESX-1, which enables MTB to escape from macrophage phagosomes and to secrete ESAT-6 and CFP-10, antigens exploited in interferon-gamma release assays for the diagnosis of infection, even in individuals vaccinated with BCG. The ESX-3 system is essential for iron and zinc acquisition. Furthermore, the complex cell wall architecture allows MTB to evade host immunity by masking pathogen-associated molecular patterns, inhibiting toll-like receptor 2 signaling, and interfering with antigen presentation, autophagy, and cytokine responses. Early recognition of MTB in the lungs involves lung epithelial cells and alveolar macrophages, which detect the bacterium through antimicrobial peptides with conserved structural motifs [10].

Drug-resistant TB, including MDR-TB and XDR-TB, presents significant challenges to public health. Resistance is often associated with epigenetic alterations in host immune cells, promoting bacterial survival and dissemination. Current treatment regimens are prolonged, toxic, and costly, highlighting the potential role of antimicrobial peptides as novel therapeutic interventions. MTB spreads almost exclusively through aerosolized droplets. Approximately 90% of exposed individuals either control the infection or contain it within granulomas. Notably, some highly exposed individuals remain uninfected, likely due to robust innate immune mechanisms involving epithelial cells, phagocytes, antimicrobial molecules, invariant T cells, and natural killer cells, underscoring the protective role of innate immunity against TB [11].

TB PATHOGENESIS

Granulomas represent a defining feature of pulmonary TB, composed of macrophages and various immune cells that work to contain MTB. In immunocompetent individuals, granulomas help limit bacterial spread; however, MTB can evade full clearance by preventing phagolysosome fusion and manipulating host immune responses, enabling long-term dormancy. Over time, some macrophages transform into lipid-laden foamy cells that surround necrotic cores, collectively referred to as caseum. Caseous granulomas emerge as necrosis progresses, forming a lipid-rich microenvironment that favors bacterial survival. Mycolic acids in the MTB cell wall contribute significantly to the development of foamy macrophages and the evolution of caseous lesions[12].

During advanced disease, the necrotic centers of granulomas may liquefy, allowing dormant bacilli to reactivate and replicate actively. The rupture of granulomas and subsequent cavity formation facilitate bacterial entry into the airways, promoting both transmission and dissemination to extrapulmonary sites. Reactivation is most commonly associated

with HIV co-infection, though it can also be triggered by malnutrition, immunosuppressive treatments, diabetes, renal impairment, sepsis, malignancy, smoking, or substance abuse. From a histopathological perspective, granulomas exist on a spectrum. Solid granulomas, featuring fibrotic walls and active immune containment, predominate during latent TB. Necrotic granulomas, exhibiting emerging necrotic centers, and caseous granulomas, which are prone to liquefaction and rupture, are more frequently associated with progression to active disease [13].

IMMUNE REACTION IN TB

The clinical outcome of MTB infection is highly contingent on the host immune status. Effective defense against MTB relies on a coordinated interaction between innate and adaptive immunity, determining whether infection is cleared, contained, or progresses to active disease. Following exposure, approximately 5% of individuals completely eradicate the bacteria, 5–10% develop active TB, and nearly 90% harbor latent TB infection (LTBI). Innate immune components, including neutrophils, macrophages, natural killer (NK) cells, and dendritic cells, interact with adaptive lymphocytes, particularly CD4+ and CD8+ T cells and B cells, to mediate bacterial containment [14].

The innate immune system serves as the initial line of defense, providing rapid, nonspecific protection while shaping subsequent adaptive responses [15].

As an intracellular pathogen, MTB necessitates robust adaptive immune responses. Cellular immunity, largely mediated by T lymphocytes (CD4+ and CD8+ subsets), is critical for controlling bacterial replication, while B cells contribute to humoral responses [16].

1. Neutrophils in Host Immunity and Their Anti-Tuberculosis Actions

Neutrophils, also known as polymorphonuclear leukocytes, are the most abundant granulocytes in circulation and serve as professional phagocytes, playing a critical role in chemotaxis and the clearance of invading pathogens. Once at the site of infection, they detect and internalize MTB via pattern recognition receptors, including TLR1, TLR2, and TLR4–10, which recognize bacterial components like lipoproteins and lipoteichoic acids [17].

Neutrophils deploy both oxygen-dependent and oxygen-independent mechanisms to eradicate MTB. Oxygen-dependent pathways involve the generation of reactive oxygen and nitrogen intermediates, including nitric oxide and peroxynitrite, whereas oxygen-independent strategies rely on antimicrobial granules loaded with cationic proteins, defensins, and permeability-enhancing peptides. Moreover, activated neutrophils release a range of chemotactic mediators, like IL-8, CXCL8, CXCL1, CXCL10, and CXCL11, which recruit additional neutrophils and coordinate with other immune cell populations. This amplifies phagocytic activity and bactericidal efficacy, thereby reinforcing the host's immune response against MTB[18].

2. Macrophages in Host Immunity and Their Anti-Tuberculosis Actions

Macrophages, differentiated from circulating monocytes. In TB, lung-resident macrophages represent the first line of defense, internalizing MTB upon entry into the pulmonary tissue. Recognition of MTB occurs through pattern recognition receptors (PRRs) like TLR2, TLR4, NOD2, and Dectin-1, which detect bacterial components including glycolipids and peptidoglycan. Engagement of these receptors triggers macrophage activation and the secretion of cytokines with anti-mycobacterial activity, notably TNF-α, IL-12, and IL-1β, which collectively enhance microbial clearance [19].

Following phagocytosis, macrophages employ multiple intracellular mechanisms to neutralize MTB. Lysosomal acid

hydrolases degrade bacterial components, while a respiratory burst generates reactive oxygen intermediates (ROIs) and reactive nitrogen intermediates (RNIs). Among these, hydrogen peroxide (H_2O_2) is a primary ROI critical for MTB eradication. Macrophage heterogeneity further influences host defense. Classically activated M1 macrophages, stimulated by LPS and IFN-γ, secrete pro-inflammatory mediators like TNF-α, IL-1, and IL-6 and induce inducible nitric oxide synthase (iNOS) to produce nitric oxide, a potent bactericidal molecule. These functional subsets are essential for maintaining immune homeostasis and effectively controlling MTB infection [20].

3. NK cells in Host Immunity and Their Anti-Tuberculosis Actions

Natural killer (NK) cells are a distinct lineage of lymphocytes originating from bone marrow progenitors, serving as a cornerstone of innate immunity by rapidly targeting infected or transformed cells. Unlike conventional lymphocytes, NK cells detect and eliminate targets in an MHC-unrestricted, antibody-independent manner, enabling swift recruitment to sites of infection. In humans, NK cells are divided into subsets: CD56^low CD16^high NK cells, which circulate in peripheral blood and exhibit potent cytotoxicity, and CD56^high NK cells, primarily residing in lymphoid tissues and functioning as robust cytokine producers owing to elevated IL-2 receptor expression[21].

NK cell effector functions are determined by a balance between activating and inhibitory signals. During MTB infection, downregulation of MHC class I on infected cells reduces inhibitory signaling, thereby facilitating NK-mediated cytotoxicity. Activating receptors, including NKp44, NKp46, and NKp30, engage MTB cell wall components like arabinogalactan–peptidoglycan complexes and mycolic acids, stimulating NK cells to secrete IFN-γ and IL-22, which exert antimicrobial effects. Additionally, NK cells mediate killing of infected cells via granule exocytosis (perforin, granzymes) and through death receptor pathways involving Fas/FasL [22].

Beyond direct cytotoxicity, NK cells can be activated through antibody-dependent cellular cytotoxicity (ADCC), releasing cytokines and chemokines that shape adaptive immune responses. Within TB granulomas, NK cells contribute to both pathogen clearance and immunoregulatory functions, highlighting their dual role in controlling MTB and modulating host immunity [23].

4. Dendritic cells (DCs) in Host Immunity and Their Anti-Tuberculosis

Upon encountering MTB, immature dendritic cells (iDCs) recognize and internalize bacilli through pattern recognition receptors (PRRs) like TLR2, TLR4, and DC-SIGN. Following antigen uptake, iDCs upregulate the chemokine receptor CCR7, facilitating migration to secondary lymphoid organs where they undergo maturation. Mature DCs process and present MTB antigens on MHC molecules and express co-stimulatory markers, including CD80 and CD86, to activate T cells and direct their differentiation toward CD4+ subset[24].

Cytokines produced by mature dendritic cells (mDCs) including IL-12, TNF-α, and IFN-α, promote the polarization of CD4+ T cells into Th1 effector cells, which secrete IFN-γ to enhance macrophage activation. Through these processes, DCs orchestrate the interplay between innate and adaptive immune responses, playing an indispensable role in controlling MTB infection and shaping protective immunity [25].

5. T lymphocytes in Host Immunity and Their Anti-Tuberculosis Actions

T-cell responses against MTB are initiated when antigen-presenting cells (APCs), especially mature dendritic cells, process and display MTB antigens on major histocompatibility complex (MHC)

molecules. Engagement of the T-cell receptor (TCR) with these MHC–peptide complexes trigger T-cell activation. CD4+ T cells recognize antigens presented on MHC class II, whereas CD8+ T cells respond to antigens on MHC class I, eliciting distinct but complementary immune functions. For full activation, T cells depend on co-stimulatory input delivered by APCs [26].

Upon activation, T cells differentiate into specialized subsets. Naïve $CD4^+$ T helper cells can develop into Th1, Th2, Th17, or Treg lineages. Th1 cells are particularly critical in TB defense, producing IL-2, IFN-γ, and TNF-α, which enhance macrophage bactericidal action, recruit neutrophils, and stimulate the release of reactive intermediates and inflammatory mediators to control MTB infection. Th17 cells contribute by secreting cytokines like IL-17A, -21, -22, and -26, that promote neutrophil recruitment and amplify inflammatory responses [27].

Concurrently, $CD8^+$ T cells undergo proliferation and developed into cytotoxic T lymphocytes (CTLs) upon recognition of MTB-derived peptides presented by MHC class I. CTLs eliminate infected cells through granule exocytosis (perforin and granulysin) or via the Fas–FasL apoptotic pathway, while also secreting IFN-γ to enhance macrophage antimicrobial functions [28;29]. Collectively, these cellular mechanisms underscore the central role of T-cell-mediated immunity in controlling MTB infection and highlight its significance as a target for TB vaccine development.

6. B lymphocytes in Host Immunity and Their Anti-Tuberculosis Actions

In response to MTB, B cells act as specialized APCs by capturing Ags through surface receptors and presenting them to $CD4^+$ T cells for activation. $CD4^+$ T cells then differentiate into Th1 and Th2 subsets, which regulate B-cell Ab release and mediate apoptosis of MTB-infected cells [30].

B cells also differentiate into subsets like B effector 1 (Be1), B effector 2 (Be2), and B regulatory cells (Breg). Be1 and Be2 subsets produce cytokines that drive Th1 and Th2 differentiation, aiding MTB clearance. B cell–derived antibodies are essential for neutralizing microbial toxins and defending against infection. Importantly, antibody-mediated antigen presentation via Fcγ receptors (FcR) has been proposed as an effective vaccination mechanism [31].

Although not fully understood, Fcγ receptors (FcRII/CD32, FcRI/CD64, FcRIII/CD16) are key immunoregulatory molecules. Depending on their signaling motifs (ITAM or ITIM), FcRs exert activating or inhibitory functions, influencing T-cell activation as well as DC maturation and antigen presentation, thereby shaping adaptive immunity [32].

7. Immune defense mechanism of MTB

The conflict between humans and MTB has persisted over millennia. Through extensive evolutionary adaptation, MTB has acquired sophisticated strategies to circumvent host immune defenses. These evasion mechanisms hinder effective immune recognition and pathogen clearance, contributing to the establishment of LTBI or progression to ATB. Broadly, MTB's immune evasion can be grouped into three principal categories: intrinsic bacterial virulence factors, subversion of innate immune responses, and interference with adaptive immunity [33].

CONCLUSIONS

TB continues to pose a major worldwide health burden, where the immune balance determines disease outcome. Th2 cytokines, particularly IL-4 and-10, had a dual function: moderating inflammation but also weakening protective Th1 responses, allowing bacillary persistence and contributing to fibrosis and cavitation. Their influence on disease severity, bacterial load, and pulmonary involvement emphasizes their importance as

investigational biomarkers and therapeutic. Greater understanding of Th2-mediated immune modulation may guide future diagnostic tools, vaccines, and adjunctive treatments, ultimately improving TB control and patient outcomes.

Conflict of Interest: None

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The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work, if that information is not provided in another

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