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# Cytokine-Mediated Immune Responses in *Mycobacterium tuberculosis* Infections: Mechanisms, Regulation, and Therapeutic Implications

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**ABSTRACT**

Cytokines are key players in the coordination of immune responses against bacterial pathogens, and their dysregulation leads to immunopathology and normal protective immunity. This review article analyses the elaborate cytokine interactions present in *Mycobacterium tuberculosis* infections, which is one of the major bacterial pathogens posing health challenges in the world. We study the various roles played by pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6) and Interleukin-12 (IL-12), as well as anti-inflammatory cytokines such as Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF-β) in the pathogenesis of tuberculosis. The review examines the effects of *M. tuberculosis* on cytokine responses that promote persistent infection, the importance of cytokine balance in forming and maintaining granulomas, and the role of cytokine dysregulation in severe disease manifestations. In addition, we discuss genetic polymorphisms in cytokine genes as determinants of susceptibility to contracting tuberculosis, as well as the effect of co-infection on the cytokine profiles and future therapeutic interventions focusing on cytokine pathways. It is essential to understand these complex cytokine-based mechanisms to devise new immunotherapeutic strategies and enhance the outcomes of the treatment of tuberculosis and other mycobacterial infections.

***Keywords:*** Cytokines, *Mycobacterium tuberculosis*, Inflammation, Interleukins, TNF-α, granuloma, Immunopathology.

## 1. Introduction

### 1. 1. Global Impact of *Mycobacterium tuberculosis*

*Mycobacterium tuberculosis* (Mtb) has been among the major causes of morbidity and mortality worldwide, with an estimated 10 million cases and 1.5 million deaths occurring each year (Chakaya et al., 2021; *Global Tuberculosis Report*, 2024). Although there is now much more knowledge about tuberculosis (TB) pathogenesis, as well as the presence of effective antimicrobial therapy, the appearance of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has brought a pressing issue of the necessity to develop new therapeutic modalities (Dheda et al., 2017; Seung et al., 2015). The interplay between the Mtb and the host immune system is a very complicated phenomenon that can be considered a critical determinant of the disease outcome, and cytokines are one of the main mediators of this complex biological communication (Flynn & Chan, 2022; Philips & Ernst, 2012). Importantly, cytokine profiling among drug-resistant individuals has recently revealed exaggerated hyperinflammatory cytokine signatures associated with disease severity in recent cohorts, highlighting the need to consider cytokine biology in MDR/XDR-TB strategies (Zhang et al., 2023).

Mtb has been successful as a human pathogen due to its amazing power to survive and reproduce inside the host macrophages, which are the same cells that are meant to destroy the pathogens that invade them (Cambier et al., 2014). The intracellular lifestyle requires complex processes of immune evasion and control of host cell functions, primarily through the regulation of cytokine synthesis and signalling pathways (Kleinnijenhuis et al., 2011). Elucidating the role of cytokines in the immune response to Mtb infection is critical to the development of effective immunotherapies that can boost antimicrobial immunity while reducing tissue damage (Zumla et al., 2016).

### 1. 2. Cytokines: Definition and Classification

Cytokines are minuscule secreted proteins that serve as cell-to-cell messengers, mediating communication among immune cells and coordinating inflammatory and immune responses (Turner et al., 2014). These soluble mediators may be categorized according to their structure, cellular source or biological function. The general classification of cytokines in the case of bacterial infections is into pro-inflammatory cytokines, which induce antimicrobial effects and tissue inflammation, and anti-inflammatory cytokines, which control and resolve inflammatory reactions (Opal & DePalo, 2000).

Among the pro-inflammatory cytokines are tumor necrosis factor-alpha (TNF-alpha), interleukin-1β, interleukin-6 (IL-6), interleukin-12 (IL-12), and interferon-gamma (IFN-gamma) (Parameswaran & Patial, 2010). These cytokines mobilise the immune cells, stimulate phagocytic functions, stimulate the attraction of leukocytes to infection sites, and develop adaptive immune responses. Pro-inflammatory reactions are neutralised by anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which inhibit excessive tissue injury and help resolve inflammatory events (Couper et al., 2008).

The chemokine family is a distinct group of cytokines whose main action is to serve as chemoattractants to guide the movement of immune cells to the location of inflammation or infection (Charo & Ransohoff, 2006). Some of the important chemokines implicated in TB pathogenesis are CCL2 (MCP-1), CCL5 (RANTES), CXCL8 (IL-8), CXCL9, and CXCL10 (Zhuang et al., 2024). These molecules are important in the formation of granulomas, the recruitment of immunological cells, and the spatial arrangement of immune responses in infected tissues.

## 2. The Pathobiology of *Mycobacterium tuberculosis* Infection

The transmission of Mtb happens mainly by breathing in aerosol droplets containing the bacteria, which are lodged along the lung alveoli, where they interact with alveolar macrophages (Ernst, 2012). Host cells respond to the initial contact with Mtb through a cascade of events that helps in defining whether the infection will be suppressed, develop active disease or enter into

a state of latency (Flynn et al., 2011). This is a critical period of infection during which there will be excessive interaction between innate immune cells and a series of cytokines produced that influence further adaptive immune responses.

After being phagocytosed by alveolar macrophages, Mtb has several mechanisms of surviving in the hostile intracellular environment (Weiss & Schaible, 2015). The bacteria are able to prevent phagosome-lysosome fusion, control phagosomal pH, withstand oxidative and nitrosative stress, and regulate host cell death. These survival responses are closely connected with the capacity of the bacterium to disrupt the cytokine signalling, directly regulating the cytokine production or changing the response of the cell to the cytokine stimulation (Stanley & Cox, 2013).

The characteristic pathological process in the case of TB is the appearance of granulomas, which are organized formations of infected macrophages with the presence of other types of immune cells such as lymphocytes, neutrophils, fibroblasts and multinucleated giant cells (Ramakrishnan, 2012). The formation of granulomas is a host mechanism to localize the infection and avoid the spread of bacteria; yet, at the same time, it offers a niche under which Mtb can survive in a metabolically inactive form. The local cytokine milieu also has a significant impact on the development of granulomas and their ultimate outcome, and the knowledge of cytokine networks is critical to understanding the pathogenesis of TB (Gideon et al., 2015).

One of the most important aspects of granuloma biology, yet one that is frequently overlooked, is the polarization of macrophages in granulomas. Macrophages expressing a pro-inflammatory (M1) phenotype, stimulated by signaling pathways activated by IFN-γ and TNF-α, have enhanced antimicrobial activity, including the production of reactive oxygen and nitrogen species, the secretion of pro-inflammatory cytokines, and the upregulation of MHC class II molecules. However, alternatively activated (M2) macrophages, stimulated by IL-4, IL-13 and IL-10, have anti-inflammatory functions like tissue repair and fibrosis and reduced bactericidal activity. TNF-α and IFN-γ stimulate the M1 phenotype, which is associated with an inflammatory response, increasing bacterial clearance, while IL-10 and TGF-β stimulate the M2 repair phenotype. Mtb takes full advantage of this balance, inducing production of IL-10 to polarise macrophages to M2 in order to dampen antimicrobial responses and promote the persistence of infection in granulomas. Thus, understanding the regulation of macrophage polarization by cytokines is important for understanding the mechanism of granuloma formation, maintenance and ultimate disease outcome (Ahmad et al., 2022; Gideon et al., 2015).

## 3. Pro-Inflammatory Cytokines in TB Immunity

### 3. 1. Tumor Necrosis Factor-Alpha (TNF-α)

One of the most important cytokines in anti-mycobacterial immunity is TNF-alpha, and the relevance of this particular cytokine has been emphasized in a dramatic manner by the higher rates of TB reactivation in patients undergoing anti-TNF therapy for autoimmune disease (Keane et al., 2001). Activated T cells and macrophages are the major producers of this pleiotropic cytokine after they recognise Mtb pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) (Roach et al., 2002).

The multifunctional TNF-α plays multiple roles in TB immunity, including enhancing macrophage antimicrobial processes by stimulating phagosome maturation, triggering the production of reactive oxygen and nitrogen species, inducing autophagy, and regulating apoptosis (Divangahi et al., 2009). TNF-α is also a highly important consideration in the formation and maintenance of granulomas, which regulate the spatial arrangement of immune cells and eliminate the dissemination of bacteria (Marino et al., 2015). At the molecular level, TNF-α is signalled by two receptors, TNFR1 and TNFR2, which signal through different downstream pathways, including NF-κB, MAPK and death receptor signalling cascades.

Mice lacking TNF-α have also been proved to have a strict need for this cytokine in Mtb infection control whereby knockout mice succumb to bacterial overload and spread the disease within a very short time (Flynn et al., 1995).

Nonetheless, the excessive production of TNF-α may lead to immunopathology, tissue necrosis, and cachexia; therefore, there is a need to regulate the levels of TNF-α that is produced during the infection with specific precision (Harris & Keane, 2010). This paradoxical effect of TNF-alpha as both a defensive and potentially harmful cytokine is an example of a narrow range of response needed to optimally protect against Mtb (**Figure 1**).

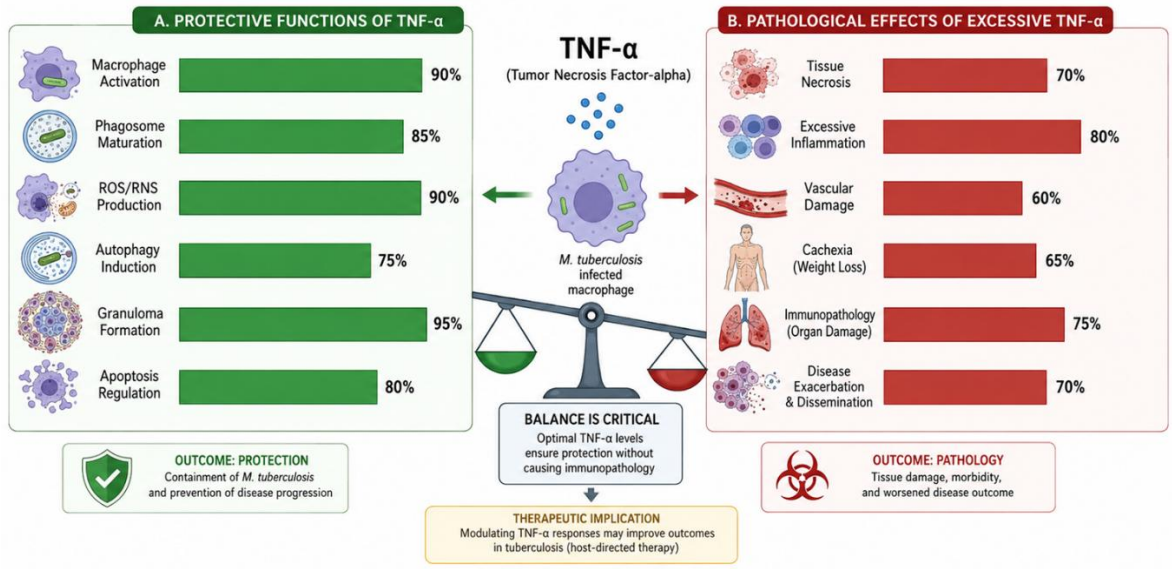



**Figure 1.** Dual role of TNF-α in TB immunity. TNF-α is important for the activation of macrophages, the development of granulomas, autophagy and controlling bacteria, but excessive levels of TNF-α can lead to inflammation, tissue necrosis and immunopathology. It is crucial to have a balanced response to TNF-α if you are to provide protection against Mycobacterium tuberculosis.

### 3. 2. Interleukin-1 B (IL-1β)

Another important pivotal pro-inflammatory cytokine in anti-TB immunity refers to IL-1β, which is mainly generated when the NLRP3 inflammasome is activated due to Mtb infection (Fremond et al., 2007). The inflammasome is a complex of multiple proteins that is able to detect pathogen-associated and danger-associated molecular patterns, which causes caspase-1 to be activated and pro-IL-1β to be processed into its active, bioactive form. Mtb elements like the ESX-1 secretion apparatus and bacterial DNA have been found to be important inducers of inflammasome activation (K. D. Mayer-Barber et al., 2011).

Protective roles of IL-1β in TB encompass improvement of antimicrobial effector functions, T helper 17 (Th17)-cell differentiation, eicosanoid synthesis and regulation of type I interferon responses, which are potentially pathological during Mtb infection and excessively activated (Mishra et al., 2013). The role of IL-1β is also related to the fevers and the acute-phase response, which are the traditional symptoms of the TB disease. Researchers have found that the association of TB vulnerability with the polymorphism of IL1B exists in multiple populations, highlighting the clinical importance of the cytokine (K. Mayer-Barber et al., 2010).

Nevertheless, like TNF-α, IL-1β activity also needs to be strictly regulated to avoid immunopathology. The natural antagonist, IL-1 receptor antagonist (IL-1Ra), is an endogenous antagonist that competes with IL-1β in receptor binding but does not promote signalling. Dysregulation of the IL-1β/IL-1Ra balance has been referred to as a cause of severe manifestations of TB and immune reconstitution inflammatory syndrome (IRIS) during the treatment (McGeachy et al., 2019).

### 3. 3. Interleukin-6 (IL-6)

IL-6 is a pleiotropic cytokine that has both pro-inflammatory and anti-inflammatory functions during Mtb infection (McGeachy et al., 2019). IL-6 is produced by the response of macrophages, dendritic cells and stromal cells against TLR signalling and other pro-inflammatory cytokines and has a significant role in the regulation of both innate and adaptive immunity. The cytokine binds to a hexameric IL-6/ IL-6 receptor (IL-6R) / gp130 receptor complex, leading to the activation of the JAK-STAT3 pathway, among other signalling pathways.

IL-6 plays a role in TB pathogenesis in the acute response, T cell activation and differentiation, production of antibodies, and regulation of local inflammatory response in granulomas (Saunders et al., 2000). It has always been shown in clinical studies that IL-6 levels are higher in patients with an active TB disease, which is associated with the severity of the disease and the quantity of bacteria. The levels of plasma IL-6 reduce after the effective completion of anti-TB treatment, suggesting that IL-6 could be used as a biomarker for treatment monitoring (Walzl et al., 2018). These findings have been reinforced by more recent multiplex cytokine panel studies, which identified IL-6 and other cytokines that responded to treatment as composite signatures that predicted poor treatment outcomes in pulmonary TB (Pandiarajan et al., 2024; Zhang et al., 2023).

The dualism of IL-6 is evident, bearing in mind its involvement in both protective immunity and immunopathology. Although IL-6 is required to maximise T cell response and maintenance of granuloma, a large production of IL-6 has been linked to tissue damage, cachexia, and systemic inflammation. It has also been shown that IL-6 can suppress Th1 responses while promoting Th17 differentiation, which complicates the role of IL-6 in anti-mycobacterial immunity.

### 3. 4. Interleukin-12 (IL-12) and the IL-12/IFN-γ Axis

IL-12 is an important link between innate and adaptive immunity in TB, as it is mainly produced by antigen-presenting cells such as macrophages and dendritic cells after the recognition of Mtb (Trinchieri, 2003). It is a heterodimeric cytokine composed of the p35 and p40 subunits and is a strong stimulator of IFN-γ production by the NK cells and T cells. The IL-12/IFN-γ axis can be deemed the backbone of protective immunity against Mtb, wherein genetic mutations in the IL-12/IFN-γ pathway lead to a highly susceptible nature to mycobacterium infections (Ottenhoff et al., 1998).

The relevance of IL-12 in TB immunity has been supported by the fact that IL-12-deficient mice have defective Th1 responses, decreased production of IFN-γ, poor granuloma formation, and a failure to contain bacterial replication (Cooper et al., 1993). In human beings, gene mutations in IL-12 or its receptor (IL12RB1) cause Mendelian susceptibility to mycobacterial disease (MSMD), which are the severe infections caused by environmental mycobacteria and BCG vaccine strains.

The biological activity of IL-12 acting on the IL-12 receptor (IL-12R), which is composed of two chains, namely IL-12Rβ1 and IL-12Rβ2, causes the stimulation of STAT4 and the resultant activation of the IFN-γ gene and other Th1-like genes. In addition to its effect on IFN-γ, IL-12 stimulates NK cell cytotoxicity, stimulates T cell growth and survival, and balances the different T helper cell subsets. The resulting IFN-γ induced by IL-12 further induces a feedback effect on the macrophage antimicrobial capacities and forms a positive feedback mechanism critical in controlling bacteria (**Figure 2**).

### 3. 5. Interferon-Gamma (IFN-γ)

The prototypical Th1 cytokine and arguably the most critical effector of Th1 immunity against Mtb is IFN-γ (Schroder et al., 2004). IFN-γ is the main macrophage-sensitising factor, produced mainly by CD4+ and CD8+ T cells and NK cells. It causes a programme of antimicrobial reactions that involve heightened phagolysosome maturation, augmented production of reactive oxygen and nitrogen intermediates, amplified autophagy, and augmented expression of the MHC class II (Ehrt et al., 2001).

The contribution of IFN-γ to TB immunity has been clearly demonstrated in experiments on IFN-γ-KO mice, which immediately become infected with Mtb, with active bacterial multiplication and spreading of the disease (Flynn et al., 1993).

On the same note, humans lacking IFN-γ or its receptor (IFNGR1 or IFNGR2) genetically develop serious infections of mycobacteria, which confirms again the non-redundant role of this cytokine. Interestingly, although IFN-γ is vital in the early management of Mtb infection, high concentrations that persistently rise may contribute to tissue damage and disease progression, highlighting the value of proper regulation.

IFN-γ expresses the IFN-γ receptor (IFNGR), a heterodimeric receptor complex of IFNGR1 and IFNGR2 chains, which triggers the JAK-STAT1 pathway with hundreds of interferon-stimulated genes (ISGs) activated. Some of these ISGs include genes that encode antimicrobial effector molecules, antigen presentation machinery, and cellular metabolic regulators. The magnitude and duration of IFN-γ signalling are maintained at various levels: receptor expression, negative regulators including SOCS proteins and epigenetic changes.

**Table 1.** Major Pro-Inflammatory Cytokines in M. tuberculosis Infection.

| Cytokine | Primary Sources | Key Receptors | Main Functions in TB | Signalling Pathways | Clinical Significance |
|---|---|---|---|---|---|
| **TNF-α** | Macrophages, T cells | TNFR1, TNFR2 | Granuloma formation, macrophage activation, apoptosis regulation | NF-κB, MAPK, death receptor | Essential for control; anti-TNF therapy increases TB risk |
| **IL-1β** | Macrophages, monocytes | IL-1R1 | Inflammasome activation, Th17 differentiation, eicosanoid production | MyD88, NF-κB | Polymorphisms associated with susceptibility |
| **IL-6** | Macrophages, DCs, stromal cells | IL-6R/gp130 | Acute phase response, T cell activation, antibody production | JAK-STAT3, MAPK | Elevated in active disease; biomarker potential |
| **IL-12** | Macrophages, DCs | IL-12Rβ1/β2 | IFN-γ induction, Th1 differentiation, NK cell activation | JAK-TYK2-STAT4 | Deficiency causes MSMD |
| **IFN-γ** | T cells, NK cells | IFNGR1/IFNGR2 | Macrophage activation, autophagy, ROS/RNS production | JAK-STAT1 | Essential for protection; genetic deficiency lethal |

## 4. Anti-inflammatory and Regulatory Cytokines

### 4. 1. Interleukin-10 (IL-10)

The prototype of anti-inflammatory cytokine is IL-10, which is an important but complex element of TB pathogenesis (Redford et al., 2011). Although IL-10 is crucial in inhibiting excessive inflammation and tissue damage, it may also suppress antimicrobial immunity as well as promote bacterial persistence. It is produced by other cell types such as macrophages, dendritic cells, regulatory T cells (Tregs) and even infected cells that react to Mtb, indicating that there is more than one cell layer of immune control (Sendide et al., 2005).

The immunosuppressive effects of IL-10 occur via the IL-10 receptor (IL-10R), which stimulates the activation of the STAT3 signalling pathway, leading to gene expression that inhibits inflammatory responses. IL-10 suppresses the expression of pro-inflammatory cytokines such as TNF-alpha, IL-1β, IL-6, and IL-12, as well as the expression of MHC class II and

costimulatory molecules on antigen-presenting cells, T cell activation and proliferation (Moore et al., 2001). Considering the case of Mtb infection, IL-10 can suppress phagosome-lysosome fusion through precise molecular mechanisms. IL-10-mediated STAT3 activation inhibits calcium signalling required for phagosomal maturation and prevents the proper recruitment and aggregation of key endosomal maturation markers, including EEA1 (Early Endosome Antigen 1) and Rab7, on the phagosomal membrane. This blockade of EEA1 and Rab7 recruitment prevents late endosome-lysosome fusion, thereby halting the acidification and enzymatic degradation necessary to kill intracellular Mtb. In addition, IL-10 decreases the production of reactive nitrogen species and inhibits autophagy, thus helping bacteria to survive.

In vivo experiments with IL-10-deficient mice have produced apparently contradictory findings, with some studies reporting improved bacterial control and others a higher incidence of immunopathology and death (Beamer et al., 2008). Such divergent results indicate the context dependence of IL-10 activity and indicate that the timing, amount, and cellular source of IL-10 production probably play a pivotal role in the outcome of a disease. Clinical studies have demonstrated increased levels of IL-10 in patients with active TB, and a high level of the IL-10/IFN-gamma ratio has been attributed to poor prognosis.

Mtb has developed mechanisms to bypass IL-10-mediated immunosuppression, whereby some secreted factors and bacterial components can induce IL-10 (Hmama et al., 2015). Such IL-10 induction by this pathogen can be an immune evasion mechanism of bacteria, thus permitting Mtb to become a chronic infection by suppressing protective immunity (**Figure 2**).

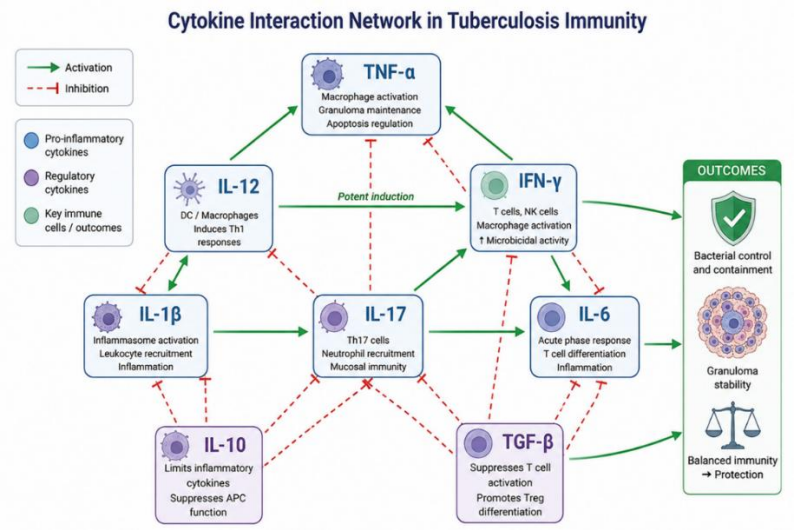



**Figure 2.** Immunity against tuberculosis, mediated by cytokines. Green arrows mean activation, red dashed lines mean inhibition. The IL-12/IFN-γ axis is linked to the protective immunity, and IL-10 and TGF-β are linked to excess inflammation.

### 4. 2. Transforming Growth Factor-B (TGF-β)

Another immunoregulatory cytokine is TGF-β, which has divergent functions in TB pathogenesis (Deng et al., 2024). TGF-β is a cytokine that has three mammalian isoforms (TGF-β1, TGF-β2, and TGF-β3) and is secreted by a wide range of cell types such as macrophages, T cells, and stromal cells. TGF-β binds to serine/threonine kinase receptors (TGFβRI and TGFβRII), which stimulate SMAD-dependent and SMAD-independent pathways.

TGF-β, in the case of Mtb infection, has immunosuppressive properties such as T cell growth and activation, macrophage activation, production of pro-inflammatory cytokines, and regulatory T cell differentiation (Toossi et al., 1995). TGF-β can also affect tissue remodelling and fibrosis, which are also pertinent to the formation of the granuloma and cavitation in TB. High levels of TGF-β have been observed in tuberculous pleural effusions and in lung lesions, indicating that there is active immunoregulation in areas of infection.

Nevertheless, TGF-β is not always harmful to TB immunity. It is a cytokine that helps maintain immune homeostasis and prevents overproduction of inflammation that may result in tissue damage. It also plays a role in applying roles in the healing of inflammation following successful treatment. The proportion between TGF-β and pro-inflammatory cytokines is probably the requirement to regulate immune responses properly or suppress them pathologically (Kuroda et al., 2018).

## 5. Chemokines and Immune Cell Recruitment

### 5. 1. C-C Chemokine Ligands (CCL)

The spatial organisation of immune responses is achieved through the coordination of the movement of certain populations of cells to the location of infection under the direction of the chemokines (Griffith et al., 2014) . There are various C-C chemokine ligands that are critical in the recruitment of immune cells and formation of granuloma in TB. One of the most highly expressed chemokines in response to Mtb infection is CCL2 (MCP-1) that attracts monocytes and macrophages to infected tissue (Dorhoi & Kaufmann, 2016). CCL2 has been observed to be elevated in serum, bronchoalveolar lavage fluid, and tissue samples of individuals with TB.

Other significant C-C chemokines in TB immunity include CCL3 (MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES), which attract T cells, NK cells, and monocytes into granulomas (Algood et al., 2004). Activated macrophages and dendritic cells produce these chemokines in the presence of Mtb and pro-inflammatory cytokines. Research with chemokine knockout mice has shown cellular recruitment of the immune cells, lack of granuloma formation, and greater vulnerability of the organism to Mtb infection.

Chemokine gradients, which are formed through the coordinated expression of several chemokines, help direct the various cell types within granulomas to distinct areas, and this is part of the organised structure of such lesions. Nevertheless, chemokine secretion may cause immunopathology with the excessive recruitment of inflammatory cells, leading to tissue destruction in case of overproduction (Gopal et al., 2013). Striking the right balance between the right cell recruitment and pathological inflammation is thus essential in the realisation of the best TB results (**Figure 3**).

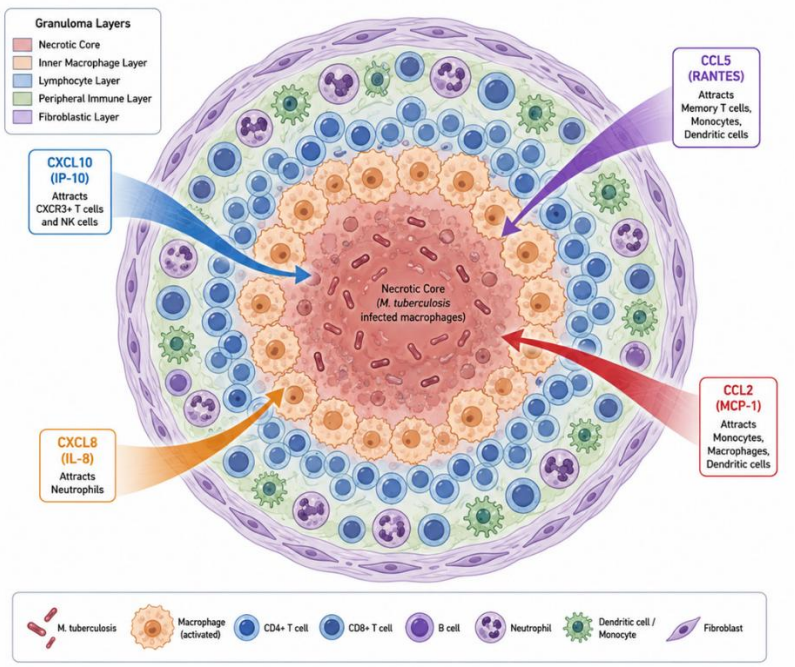



**Figure 3.** Chemokine-mediated cell recruitment in the tuberculosis granuloma. Chemokine gradients coordinate immune cell trafficking and granuloma organisation during Mycobacterium tuberculosis infection.

### 5. 2. C-X-C Chemokine Ligands (CXCL)

Another family of chemokines that plays an important role in the pathogenesis of TB is the C-X-C chemokine ligands. CXCL8 (IL-8) is a strong neutrophil chemoattractant produced in large amounts during Mtb infection (Nouailles et al., 2014). Although neutrophils are involved in the initial antimicrobial reactions, neutrophil hyper-recruitment and hyper-activation have been linked to tissue destruction and adverse disease outcomes in TB.

The induction of CXCL9, CXCL10, and CXCL11 (also known as interferon-inducible CXC chemokines) by IFN-gamma plays significant roles in targeting activated T cells and NK cells to Mtb infection foci (Antonelli et al., 2010). These chemokines communicate via the CXCR3 receptor and help in the formation and elimination of granulomas. CXCL9 and CXCL10 have been detected in active TB patients and have been found promising as diagnostic and prognostic biomarkers.

**Table 2.** Key Chemokines in Tuberculosis Pathogenesis.

| Chemokine | Alternative Names | Primary Targets | Receptor | Functions in TB | Clinical Observations |
|---|---|---|---|---|---|
| **CCL2** | MCP-1 | Monocytes, macrophages | CCR2 | Monocyte recruitment, granuloma formation | Elevated in active TB |
| **CCL5** | RANTES | T cells, eosinophils | CCR1, CCR3, CCR5 | T cell recruitment, granuloma maintenance | Elevated in TB pleurisy |
| **CXCL8** | IL-8 | Neutrophils | CXCR1, CXCR2 | Neutrophil recruitment | High levels in severe disease |
| **CXCL10** | IP-10 | Activated T cells, NK cells | CXCR3 | Th1 cell recruitment | Diagnostic potential |

## 6. Cytokine Networks and Cross-regulation

### 6. 1. The Th1/Th2 Balance

T helper 1 (Th1)-T helper 2 (Th2) balance is a well-known paradigm in immunology that is of great importance to the pathogenesis of TB (Lyadova & Panteleev, 2015). Th1 responses, which involve the production of IFN-gamma, TNF-alpha and IL-2, favour cell-mediated immunity and the activation of macrophages necessary in the process of controlling intracellular pathogens such as Mtb. Conversely, Th2 responses, characterized by the production of IL-4, IL-5 and IL-13, are usually linked to humoral immunity and allergy.

In Mtb infection, Th1 is the essential response that is important in offering protective immunity (Brighenti & Andersson, 2012). Antigen-presenting cells produce IL-12, which induces Th1 differentiation by activating the STAT4 pathway, and IL-4 stimulates Th2 differentiation by activating the STAT6 pathway. There is antagonism between these pathways, where IFN-γ suppresses Th2 responses, and IL-4 suppresses Th1 differentiation. A change towards a Th2 cytokine profile has been linked to progressive TB disease, suggesting that this imbalance has a role in failed immunity.

### 6. 2. The Th17/Treg Axis

The Th17/Treg axis is the other important axis in TB immunity (Cruz et al., 2006). Th17 cells play an important part in mucosal immunity, neutrophil recruitment, and antimicrobial peptide production because of their production of IL-17A, IL-17F, and IL-22. TGF-β together with pro-inflammatory cytokines like IL-6, IL-1β, and IL-23 induces these cells.

Th17 responses have been implicated in protection and pathology based on the situation in TB (Khader et al., 2007). Recruitment of neutrophils through IL-17 can facilitate a rapid response to bacteria, whereas a large response by Th17 cells can lead to tissue destruction and cavitation. Remarkably, the development of Th17 and Treg cells is similar, and TGF-β is necessary for both lineages; however, the final cell fate is predetermined by the presence of pro-inflammatory cytokines.

The Th17/Treg balance is dynamically maintained in the case of TB infection, and changes in this balance may affect the course of disease and treatment outcomes (Torrado & Cooper, 2010). Some studies have demonstrated that active TB is associated with an increased Th17 response, which resolves with proper treatment, whereas others have demonstrated high Treg frequencies knocking out protective immunity. The Th17/Treg cell ratio has been suggested as a possible biomarker of disease condition and response to treatment.

### 6. 3. Type I Interferon Responses

Type I interferons (IFN-α/β) are a group of cytokines that are traditionally linked to antiviral immune response but have recently been found to be key regulators of TB disease progression (Berry et al., 2010). In contrast to the protective effects of IFN-γ (type II interferon), type I interferons may be harmful during Mtb infection in some circumstances. Overactivity of type I interferon signalling has been demonstrated to inhibit protective Th1 responses, maladapt Th1 macrophage antimicrobial responses, and induce vulnerability to TB in mouse models.

The pathways of these damaging impacts of type I interferons in TB include the inhibition of IL-12 and IL-10 production, stimulation of cell death leading to the release of bacteria from infected cells, and direct inhibition of IFN-γ signalling (Mundra et al., 2023). Interestingly, the exploitation of type I interferon responses by Mtb may be active, and there are some bacterial components that tend to induce this pathway (**Figure 2**).

## 7. Cytokine Dysregulation and Disease Manifestations

### 7. 1. Cytokine Storms and Severe TB

The cytokine storm, which is characterised by the uncontrolled and excessive production of the pro-inflammatory cytokines, is a severe complication of TB that may result in acute respiratory distress syndrome (ARDS), septic shock, and multi-organ failure (Channappanavar & Perlman, 2017). The condition is hyperinflammatory and promoted by positive feedback loops of TNF-α, IL-1β, and IL-6 among other pro-inflammatory cytokines, leading to systemic inflammation and tissue destruction (**Figure 4**).

Dysregulated cytokine reaction is especially linked with certain types of TB, such as miliary TB and TB meningitis. The pro-inflammatory cytokine versus anti-inflammatory cytokine balance is, in such instances, grossly disturbed, resulting in immunopathology that is a leading cause of morbidity and mortality (Sia et al., 2015). It is fundamental to understand the causes and pathophysiology of cytokine storms in TB when designing measures to curb or attenuate these life-threatening complications.

### 7. 2. Immune Reconstitution Inflammatory Syndrome (IRIS)

TB-related IRIS develops in a group of patients after they take antiretroviral therapy during HIV-TB co-infection or when they take anti-TB medication in severely immunocompromised patients (Meintjes et al., 2008). It is a paradoxical exacerbation of clinical symptoms with the increase in microbiological improvement, mediated by the rapid reconstitution of pathogen-specific immune responses, in particular, the exaggerated production of pro-inflammatory cytokines.

It has been observed that the levels of TNF-α, IFN-γ, IL-6 and IL-18 are significantly higher in IRIS patients with inadequate regulation of cytokines such as IL-10. The IRIS cytokine profile indicates the presence of an unbalanced immune reconstitution

process in which the pro-inflammatory processes surpass regulatory processes. Targeted therapeutic interventions (i.e., TNF-α and IL-6) have been shown to be promising therapeutic options in treating severe cases of IRIS.

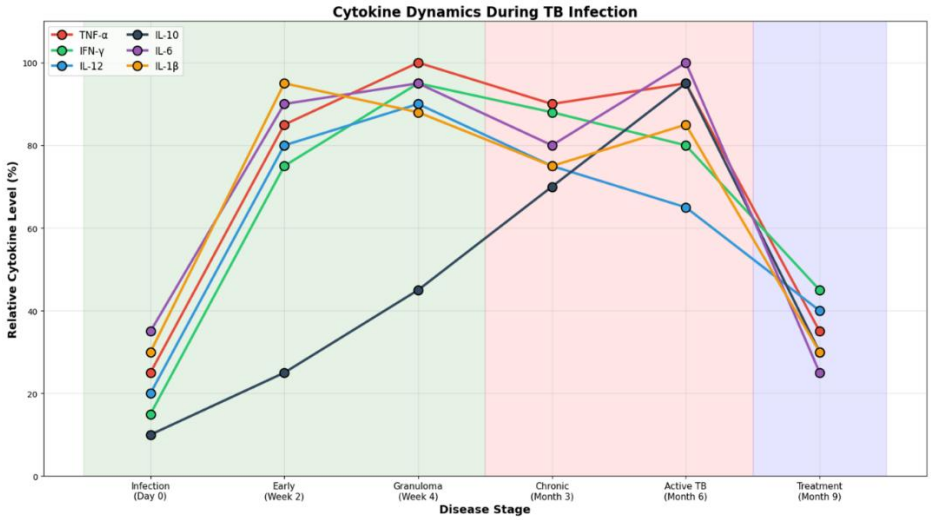



**Figure 4.** Cytokine temporality during the TB infection and treatment. This line graph will represent the relative concentrations of key cytokines (TNF-α, IFN-γ, IL-12, IL-10, IL-6, IL-1β) in six stages of disease: initial infection, early response, granuloma formation, chronic disease, active disease, and treatment disease. The graph is broken down into three phases that are represented by the shaded areas, namely, protective phase (green), pathological phase (red), and recovery phase (blue). The peak levels of pro-inflammatory cytokines are observed in the initial response phase and are sustained in the active disease phase, whereas the IL-10 levels rise gradually in the chronic and active disease phases. The outcome of the treatment is the recovery of normal cytokine levels. It is a significant pattern that can be used to consider the timing of immunotherapeutic interventions.

### 7. 3. Genetic Polymorphisms and Cytokine Responses

The individual cytokine gene variations have been major contributors to individual vulnerability to TB and disease outcomes (Schurz et al., 2024). Genomic evidence contributing to changes in TB risk includes single nucleotide polymorphisms (SNPs) in TNF-α, IL-10, IL-12, and IFN-γ, always with their respective receptors. These polymorphisms may change cytokine production levels, receptor affinity and the efficiency of the signalling process.

As an example, the TNF-α -308G/A polymorphism has been implicated in a higher risk of TB among certain populations, perhaps by placing TNF-α under the influence of changed production (Correa et al., 2005). In a similar manner, polymorphisms of IL-10 promoters leading to increased IL-10 production have been linked to an increased risk of TB, which is consistent with the immunosuppressive effects of this cytokine. Knowledge of the genetic etiology of cytokine dysregulation may facilitate individualized medicine in the treatment of TB.

## 8. Therapeutic Targeting of Cytokine Pathways

### 8. 1. Current Immunotherapeutic Approaches

The immunobiological importance of cytokines in TB immunity has led to interest in immunotherapeutic strategies to regulate cytokine responses to promote better control of this organism but with limited immunopathology (Guler et al., 2021). Some of the strategies that are being studied include cytokine supplementation, cytokine neutralisation, and alteration of cytokine signalling pathways.

The use of IFN-γ therapy as an adjunctive therapy to treat drug-resistant TB and patients with compromised immunity has also been investigated, with some clinical improvements being reported. On the other hand, countering any undesirable IL-10 or TGF-β to boost antimicrobial immunity may be another approach, but one should pay attention to preventing immunopathology. The intake of particular cytokine suppressors like anti-TNF-α agents is extremely precarious because of the danger of the reactivation of TB (**Figure 5**).

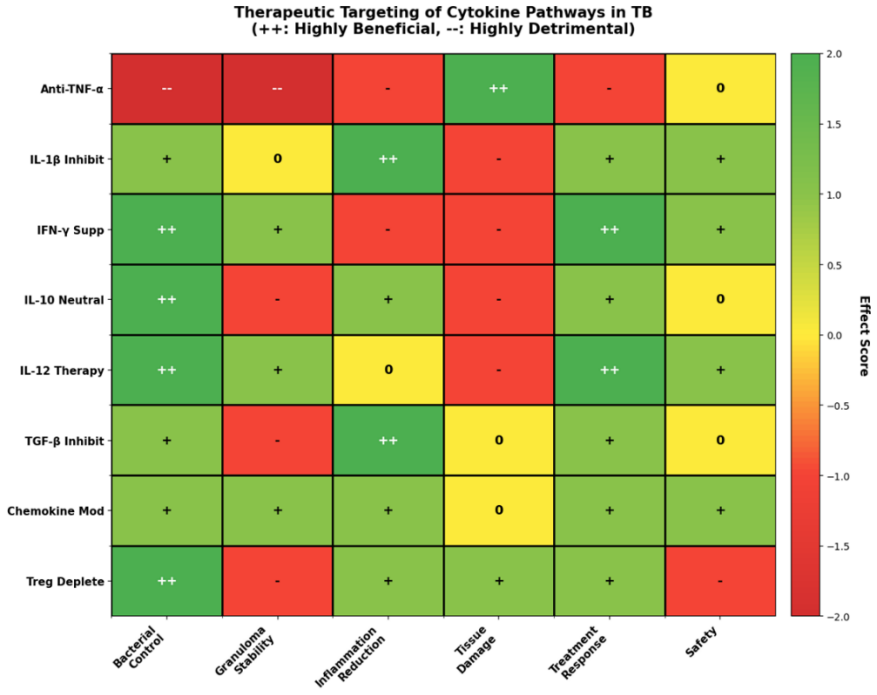



**Figure 5.** Cytokine pathway therapeutic targeting of TB. Heatmap to illustrate the predicted effectiveness of the various immunotherapeutic strategies in different outcomes. Anti-TNF-α blockade, IL-1β neutralisation, IFN-γ treatment, IL-10 neutralisation, IL-12 therapy, TGF-β inhibition, chemokine, and Treg depletion can be used as strategies. Bacterial control, granuloma stability, reduction in inflammation, tissue damage, treatment response and the safety profile are the outcomes that are assessed. There is the color coding of red (highly detrimental), yellow (neutral) and also green (highly beneficial). The heatmap demonstrates that anti-TNF-α blockade is extremely harmful to the level of bacterial control and granuloma stability, whereas such strategies as IFN-γ supplementation and IL-12 therapy have a very positive impact. This discussion offers a paradigm for the rational choice of cytokine-based therapeutic interventions in TB.

### 8. 2. Host-Directed Therapies

Instead of attacking the pathogen directly, host-directed therapies (HDTs) attempt to mediate host immune responses (Wallis et al., 2016). The benefits associated with these methods are that the risk of drug resistance is minimised and there is a possible effectiveness of the treatments against drug-resistant strains. Some of the HDTs currently being studied by researchers include cytokine pathway modulation, such as COX-2 inhibitors that regulate eicosanoid-mediated inflammation, JAK-STAT inhibitors, and inflammasome activation.

Recycling already available drugs which have immunomodulatory effects is a good approach toward expedited application to clinical practice. Metformin, statins and even vitamin D have been shown to have the potential to positively regulate cytokine responses in TB. It is important to understand the cytokine-modulating properties of these agents to use them in the best way possible (Singhal et al., 2014).

### 8. 3. Future Directions and Challenges

Combination modalities that concurrently inhibit multiple cytokine mediators, thereby providing an ideal balance of immunity, are likely to be the subject of immunotherapeutic techniques in the future. Individualized medicine (based on individual cytokine levels and genetic backgrounds) could be used to provide TB patients with immunotherapy.

The main difficulties are determining biomarkers to predict which patients will respond to certain immunotherapies, finding the most appropriate timing of interventions, and coming up with a way through which the responses to therapies could be monitored. Systems biology methods and further development of immunological profiling will be crucial in the development of cytokine-directed therapy in TB.

## 9. Critical Analysis and Current Limitations

The data presented above reveal a consistent pattern of cytokines and their networks in TB, but many of them come from murine gene knockout models and in vitro macrophage systems, which do not adequately replicate the structure of the human granuloma or the genetic variability of Mtb strains in clinical settings. This is exemplified by IL-10-deficient mice, which have been shown to have improved bacterial control in one study, no effect in others, and even worse outcomes in some. It is clear that the protective-versus-pathological balance of a particular cytokine depends on its timing, its cell of origin, and its local bacterial burden and is not a fixed, uniform property of the molecule itself. However, results obtained in one model system need to be carefully extrapolated to human disease and require independent confirmation.

Another caveat relates to the translational bottleneck between mechanistic insights and clinical utility. The majority of the host-directed, cytokine-targeting strategies mentioned here are either preclinical or based on only small case series, with a few performed in well-powered randomized trials. This gap is becoming increasingly important as MDR/XDR-TB expands, because recent cytokine profiling studies have revealed hyperinflammatory signatures in drug-resistant disease, but have not yet confirmed whether these signatures are causal drivers that are safe to target or markers of disease severity (Sampath et al., 2023). Lastly, there is no consensus or external validation of a cytokine biomarker panel. Although there are promising candidates, which remain a major hurdle in the ability to translate cytokine biology into clinical use (Pandiarajan et al., 2024; Zhang et al., 2023).

## 10. Future Directions

High-resolution characterization of cytokine networks has become more possible than ever, thanks to recent developments in single-cell RNA sequencing, spatial transcriptomics, and systems immunology. These technologies could enable the design of new treatments that act on the host and are tailored to the individual patients' needs, while also enhancing the ability to predict response to treatment.

## 11. Conclusion

Cytokines are essential intermediates of immunity against Mycobacterium tuberculosis and coordinate highly intricate networks of cell interactions that dictate the outcomes of the disease. The balance between pro-inflammatory and anti-inflammatory cytokines, which stimulate and inhibit immunopathology, respectively, is key to successful control of TB. The concept of a complex network of interactions of individual cytokines and the effects of their dysregulation has contributed to a better understanding of TB pathogenesis.

Recent breakthroughs have shown that Mtb actively controls host cytokine responses to create persistent infection, which shows the highly developed measures of immune evasion that this pathogen uses. There are context-dependent activities of

cytokines that are dependent on the stage of infection, bacterial load, and host genotype as well as co-infection, adding an additional layer of complication that needs to be taken into consideration in therapeutic schemes.

The development of immunotherapeutic interventions that focus on cytokine pathways is also a positive outcome in enhancing TB treatment outcomes, especially in cases of drug resistance. Nevertheless, one should take into account the proper balance of immune reactions, as both cytokine overstimulation and insufficient activation may lead to negative consequences.

Future research efforts are advised to aim at: (1) clarifying the exact timing and spatial patterns of cytokine generation in the presence of TB infection; (2) determining biomarkers influencing individual reactions to cytokine therapy; (3) creating an individualised methodology of immunotherapy and antimicrobial therapy based on host genetic and immunological indicators; and (4) combining cytokine regulation with standard antimicrobial therapy as a means of improving therapy efficacy and shortening of therapy.

With the current development of information about cytokine-mediated immunity in TB, the translation of this information into clinical practice is very promising as a way of dealing with the global TB epidemic, especially in the face of drug-resistant disease and HIV-TB co-infection. The overall knowledge acquired about cytokine networks will play a significant role in the development of the next-generation immunotherapies and vaccines capable of shifting the balance in favor of the host and ultimately contributing to the global eradication of tuberculosis.

## Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

## Data Availability

No data was used for the research described in the article.

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