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The Role of TNF-α (Tumor Necrosis Factor-alpha) in Pulmonary Tuberculosis

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Abstract

Background: Tuberculosis (TB) remains a primary global health concern, with Indonesia accounting for approximately 10% of international cases. Tumor necrosis factor-alpha (TNF-α) plays a crucial role in the immune response against Mycobacterium tuberculosis, particularly in pulmonary tuberculosis (TB).
Method: This article is a narrative literature review that examines the role of tumor necrosis factor-alpha (TNF-α) in pulmonary tuberculosis.
Result: This pro-inflammatory cytokine is essential for activating macrophages, promoting phagolysosome fusion, and supporting the formation and maintenance of granulomas—immune structures critical for containing infection. However, dysregulated TNF-α expression can be detrimental: excessive levels contribute to inflammation and lung tissue damage, while insufficient production—such as that induced by TNF-α inhibitor therapy—can lead to reactivation of latent TB. This narrative review examines the biosynthesis, immunological functions, and regulatory mechanisms of TNF-α in the context of pulmonary tuberculosis, highlighting its dual role in protective immunity and immunopathology.
Conclusion: A deeper understanding of TNF-α modulation may inform the development of targeted, host-directed therapies that improve treatment outcomes while minimizing tissue damage.

Keywords: cytokine, mycobacterium tuberculosis, tuberculosis, and tumor necrosis factor-alpha.

1. INTRODUCTION

Tuberculosis (TB) remains a significant public health concern, particularly in Indonesia, which ranks second globally in TB burden, with an estimated 10% of global cases. Despite ongoing efforts in prevention, diagnosis, and treatment, TB continues to pose a serious threat, highlighting the need for a better understanding of its immunopathogenesis (1,2).

Tumor necrosis factor-alpha (TNF-α) is a key pro-inflammatory cytokine involved in the immune response to Mycobacterium tuberculosis (Mtb). It activates macrophages, enhances phagocytic activity, and contributes to granuloma formation, which helps contain the infection (3,4). TNF-α is also critical for maintaining granuloma integrity—immune structures that restrict bacterial replication and dissemination in the lungs (5). However, excessive TNF-α production can trigger intense pulmonary inflammation and tissue damage, potentially leading to alveolar destruction and fibrosis that worsen clinical manifestations of pulmonary TB (6).

While TNF-α is essential for controlling disease, its dysregulation—whether excessive or deficient—can result in lung tissue damage or the reactivation of latent TB, particularly in individuals undergoing TNF-α inhibitor therapy (7).

Although the role of TNF-α in TB pathogenesis has been recognized, existing studies remain fragmented, and its dual role in both immune protection and pathology remains unclear. This

literature review aims to synthesize current findings on the biosynthesis and immunological functions of TNF-α in pulmonary TB to support the development of more effective and safer therapeutic strategies.

2. MATERIALS AND METHODS

This article is a narrative literature review that examines the role of tumor necrosis factor-alpha (TNF-α) in pulmonary tuberculosis. The literature search was conducted using several academic databases, including PubMed, ScienceDirect, and Google Scholar. Keywords used in the search included "TNF-α," "tumor necrosis factor-alpha," "tuberculosis," "pulmonary TB," and "immune response."

Articles included in this review were selected based on relevance to the topic, with a focus on original research, reviews, and meta-analyses published in English between 2015 and 2025. Studies were excluded if they were unrelated to pulmonary TB, lacked specific discussion on TNF-α, or were not accessible in full text. The final selection of literature prioritized peer-reviewed studies that provided insights into TNF-α biosynthesis, immunological functions, regulatory mechanisms, and clinical implications in the pathogenesis of TB.

The literature gathered was then organized thematically and critically analyzed to highlight the dual role of TNF-α in both immune protection and pathological processes during pulmonary tuberculosis infection. The findings are presented and discussed in the following sections.

3. Discussion

a. Tuberculosis

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis, which primarily affects the lungs but can also spread to other organs. The infection begins when the bacteria are inhaled and reach the alveoli of the lungs, where they can replicate and trigger an immune response. In the early stages, individuals may not exhibit noticeable symptoms; however, if the infection is not controlled, it can progress to active TB, characterized by symptoms such as chronic cough, fever, weight loss, and night sweats (8,9).

Mycobacterium tuberculosis is the bacterium responsible for tuberculosis. It is a facultative intracellular pathogen that replicates slowly and has an acid-fast cell wall. This bacterium can persist in the human body without causing symptoms (latent infection) and infects the lungs through the inhalation of infectious particles. During infection, M. tuberculosis evades the immune system by exploiting macrophages and forming granulomas, which can progress to active disease if the immune system becomes compromised. Transmission occurs when the infection becomes active and capable of spreading (10,11).

b. Tumor necrosis factor-alpha (TNF-α)

Tumor necrosis factor-alpha (TNF-α) is a member of the pro-inflammatory cytokine group. Cytokines are molecules that function as chemical messengers within the immune system, and pro-inflammatory cytokines refer to those released in response to inflammatory stimuli, subsequently activating inflammatory responses in target cells. TNF-α was first identified as a molecule believed to play a key role in the wasting syndrome associated with bacterial infections, and was initially named cachectin. Around the same time, another molecule was discovered that induced necrosis in certain tumors in organisms infected with Gram-negative bacteria. This molecule was later found to be identical to cachectin, and both were subsequently named tumor necrosis factor-alpha (TNF-α) (12–14).

TNF-α is a cytokine with pleiotropic effects that influence various cell types. It has been identified as a key regulator in the inflammatory response and is known to play a role in the pathogenesis of several inflammatory and autoimmune diseases.15,16 Structurally, TNF-α is a homotrimeric protein composed of 157 amino acids, primarily produced by activated macrophages, T lymphocytes, and natural killer (NK) cells (15,17).

c. Biosynthesis of TNF-α

Tumor necrosis factor-alpha (TNF-α) is a member of the TNF superfamily (18,19) which consists of proteins with highly similar structures and conserved interaction profiles (18,20) TNF-α plays a crucial role in various biological processes, including immunomodulation, fever induction,

inflammatory responses, tumor suppression, and control of viral replication (21). The synthesized pro-TNF is inserted into the cell membrane and rapidly forms a homotrimer, which is then proteolytically processed by a TNF-α converting enzyme—a multidomain metalloproteinase—releasing the mature, soluble form of TNF-α with a molecular weight of 17 kDa (18,22). Upon binding to its receptor, TNF-α activates three intracellular signaling pathways: the NF-κB-mediated pathway, the MAPK-JNK pathway, and the caspase-8 pathway. These pathways support a wide range of biological functions, including inflammatory responses, cell survival, proliferation, differentiation, and apoptosis (23).

In the control of mycobacterial infections, TNF-α plays a crucial role by acting on various types of cells. The primary producers of TNF-α are activated macrophages, T lymphocytes, and dendritic cells. This cytokine works synergistically with IFN-γ, stimulating the production of reactive nitrogen intermediates (RNIs), thereby mediating the tuberculostatic functions of macrophages. TNF-α also promotes the migration of immune cells to the site of infection, contributing to the formation of granulomas, which help control the progression of the disease (24).

In response to Mycobacterium tuberculosis or its antigens (Ag), innate immune cells, such as macrophages and dendritic cells, produce TNF after stimulation of pattern-recognition receptors (PRRs) through intracellular signaling pathways involving NF-κB activation (25). The recognition of TNF by the producing cells or their neighboring cells through TNF receptors (TNFRs) leads to various biological responses, including inflammation, oxidative stress, antimicrobial mechanisms, and cell death (7,26). RNA sequencing analysis of single cells has revealed that TNF originates from a diverse range of cellular sources, including blood cell groups such as myeloid-like cells and CD8+ cells (7,27).

Human TNF was first purified from the supernatant of PMA-stimulated HL-60 promyelocytic leukemia cell culture. 7 This TNF is primarily produced by activated immune cells, including macrophages and monocytes. In response to microbes, TNF is also made in smaller amounts by activated non-immune cells, including specific subsets of endothelial cells, fibroblasts, adipocytes, cardiomyocytes, and astrocytes. 28 The synthesis and secretion of TNF are controlled through a series of steps mediated by proteins and enzymes. Initially, TNF is translated as a membrane-bound form (26 kDa, mTNF), which has intracellular and transmembrane domains at the N-terminus and an extracellular domain at the C-terminus. This form assembles into a non-covalent homotrimer, functioning both as an external signal receptor and ligand. mTNF is then converted into soluble TNF (17 kDa, sTNF) through cleavage of the extracellular domain by the TNF-converting enzyme, a metalloprotease (TACE; disintegrin and metalloprotease 17). This highly regulated process releases the sTNF homotrimer into the extracellular environment,20 which is necessary for TNF function and signaling in various physiological and pathological contexts (7).

d. Role of TNF-α in Pulmonary TB

TNF-α mediates multiple cellular and molecular processes in response to Mycobacterium tuberculosis infection. Upon recognition of bacterial antigens, TNF-α is produced by activated macrophages and dendritic cells, triggering a cascade of signaling pathways that promote macrophage activation, the production of reactive nitrogen intermediates, and the formation of granulomas. TNF-α also enhances apoptosis in infected cells, which facilitates antigen presentation and T-cell priming. However, excessive TNF-α production can result in immunopathology, including lung tissue damage, while TNF-α inhibition—commonly used in autoimmune therapy—can increase the risk of latent TB reactivation. These complex functions are summarized in Figure 1.

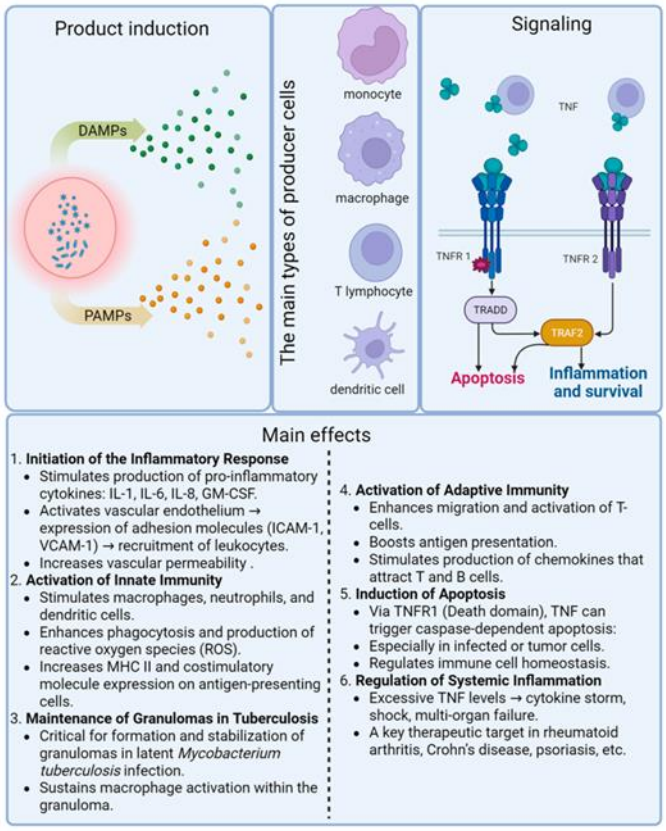

Figure 1. Overview of TNF-α signaling and functions during Mycobacterium tuberculosis infection, including macrophage activation, apoptosis, granuloma formation, and potential immunopathology during dysregulation or anti-TNF treatment (Cechetto, 2001).

Several key studies have investigated the role of TNF-α in tuberculosis pathogenesis and therapy, as summarized in Table 1.

Table 1. Summary of studies examining TNF-α levels and immunological roles in pulmonary tuberculosis

Author (year)	Study type	Key findings on TNF-α	Implications
Yuk et al. (2024) [7]	Review	TNF-α is essential for infection control but acts as a double-edged sword when dysregulated.	Need to balance TNF-α for optimal therapy.
Sinaga & Amir (2021) [29]	Case-control study	TNF-α polymorphism (−308G/A) linked to increased TB risk in Medan, Indonesia.	Genetic variation may influence TNF-α response and TB susceptibility.
Robert & Miossec (2021)[30]	Experimental + clinical	TNF inhibitor therapy led to TB reactivation; the IL-12 receptor role is also implicated.	Anti-TNF treatment requires TB screening and monitoring.
Mirzaei & Mahmoudi (2018) [31]	Observational study	Serum TNF-α is higher in TB patients than in healthy controls	TNF-α can serve as a biomarker of active TB.
Khelghati et al. (2024) [32]	Meta-analysis	TNF-α antagonists significantly increase TB risk.	TNF-α blockade must be used with caution in endemic regions.

Sample Characteristics shows that the number of donors who failed blood donor selection due to low haemoglobin levels was dominated by women, with the number of failed donors 75TNF-α is a pro-inflammatory cytokine that plays a critical role in the immune response to Mycobacterium tuberculosis infection. Monocytes, macrophages, neutrophils, T cells, and natural killer cells produce this cytokine. One of the primary functions of TNF-α is to activate macrophages, which are crucial in killing TB bacteria, as well as in the formation and maintenance of granulomas. These granulomas serve as the body's natural barrier to isolate Mtb within lung tissue, thereby preventing further spread (7,29). The role of TNF-α in this process was first demonstrated in mouse experiments in the 1990s and later confirmed through observational studies, which showed the reactivation of TB in patients using TNF-α inhibitors (TNFi) (30).

TNF-α enhances the T cell response by promoting the fusion of macrophage phagosomes and lysosomes, optimizing antigen presentation to CD4+ T cells, and increasing phagocytic activity. Additionally, TNF-α stimulates macrophage apoptosis, which can lead to cross-priming of CD8+ T cells. However, some components of Mtb can inhibit the production of TNF by host cells, thus evading the immune response. Mtb mutants that can increase TNF production by host cells show potential as vaccine candidates with improved immunogenicity (33).

Research indicates that TNF-α levels in the serum of patients with pulmonary TB are higher compared to healthy control groups, suggesting that TNF-α plays a role in the body's defense mechanisms against this infection. However, excessive TNF-α production may also contribute to excessive inflammation, leading to lung tissue damage. Furthermore, TNF-α levels tend to decrease significantly after patients undergo anti-TB therapy, indicating that this cytokine plays a role in the inflammatory process during infection (31).

Research has also shown that elevated levels of TNF-α can contribute to lung tissue damage after TB treatment. While TNF-α is essential for controlling infection, excessively high or uncontrolled levels can lead to tissue damage. Understanding the balance between an effective immune response and the potential for tissue damage can aid in developing more effective therapies for TB. Additionally, treatment with anti-TNF-α agents has been linked to an increased risk of opportunistic infections, including TB. Patients undergoing this therapy should be closely monitored for signs of new infections and provided with appropriate care (32,34).

4. CONCLUSIONS

Tumor necrosis factor-alpha (TNF-α) plays an essential role in the immune response against Mycobacterium tuberculosis, particularly through the activation of macrophages and the formation of granulomas that help contain the infection. Maintaining a balanced level of TNF-α is crucial; excessive production can lead to inflammation and damage to lung tissue, while insufficient levels increase the risk of latent tuberculosis (TB) reactivation. Therefore, proper regulation of TNF-α is key to ensuring effective immune defense and minimizing immunopathological consequences in pulmonary tuberculosis. These findings highlight the potential of TNF-α modulation as a therapeutic target, suggesting that future research should focus on developing host-directed therapies that can fine-tune TNF-α activity to enhance treatment outcomes without exacerbating lung damage.

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