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IMMUNOPATHOGENESIS OF PULMONARY TUBERCULOSIS

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Abstract: Tuberculosis (TB) is caused by the intracellular pathogen Mycobacterium Mtb tuberculosis (Mtb) remains one of the leading causes of infectious disease mortality worldwide. The outcome of a host encounter with Mtb is determined by a complex and multifaceted immune response that evolves from initial infection control to the formation of a specific granuloma and, in some cases, to destructive progressive disease. This review systematizes current understanding of the key immunological changes in the human body during pulmonary tuberculosis, encompassing both innate and adaptive immune mechanisms. We examine the role of various immunocompetent cells (macrophages, dendritic cells, neutrophils, T- and B-lymphocytes), cytokine networks, and immunopathological processes that underlie defense against Mtb but also contribute to lung tissue damage. Particular attention is paid to the mechanisms that allow Mtb to evade the immune response and the factors determining the transition from latent infection to active disease.

Key words: tuberculosis, Mycobacterium tuberculosis , immunopathogenesis , granuloma, macrophages, T-lymphocytes, cytokines, immune evasion.

Introduction

Mycobacterium Mtb (tuberculosis) is a highly successful pathogen, infecting approximately a quarter of the world's population [1]. Most infected individuals develop latent tuberculosis infection (LTBI), characterized by control of the bacterium without clinical symptoms. However, approximately 5-10% of infected individuals develop active TB during their lifetime, with 80-85% of cases involving the lungs [2]. The transition from LTBI to active disease is a consequence of a failure of the host immune system. Thus, pulmonary tuberculosis represents a clear model of the dynamic interplay between a pathogen and the immune system, where the outcome is determined by the delicate balance between the protective and pathological components of the immune response.

1. Innate Immunity: The First Line of Defense and Its Limitations

Mtb invasion of the lungs via the aerosol route initiates an immediate innate immune response.

1.1 Pathogen recognition. Pattern recognition receptors (PRRs) on innate immune cells, such as Toll -like receptors (TLRs), NOD-like receptors (NLRs), and C- lectin receptors (e.g., Dectin-1, DC-SIGN), play a key role in Mtb recognition [3]. Ligand interactions Mtb (e.g. lipoarabinomannan , cord factor) with TLR2, TLR4 and TLR9 leads to activation of signaling pathways (NF- κB , MAP kinase) and induction of proinflammatory cytokines (FNO - α, IL-1β, IL-6, IL-12) and chemokines (MCP-1, IL-8), which recruit other immune cells to the site of infection [4].

1.2 Alveolar macrophages and phagocytosis. Alveolar macrophages are the first cells to phagocytose Mtb . However, Mtb has multiple mechanisms for survival within macrophages:

Inhibition of phagolysosomal fusion: Mtb proteins (e.g., PtpA , SapM) disrupt the maturation process of phagosomes by preventing their acidification and contact with lysosomal enzymes [5].

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Resistance to reactive oxygen species (ROS) and nitrogen species (RNS): Despite the activation of NADPH oxidase and inducible NO synthase (iNOS), Mtb has powerful antioxidant systems that allow it to neutralize bactericidal molecules.
Exploitation of lipid metabolism: Mtb reprograms macrophage metabolism by directing lipid flow into the phagosome , using them as a nutrition source [6].
1.3. The Role of Neutrophils. Neutrophils rapidly arrive at the site of infection. They can phagocytose and destroy Mtb using their granules and NETosis (neutrophil extracellular traps). However, their role is ambiguous. On the one hand, they may limit the early spread of infection. On the other hand, an excessive neutrophil response is associated with severe forms of TB and promotes tissue destruction by releasing proteases and proinflammatory mediators [7]. Neutrophils can even serve as a "Trojan horse" for bacterial dissemination.
2. Adaptive immunity: Granuloma formation and infection control
Approximately 2-3 weeks after infection, the adaptive immune response develops, which is central to the control of Mtb .
2.1. Granuloma formation. Granuloma is a characteristic pathognomonic sign of tuberculosis, representing an organized structure consisting of macrophages, epithelioid cells, multinucleated Pirogov- Langhans cells , lymphocytes, fibroblasts, and a collagen capsule. Granuloma serves as a "prison" for bacteria, isolating them and creating a microenvironment unfavorable for their proliferation [8].
2.2 The key role of T-lymphocytes.
CD4+ T-helper type 1 (Th1) cells: These are the cornerstone of anti-TB immunity. By recognizing Mtb antigens presented in the context of MHC-II, they produce key cytokines IFN - γ and TNF-α. IFN-γ activates macrophages, enhancing their bactericidal activity (induction of iNOS , autophagy) [9]. CD4+ T-cell deficiency (as in HIV infection) is a powerful risk factor for the development of active TB.
CD8+ T lymphocytes: Recognize antigens in the context of MHC-I and are able to lyse infected macrophages, releasing bacteria for subsequent phagocytosis by "fresh" macrophages. They also produce IFN - γ and perforin / granzymes [10].
Unconventional T lymphocytes: These include CD1-restricted T cells (recognizing lipid antigens), MAIT cells (mucosal- associated invariant T cells), and γδ T cells. They provide a rapid, non-specific response at sites of entry of infection and contribute to IFN - γ production and cytolytic activity [11].
2.3. Humoral immunity. The role of B cells and antibodies in tuberculosis was long considered secondary. However, modern data indicate that B cells not only produce antibodies (possibly opsonizing bacteria), but also act as antigen- presenting cells and organize the structure of the granuloma, forming lymphoid follicles at its periphery [12].
3. Cytokine Balance: The Axis of Defense and Destruction
Cytokines are conductors of the immune response in TB.
Protective cytokines: IL-12 (induces Th1 differentiation), IFN - γ (activates macrophages), TNF-α (critical for maintaining granuloma integrity) [13]. Blockade of TNF - α in the treatment of autoimmune diseases leads to reactivation of LTBI, which emphasizes its key role.

Immunosuppressive and pathological cytokines: IL-10 suppresses macrophage activity and T-cell function. TGF-β has a potent anti-inflammatory effect but also promotes fibrosis. As the disease progresses, an imbalance is observed in favor of the Th2 response (IL-4, IL-13) and the production of IL-17, which, by recruiting neutrophils, can exacerbate inflammation and tissue damage [14].

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4. Immunopathology and disease progression
Active pulmonary tuberculosis is characterized by destruction of lung tissue, caseous necrosis, and cavitation. This is a direct consequence of the host's immune response.
Caseous necrosis: This is the result of the death of infected and uninfected cells in the center of the granuloma. This process is triggered by excessive macrophage activation, cytotoxic T cells, and ischemia due to compression of blood vessels. In the liquid caseous debris, Mtb finds ideal conditions for extracellular proliferation [15].
Cavity formation: Proteolytic enzymes (matrix metalloproteinases - MMPs), released by macrophages and neutrophils, destroy the lung's collagen matrix. Neutrophil elastase plays a key role in this process. The resulting cavity becomes a reservoir for a large number of bacteria, which can be released into the environment during coughing [16].
5. Mechanisms of Mtb evasion from the immune response Mtb is a master of immune evasion:
Inhibition of phagolysosomal fusion (see above). Inhibition of antigen presentation : Mtb can suppress the expression of MHC-II molecules on macrophages [17].
Induction of immunosuppression : The bacterium stimulates the production of IL-10 and TGF-β, and also promotes the expression of inhibitory receptors (e.g. PD-1 on T cells and its ligand PD-L1 on macrophages), which leads to the "exhaustion" of T lymphocytes (T- cell exhaustion) and their inability to effectively respond to infection [18].
Polarization of macrophages to the alternatively activated (M2) phenotype, which promotes healing and fibrosis but not efficient bacterial killing.
Conclusion. The immune response in pulmonary tuberculosis is a complex and dynamic process, a double-edged sword. On the one hand, the coordinated interaction of innate and adaptive immunity, culminating in the formation of a stable granuloma, allows 90-95% of infected individuals to control the infection. On the other hand, this same immune response, when excessive, inappropriate, or unbalanced, leads to lung tissue destruction, necrosis, and disease progression. Understanding the subtle mechanisms regulating this balance, including the molecular basis of Mtb evasion and the phenomenon of T-cell exhaustion, opens avenues for the development of new treatment and prevention strategies, such as immunotherapeutic adjuvants, therapeutic vaccines, and drugs aimed at modulating pathological inflammation.

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