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HOST-PATHOGEN INTERACTIONS IN MYCOBACTERIUM TUBERCULOSIS: MOLECULAR MECHANISMS AND IMPLICATIONS FOR TREATMENT

ZAINAB M. LATEEF [1], ZAHRAA HAMID ALWAN AL-SAADI [2], KARAM R ALJARAH [3]

[1,2,3]Al_Karkh University for Science /College of Science.

ABSTRACT

Worldwide, tuberculosis (TB) due to Mycobacterium tuberculosis is a major public health problem with high morbidity and mortality. This review reviewed the molecular mechanisms and their implications for treatment of M. tuberculosis infection, as well as the complex host pathogen interactions underpinning M. tuberculosis infection. The ability of the pathogen to avoid the host immune responses by utilizing critical strategies for the evasion, for instance, inhibition of phagosome-lyosome fusion and modulation of the host cell pathways are discussed first. T cells play a critical role in the adaptive immune response, and granulomas develop, which are then examined in detail.

It importantly informs current treatment protocols which struggle to overcome issues of patient compliance, drug resistance and toxicity. Explored are novel therapeutic approaches targeting bacterial cell wall synthesis, virulence factors and the use of host directed therapies. Recent advances in the development of vaccines, including the innovative endeavors that hope to improve or replace the BCG vaccine, are also reviewed.

The review ends by anticipating future directions in TB management, which could be facilitated through efforts related to personalized medicine, and combination therapies, as well as rapid diagnostics to change how we think about treatment. The insights from this study are important for developing novel strategies to fight TB and to bring down its burden globally.

INTRODUCTION

Despite more than 100 years since the discovery of the bacteria that causes tuberculosis (TB), Mycobacterium tuberculosis, it is still a major Global Health concern, with millions of new cases and deaths each year. The disease is so resistant to control, that TB remains the leading cause of death from a single infectious agent. One of M. tuberculosis's major survival strategies for persistent infection in humans is its ability to interact with the host immune system at such a fine (and sophisticated) level. We must understand these host pathogen interactions in order to make more powerful interventions [(1)].

Interactions between the bacterium and host immune defenses in TB are complex and dynamic host-pathogen interactions. M. tuberculosis has developed multiple strategies to evade immune detection, survive within host macrophages and exploit host cellular functions to its aid. These interactions not

only dictate the course of infection but also complexes with influence on disease pathology and disease manifestations [2].

Advances in molecular biology and immunology in recent decades have given deeper knowledge into how M. tuberculosis uses such mechanisms to defeat host defenses and survive the host. The implications of these discoveries for the development of host directed therapies, as well as improved vaccines, are significant. By focusing them on recent advances and future research direction, this review will explore the molecular mechanisms of M. tuberculosis host pathogen interaction and its implication for treatment.

Mycobacterium tuberculosis: A Brief Overview

Despite the complex biology of Mycobacterium tuberculosis, the pathogen remains a formidable disease entity. It is the causative agent of tuberculosis and is a major public health problem worldwide.

Pathogen Characteristics

Several closely related mycobacterial species that can cause TB in humans and animals belong to the Mycobacterium tuberculosis complex of which M. tuberculosis is a member. Lipid rich cell wall of the bacterium is unique and marks the pathogenicity of the bacterium. In addition to creating a barrier to host defenses, the cell wall of a mycolate bacterium also enables survival of the intracellular form by resisting phagocytic killing [3].

M. tuberculosis is a facultative intracellular pathogen that, for most part of its life, resides within macrophages and alters host cell responses to sustain itself. Key to its ability to establish long term infections, this adaptation [4].

Lifecycle and Transmission

Transmission of M. tuberculosis is mainly through the airborne form of infection, what are called droplet nuclei, which are shed from individuals with active pulmonary TB by coughing, sneezing, or speaking. Once these particles become entrapped in the air, they can remain suspended there for extended periods of time, and are inhaled by susceptible individuals, reaching the pulmonary alveoli [5].

M. tuberculosis enters alveoli and is engulfed by alveolar macrophages. The bacteria contain many virulence factors that prevent phagosome–lysosome fusion, avert degradation and enable a niche for replication. M. tuberculosis persists in a dormant state within the granulomatous lesions that develop to respond to infection, and is considered incriminated in latent TB infection. For example, we estimate that about one-quarter of the globe, defines about one quarter of the global population has latent TB, the risk of which developing is about 5% to 10% [3, 6].

Adaptations and Survival Strategies

Several of these strategies are used by M. tuberculosis to thrive inside its host. The products have the ability to modulate the host immune response, facilitating both the suppression of an effective immune activation and conditions conducive to bacterial survival. In granulomas, the pathogen can persist and survive in a non-replicating state that enables escape from hostile conditions that are typically experienced, including nutrient deprivation, hypoxia, and other stressors that nonreplicating states have been known to confer [4, 7, 8].

Additionally, they have an ability to be adapted to its genetic changes allowing it to become resistant to antibiotics and resist host immune responses. This adaptability makes treatment efforts more complicated and underscores the requirement of a novel therapeutic strategy aimed at novel targets: the pathogen and the interfaces of the pathogen with the host [9].

Mycobacterium tuberculosis Immune Response.

The immune response to Mycobacterium tuberculosis is a robust, complex and highly orchestrated process of the innate and adaptive arms of the immune system. Consequently, the outcome of infection depends on the interaction between the host's immune defenses and the pathogen that determines whether the pathogen is cleared, the host remains latent, or the host clinical progress with active disease [10-15].

Table 1*(Overview of Host Immune Response to Mycobacterium tuberculosis.)*

Component	Key Functions and Features	Role in TB Infection
Innate Immune Response		
Macrophages	Phagocytosis, production of pro-inflammatory cytokines	Engulf *M. tuberculosis*; survival mechanism for bacteria
Dendritic Cells	Antigen presentation, cytokine production	Bridge innate and adaptive immunity; present antigens to T cells
Neutrophils	Phagocytosis, release of antimicrobial peptides	Early responders; can contribute to inflammation
Pattern Recognition Receptors (PRRs)	Recognition of PAMPs, activation of signaling pathways	Initiate immune response upon detecting mycobacterial components
Cytokines (e.g., TNF-α, IL-12)	Mediate inflammation, activate immune cells	Essential for granuloma formation and macrophage activation

Table 2 *(Adaptive Immune Response to Mycobacterium tuberculosis.)*

Component	Key Functions and Features	Role in TB Infection
CD4+ T Cells	Cytokine production (e.g., IFN-γ), macrophage activation	Enhance macrophage bactericidal activity; contain infection
CD8+ T Cells	Cytotoxic activity, lysis of infected cells	Kill infected host cells, control infection

Regulatory T Cells (Tregs)	Modulate immune response, prevent excessive inflammation	Balance immune activation to limit tissue damage
B Cells and Antibodies	Antibody production, opsonization	Facilitate phagocytosis; less central in TB response

Table 3 *(Evasion Strategies by Mycobacterium tuberculosis.)*

Evasion Strategy	Mechanism	Impact on Infection
Inhibition of Phagosome-Lysosome Fusion	Prevents bacterial degradation within macrophages	Allows survival and replication within host cells
Modulation of Host Apoptosis	Alters cell death pathways to favor bacterial persistence	Enhances long-term survival within host
Antigen Presentation Inhibition	Reduces effectiveness of adaptive immune response	Contributes to chronic infection
Granuloma Formation	Concentrates immune response, limits spread	Provides niche for bacterial persistence and latency

Molecular Mechanisms of Pathogen Interaction

Without its ability to finesse host cell machinery, Mycobacterium tuberculosis would not be such a successful pathogen. Such strategies are described in detail at the molecular level in this section.

Entry and Survival within Host Cells

M. tuberculosis infects other cell types, but its main target for entry is the macrophage. Entry is achieved by exploiting multiple receptors on the macrophage surface, including complement receptors (CR3), mannose receptors, and Fc gamma receptors. When these receptors are engaged the phagocytosis occurs, but without an aggressive inflammatory response that lets the bacteria slink it entrance to the host cell [12, 16, 17].

M. tuberculosis resides in a modified phagosome once it is internalized. In order to survive, it blocks the acidification of the phagosome, as well preventing this from fusing with lysosomes. Specific bacterial proteins (e.g. PknG, a putative serine/threonine kinase) are secreted to interfere with host signaling pathways that control phagosome-lysosome fusion [18].

Manipulation of Host Cellular Pathways

M. tuberculosis employs various strategies to manipulate host cell functions:

- **Autophagy Modulation:** Autophagy is a cellular process where degraded and recycled cellular components are made. M. tuberculosis can protect itself from autophagic pathways, allowing it to survive by hitching a ride to lysosomes [19].
- **Apoptosis Inhibition:** M. tuberculosis secretes antiapoptotic factors that reduces host cell death, allowing the infected cells to live longer (or 'revive') and, so, have more time to replicate the bacteria [20].
- **Metabolic Reprogramming:** Host cell metabolism is rearranged by the pathogen so that it can survive on its host cell. It biases to a switch in lipid metabolism using host lipid droplets as a nutrient source [21].
- **Immune Modulation:** M. tuberculosis subverts the path of immune signaling events involving, for example, MAPK and NF-κB to suppress antiinflammatory cytokine such as IL-10 to promote proinflammatory cytokines and thus decrease the ability to mount a successful immune response [2, 4].

Role of Virulence Factors

Virulence factors are crucial for M. tuberculosis pathogenicity [6, 22]:

- **ESX-1 Secretion System:** Secrecion of ESAT-6 and CFP-10, which are known to modulate host immune responses and promote bacterial dissemination by degrading phagosomal membranes, requires this type VII secrecion system.
- **Cell Wall Lipids:** Mycolic acids, lipoarabinomannan (LAM), and trehalose dimycolate (cord factor) are required for maintenance of cell wall integrity and for modulation of host immune responses. They serve as immunomodulators, and can inhibit T cell activation and cause granuloma formation.
- **Superoxide Dismutase (SodA) and Catalase-peroxidase (KatG):** These enzymes protect the bacteria from the oxygen stress that normally causes such reactive oxygen species in host cells to be neutralized.

Recent Discoveries and Implications

Recent advances in high-throughput technologies have identified novel molecules involved in M. tuberculosis pathogenesis [23-25]:

- **Proteomics and Transcriptomics:** These approaches have revealed new proteins and regulatory RNAs that have previously been unknown to be associated with bacterial virulence and host interaction.
- **CRISPR-Cas9 Screens:** Host acting factors are identified by genome wide CRISPR screens to survive in M. tuberculosis and serve as potential therapeutic targets.
- **Metabolomics:** Metabolic pathways used by the bacterium to survive were found to be exploitable in studies, and metabolic vulnerabilities that could be targeted by new drugs.

Implications for Treatment and Drug Development

This molecular view of the interaction between Mycobacterium tuberculosis and the host is in full agreement with the complexity of the TB pathogenesis, but also underlines key molecular targets for therapeutic intervention. Such understanding is critical for successful development of treatment strategies and combating drug resistant strains [24, 26].

Table 4 *(Implications for Treatment and Drug Development in Tuberculosis.)*

Category	Key Aspects	Implications and Strategies
Current Treatment Challenges		
Patient Compliance	Long treatment duration	Development of shorter, more manageable regimens
Drug Resistance	Emergence of MDR and XDR strains	Need for new drugs with novel mechanisms
Toxicity and Side Effects	Adverse effects from current TB drugs	Research into safer therapeutic options

Table 5 *(Potential Targets for New Therapeutics in Tuberculosis.)*

Target	Mechanism	Therapeutic Implications
Cell Wall Synthesis	Inhibition of mycolic acid biosynthesis	Disruption of bacterial cell wall integrity
Virulence Factors	Targeting ESX-1 secretion system	Reduction of bacterial virulence
Host-Directed Therapies (HDTs)	Modulating host pathways such as autophagy	Enhancement of host immune responses, restriction of bacterial growth

Table 6 *(Future Directions in Tuberculosis Treatment.)*

Strategy	Description	Expected Outcomes
Personalized Medicine	Use of genomic and pharmacogenomic approaches	Tailored treatments based on indiv idual profiles

Combination Therapies	Combining traditional antibiotics with novel agents or HDTs	Shortened treatment durations and improved clinical outcomes
Rapid Diagnostic Tools	Development of tools for quick identification of resistant strains	Improved management of drug resistance and tailored treatments

CONCLUSION

Host-pathogen interactions in Mycobacterium tuberculosis are particularly complicated, making the treatment of tuberculosis an enormous challenge. Current treatment limitations of drug resistance and lengthy regimens notwithstanding, new insights into the molecular mechanisms of the pathogen provide novel direction for innovation. Pathways targeted for inhibition, boost for host directed therapies, and vaccines can transform the management of TB. Further research and working in interdisciplinary collaboration are required to identify the best interventions for effective TB burden reduction around the world.

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