Opinion

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Host–Pathogen Interactions in Tuberculosis: Mechanistic Insights and Immunological Implications

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Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains one of the most devastating infectious diseases worldwide, responsible for millions of deaths each year. Despite decades of research and global vaccination efforts, TB continues to pose a major public health challenge due to the bacterium's ability to establish latent infection and evade immune clearance. Understanding host–pathogen interactions at the cellular and molecular levels is crucial to developing novel therapeutic and preventive strategies. Mtb's success as a pathogen lies in its ability to manipulate host immune responses, survive within macrophages, and modulate cytokine signaling to create a favorable niche for persistence. Advances in genomics, proteomics, and immunometabolomics have provided a comprehensive view of how Mtb orchestrates immune modulation, leading to chronic infection and tissue pathology [1].

Description

The interaction between Mtb and host macrophages defines the course of TB infection. Upon inhalation, Mtb bacilli are engulfed by alveolar macrophages, where they resist phagolysosomal degradation through multiple evasion mechanisms. Mtb secretes effector proteins such as ESAT-6 and CFP-10, which disrupt phagosome maturation and inhibit antigen presentation, allowing bacterial survival.

Additionally, Mtb's complex cell wall lipids, including Lipoarabinomannan (LAM) and phthiocerol dimycocerosate (PDIM), modulate Toll-like receptor (TLR) signaling and reduce pro-inflammatory cytokine release. This immune modulation impairs the activation of bactericidal mechanisms, such as nitric oxide production and autophagy, which are essential for pathogen clearance [2].

The adaptive immune response also plays a dual role in TB pathogenesis. While Th1-type cytokines such as IFN-γ and TNF-α are crucial for controlling infection, excessive immune activation can lead to granuloma formation and tissue necrosis. Granulomas, once considered a hallmark of host protection, are now recognized as complex microenvironments where Mtb can persist in a dormant state. Recent transcriptomic studies have revealed that Mtb exploits metabolic reprogramming of host cells to enhance lipid storage, providing an energy source during latency. Moreover, immune checkpoints such as PD-1/PD-L1 are upregulated in chronic TB, leading to T-cell exhaustion and impaired bacterial clearance. These insights underscore the delicate balance between protective immunity and immune-mediated pathology [3].

Advances in single-cell RNA sequencing and high-resolution imaging have further elucidated the heterogeneity of immune responses within TB lesions. Such technologies have uncovered distinct macrophage subsets with differential antimicrobial capacities, revealing potential targets for host-directed therapies. By manipulating host pathways that Mtb exploits such as autophagy, apoptosis, and metabolism novel therapeutic interventions can enhance bacterial clearance and prevent reactivation of latent TB. These findings highlight the complexity of host–parasite interactions, where helminths fine-tune immune responses not only through direct immunomodulation but also by reshaping the microbial landscape [4,5].

Conclusion

Understanding host–pathogen interactions in TB is fundamental for developing next-generation vaccines and host-directed therapies. Mtb's ability to manipulate innate and adaptive immunity highlights the need for multifaceted intervention strategies that restore immune balance while enhancing pathogen clearance. Integrating systems biology approaches with clinical research will enable the identification of key immune signatures predictive of disease outcome. Future efforts should focus on translational studies that bridge basic immunology with therapeutic innovation, ultimately moving closer to global TB elimination.

Acknowledgement

None

Conflict of Interest

None

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