Exploring the Crossroads of Innate and Adaptive Immunity Against Mycobacterium Tuberculosis

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ABSTRACT: This review examines the complex interactions between *Mycobacterium tuberculosis* and host immunity, with a focus on *Mtb* and immune evasion. Upon inhalation, *Mtb* infects alveolar macrophages, inhibiting phagosome-lysosome fusion to survive. Dendritic cells are later activated, driving CD4+ T cell differentiation and IFN-γ release to enhance macrophage bactericidal activity. *Mtb* may be sequestered in granulomas, which contain the infection but facilitates *Mtb* persistence during latency. Further, cytotoxic T lymphocytes eliminate infected cells, while regulatory T cells modulate immunity. Overall, host immune responses must balance between pathogen control and tissue damage. Thus, *Mtb's* immune evasion mechanisms pose a significant challenge for vaccine development and therapeutic intervention. Understanding these interactions is critical for uncovering novel strategies against *Mtb* infection and improving public health outcomes.

KEYWORDS: Mycobacterium tuberculosis, Tuberculosis, Innate immunity, Adaptive immunity, Host-pathogen interaction, Immune evasion, Granuloma formation, Macrophages, Complement system

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The Mucosal Barrier and Innate Inflammatory Signalling

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*), is an airborne infectious disease that remains one of the leading causes of death globally.[1] The clinical spectrum of TB ranges from latent, asymptomatic, and non-transmissible states to active, transmissible, and potentially life-threatening forms.[2] *Mtb* primarily infects the mucosal tissue of the respiratory tract, leading to symptoms such as persistent cough, fever, and fatigue.[3] A deeper understanding of the pathogen's disease mechanisms and its interaction with the host immune system is essential for developing more effective therapeutic strategies and controlling the global TB burden.[4]

Upon inhalation, *Mtb* settles within the alveoli of the lungs, initiating its interaction with the lung mucosal barrier.[5] This barrier consists of the alveolar lining fluid (ALF), an aqueous-hypophase, which serves as the first line of defence within the alveolar space.[6] ALF contains essential soluble innate components, including complement proteins, which play a critical role in early immune responses against *Mtb*.[7] Notably, ALF-hydrolases actively alter the *Mtb* cell wall, enhancing the ability of human macrophages to recognize and eliminate the pathogen.[8]

Simultaneously, *Mtb* activates a family of human toll-like receptors (TLRs) on the membrane surfaces of immune cells, such as macrophages.[9] Among these, TLR2 and TLR4 play pivotal roles in initiating antimicrobial responses against *Mtb.*[10] These receptors initiate intracellular signalling pathways in leukocytes through both pro- and anti-inflammatory cytokines, enhancing the expression of adhesion molecules on immune cell surfaces.[11] Although the role of TLR4 remains debated, Park et al. demonstrated its importance in regulating neutrophil recruitment and cytokine production.[12] For instance, proinflammatory cytokines such as interferon-gamma (IFN-γ) and anti-inflammatory cytokines such as interleukin 10 (IL-10) are triggered by TLR4 during *Mtb* infection.[13] Notably, TLR4 deficiency in mice resulted in an uncontrolled *Mtb* infection due to disrupted IL-10 signalling and neutrophil depletion.[14] TLR2, on the other hand, is critical for inducing tumour necrosis factor-alpha (TNF-α), a key

Immune Cell Recruitment Through Complement Activation

Early interactions between the complement system and other innate immune factors play a critical role in the formation and maintenance of granulomas.[31] Complement regulatory proteins, such as C3b and C4b, coat the surface of *Mtb* through opsonization, enhancing macrophage recognition and phagocytosis to promote bacterial lysis.[32] [33] Additionally, complement proteins like C5a and C3a enhance inflammation, which engages natural killer (NK) cells and neutrophils to the site of infection.[34] These cells contribute to the immune defence by limiting infection and minimizing tissue damage.[35] [36] These coordinated interactions between complement proteins and immune cells are essential for controlling the pathogen and maintaining immune homeostasis during infection.

The complement system also actively engages with NK cells, which are key early responders in innate immunity recruited to sites of *Mtb* infection.[37] Although traditionally known for targeting tumours and virally infected cells, NK cells have also been shown to bind to and kill *Mtb*.[38] Vankayalapati et al. reveal that NK cells express cytotoxic receptors—NKp30, NKp44, and NKp46—that enable them to recognize and lyse *Mtb*-infected macrophages.[39] The cytokines IL-2 and IL-12 enhance the antimycobacterial activity of NK cells by inducing the expression of NKp44.[40] This facilitates direct interactions with its corresponding ligand on the surface of *Mtb*-infected macrophages, leading to the production of IFN-γ and further activating macrophages to contain and eliminate the infection.[41] By activating NK cells, these cytokines strengthen immune defences, making bacterial replication and spread more difficult.[42] [43] Additionally, Lu et al. propose a direct killing mechanism in which NK cells release cytoplasmic granules containing perforin and granulysin through nanotube-like structures.[44] These granules compromise the integrity of the bacterial cell wall, contributing significantly to *Mtb* death and reinforcing the importance of NK cells in controlling TB infections.[45]

The complement system's final interaction involves neutrophils–highly motile innate immune cells that migrate to the

lungs in response to chemokine signals, particularly IL-8, released by macrophages.[46] Neutrophils express complement receptors, Fc-receptors, and TLRs, enhancing pathogen recognition and facilitating phagocytosis through specialized phagosome vesicles.[47] These phagosomes fuse with granules containing antimicrobial enzymes and ROS, aiding pathogen clearance.[48] Furthermore, neutrophils amplify the immune response by secreting TNF-α, a proinflammatory cytokine that promotes granuloma formation and macrophage activation.[49] They also release interleukins such as IL-1β and IL-6, contributing to inflammatory signalling and immune cell recruitment.[50] Additionally, neutrophils can undergo a unique form of cell death known as NETosis, releasing neutrophil extracellular traps (NETs) to capture and immobilize *Mtb*.[51] In contrast, Hedlund et al. demonstrated that following interactions with *Mtb*, neutrophils can undergo accelerated apoptosis instead.[52] These apoptotic neutrophils, unlike those undergoing NETosis, do not release NETs but instead activate mucosal dendritic cells (DCs) through specific surface molecules, further supporting immune responses and strengthening host defence mechanisms.[53]

Adaptive Immunity Initiated by Dendritic Cells and T Cells

Dendritic cells serve as essential antigen-presenting cells (APCs), bridging the innate and adaptive immune response.[54] Upon infection, DCs residing in the lung mucosa recognize *Mtb* through TLRs and initiate phagocytosis for antigen processing.[55] These infected DCs then migrate to the draining lymph nodes, where they present *Mtb*-derived antigens to $CD4^+$ and $CD8^+$ T cells via MHC class I and II molecules, respectively.[56] Tian et al. demonstrated that DC depletion in mice impaired the generation of effective $CD4^+$ T cell responses, leading to uncontrolled *Mtb* replication in the lungs.[57] Through MHC class II presentation, DCs activate $CD4^+$ T cells, which rely on cytokine signalling to mount a strong inflammatory response.[58] IL-12, released from APCs such as macrophages, promote the differentiation of $CD4^+$ T cells into T helper 1 (Th1) cells.[59] Th1 cells produce IFN-γ, a critical cytokine that enhances macrophage activity,

improving their ability to engulf and kill *Mtb*.[60] Once the infection is controlled, the immune system generates memory $CD4^+$ T cells that retain antigen recognition, facilitating a faster and more robust response upon re-exposure to *Mtb*.[61] This protective memory immunity ensures an efficient defence in future encounters. Murine studies further underscore the importance of $CD4^+$ T cells, showing that their depletion results in compromised immune responses, increased bacterial burden, and TB progression, highlighting their critical role in controlling *Mtb* infection.[62]

Substantial evidence supports the protective role of $CD4^+$ T cells against *Mtb*, but determining the specific contribution of $CD8^+$ T cells remains challenging due to differences in antigen recognition.[63] $CD4^+$ T cells recognize exogenous antigens presented on MHC class II molecules, while $CD8^+$ T cells detect cytosolic antigens through MHC class I molecules.[64] Since *Mtb* primarily resides within infected cells, extracellular antigen presentation by $CD4^+$ T cells is more easily observed than the intracellular presentation required for $CD8^+$ T cell activation.[65] However, Flynn et al. demonstrated that $CD8^+$ T cells play a crucial role in controlling *Mtb* infections, as mice deficient in $CD8^+$ T cells due to β2-microglobulin gene disruption exhibited impaired control of infection compared to wild-type mice.[66] Like $CD4^+$ T cells, $CD8^+$ T cells produce IFN-γ, enhancing macrophage antimicrobial functions and promoting granuloma formation.[67] In vitro studies of human cells show that $CD8^+$ T cells also possess cytolytic capabilities similar to NK cells, releasing perforin and granzymes into the synapse between the $CD8^+$ T cell and *Mtb*-infected cells.[68] Perforin creates pores in the membranes of infected cells, enabling granzymes to enter and induce apoptosis.[69] Proper regulation of these cytolytic functions is essential for maintaining immune homeostasis and preventing excessive tissue damage during infection.

Regulatory T cells (Tregs), a subset of both $CD8^+$ and $CD4^+$ T cells, modulate immune responses against *Mtb*.[70] Tregs use anti-inflammatory cytokines to suppress the proinflammatory responses necessary for controlling *Mtb* growth, preventing excessive tissue damage.[71] However, this immunosuppression can also be detrimental

in limiting the spread of *Mtb.*[72] Yu et al. found that as TB severity increases, $CD8^{+}CD28^{-}$Treg cells increase to control excessive immune activation.[73] They also reported elevated levels of $CD4^{+}CD25^{++}$ Treg cells in the peripheral blood of TB patients compared to healthy individuals, indicating that persistent immune activity promotes Treg expansion.[74] This increase in Treg cells can be problematic, as their heightened anti-inflammatory activity may impair the body's ability to clear *Mtb*, suppressing the production of key immune factors such as Th17 cells and IFN-γ.[75] [76] Such conditions allow *Mtb* to survive and potentially transition into a chronic disease state.[77] Although Tregs primarily target T cells, Xu et al. demonstrated that they can also act on other immune cells, such as B cells, further suppressing immune responses essential for pathogen clearance.[78]

B Cell-Mediated Antibody and Phagocytic Responses

B cells play complex and sometimes contentious roles during an *Mtb* infection, with antibody production being a key mechanism, particularly involving immunoglobulin G (IgG) and A (IgA).[79] Studies indicate that children with disseminated TB exhibit significantly reduced IgG levels compared to those with localized TB, suggesting a correlation between IgG responses and disease severity.[80] This is further supported by findings of elevated IL-21 in TB lesions of IL-21R-deficient mice, highlighting IL-21's role in promoting IgG isotype switching in modulating IL-10 production.[81] [82] [83] B cell-deficient mice display elevated IL-10 levels, while B cell transfer reduces mortality, decreases lung bacterial burden, and limits granuloma progression.[84] However, some research indicates that variations in IL-21 and IL-10 expression may not directly influence disease outcomes.[85] IgA also plays a protective role in *Mtb* defence.[86] IgA-deficient mice show increased lung bacterial loads, reduced IFN-γ and TNF-α production, and elevated IgM levels, indicating heightened susceptibility.[87] Beyond conventional antibody pathways, recent studies suggest an alternative mechanism known as antibody-dependent cellular phagocytosis (ADCP).[88] Through ADCP,

antibodies bind to Fcγ receptors on alveolar macrophages, promoting opsonization, enhanced phagosome maturation, and increased microbicidal activity, thus restricting *Mtb* growth.[89] [90] Despite these insights, further research is necessary to fully understand the diverse and sometimes contradictory roles of B cells in both defensive and regulatory processes during *Mtb* infection.

Conclusion

The innate and adaptive immune systems coordinate a complex, multifaceted response during *Mtb* infection. From the initial encounter in the alveoli, TLRs enable early pathogen recognition, while macrophages attempt to eliminate *Mtb* through phagocytosis.[91] [92] Upon macrophage infection, TNF-α upregulation drives the formation of granulomas, which act as containment structures to isolate the bacteria and prevent its spread.[93] [94] The complement system plays a crucial role by recruiting NK cells and neutrophils—NK cells kill infected cells via cytotoxic receptors, while neutrophils immobilize *Mtb* with NETs, an essential mechanism in limiting bacterial dissemination.[95] [96] Additionally, neutrophil apoptosis activates mucosal DCs, which connect innate and adaptive immunity through antigen presentation.[97] Within the adaptive response, $CD4^+$ and $CD8^+$ T cells release IFN-γ, enhancing macrophage activity, while Tregs regulate inflammation to prevent excessive tissue damage.[98] [99] B cells, activated later in TB infection, produce IgG and IgA antibodies that influence disease severity; reduced IgG levels correlate with more severe, disseminated TB, while IL-21 regulates IgG production and immune responses.[100] [101] [102] B cell deficiency worsens infection outcomes, but B cell transfer reduces bacterial load and limits granuloma progression.[103] Through the coordinated efforts of these immune components, the body establishes an intricate defence that not only controls infection but also informs the development of long-term therapeutic interventions against TB.

Despite extensive research into the immune response against *Mtb*, significant gaps remain, hindering the development of effective interventions primarily due to the limited investigation of subclinical

Mtb infection.[104] Though research into early disease manifestations has gained momentum, routine diagnostic tools–most prominently tuberculin skin tests–have yet to distinguish between latent and active disease, delaying treatment and increasing transmission risk.[105] However, advances in IFN-γ release assays (IGRA), digital PCR, and host blood transcriptomics present a promising avenue.[106]

Further complicating intervention development is the incomplete understanding of TBs complex interplay between innate and adaptive immune responses. While innate immunity is crucial for early pathogen recognition and initial control, the precise roles of adaptive immune components, including T cell subsets and B cells, in long-term protection remain unclear.[107] In particular, the balance between proinflammatory and regulatory T cell responses and the contribution of CD8+ T cells requires deeper exploration.[108]

Moreover, *Mtb* remains a formidable global health threat, mainly due to its evolved ability to rapidly develop multidrug resistance.[109] The development of resistance to drugs like rifampin highlights the need for more targeted and effective treatments, regardless of the financial return.[110] Understanding the interplay between innate and acquired resistance mechanisms in *Mtb* will be key in identifying new drug targets, improving existing therapies, and overcoming the challenges posed by resistant strains.[111] While several medications previously overlooked for TB treatment are available or under clinical investigation, a more precise understanding of the bacterium's resistance mechanisms is necessary to make these treatments more effective.[112]

Addressing these gaps will not only improve therapeutics but also drive the development of strategies to predict and control TB progression in diverse, immunocompromised and coinfected populations, ultimately enabling more personalized approaches to TB treatment and prevention.

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