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Host-Pathogen Interactions in *Mycobacterium tuberculosis*: From Phagosome Arrest to Granuloma Dynamics- A review

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Abstract

Mycobacterium tuberculosis (Mtb) remains one of the leading causes of death from a single infectious agent despite effective antimicrobial therapy. Its success is largely attributed to its ability to survive within host macrophages, evade immune clearance, establish latent infection, and develop phenotypic drug tolerance, complicating disease control and treatment. Although these mechanisms have been widely studied, their interrelationship remains incompletely understood. This mini narrative review examines five key aspects of Mtb pathogenesis: macrophage survival, inhibition of phagosome–lysosome fusion, granuloma formation, latent versus active tuberculosis, and drug tolerance. A literature search was conducted using PubMed, Web of Science, Google Scholar, and Scopus with relevant keywords and Boolean operators. Articles published predominantly between 2016 and 2026 were included. The findings indicate that Mtb manipulates macrophage antimicrobial functions, inhibits phagosome maturation and lysosomal fusion, promotes granuloma formation that both restricts and protects bacilli, transitions between latent and active disease in response to host and environmental factors, and develops drug-tolerant persister populations that contribute to prolonged treatment and relapse. Together, these interconnected mechanisms enable long-term bacterial persistence and immune evasion. Understanding these dynamic host–pathogen interactions is essential for developing integrated diagnostic, therapeutic, and host-directed strategies to improve tuberculosis control.

Introduction

Tuberculosis (TB) remains one of the world's leading infectious causes of morbidity and mortality despite major advances in diagnosis, treatment, and disease control. Caused by the intracellular pathogen *Mycobacterium tuberculosis* (Mtb), TB continues to disproportionately affect low- and middle-income countries, where HIV co-infection, malnutrition, poverty, and limited healthcare access facilitate disease transmission and progression (Glaziou et al., 2018).

Although effective chemotherapy has substantially reduced mortality, disease control remains challenging because of prolonged treatment regimens, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR)

strains, and the remarkable ability of Mtb to persist within host tissues despite antimicrobial therapy and robust immune responses (Datta et al., 2024). These challenges emphasize that successful TB control depends on understanding not only bacterial biology but also the intricate interactions between Mtb and the host immune system (Cambier et al., 2018).

Unlike many bacterial pathogens that cause acute infections, Mtb has evolved to establish long-term persistence within its human host. Rather than existing in states of unrestricted replication or complete dormancy, the pathogen maintains a dynamic equilibrium with host immunity that promotes bacterial survival while limiting excessive host damage. Consequently, tuberculosis is now recognized as the outcome of continuous host–pathogen interactions involving coordinated molecular, cellular, and metabolic responses rather than bacterial virulence alone (Ehrt et al., 2018).

Current evidence also indicates that TB exists along a disease spectrum extending beyond the traditional classification of latent and active infection. Intermediate stages, including incipient and subclinical tuberculosis, are characterized by distinct bacterial metabolic states and varying levels of immune control (Drain et al., 2018). This evolving concept highlights the importance of host–pathogen interactions throughout disease progression and suggests that subtle changes in early immune regulation may determine whether infection is cleared, contained, or progresses to active disease (Samuels et al., 2022).

The earliest events following inhalation of aerosolized Mtb are particularly important in determining disease outcome. After reaching the terminal alveoli, bacilli encounter resident alveolar macrophages, dendritic cells, epithelial cells, and other innate immune populations that constitute the first line of defense. These early interactions influence bacterial dissemination, adaptive immune activation, granuloma formation, and long-term disease progression (Cambier et al., 2018). Because they occur before effective adaptive immunity develops, these events provide Mtb with either an opportunity to establish a protected intracellular niche or to be eliminated by innate immune mechanisms.

Recognition of Mtb begins when macrophages and dendritic cells detect mycobacterial pathogen-associated molecular patterns through multiple pattern-recognition receptors, including Toll-like receptors, C-type lectin receptors, NOD-like receptors, and cytosolic sensing pathways. Activation of these receptors triggers signaling cascades that regulate phagocytosis, inflammatory cytokine production, antigen presentation, autophagy, and adaptive immune priming. Simultaneous engagement of multiple receptors coordinates protective immunity while also creating opportunities for immune modulation by the pathogen (Sankar & Mishra, 2023; Zihad et al., 2023).

Despite these antimicrobial defenses, Mtb possesses numerous virulence factors that promote intracellular survival. Following phagocytosis, the bacterium manipulates intracellular trafficking, inhibits phagosome maturation and phagolysosomal fusion, suppresses antimicrobial effector functions, alters cytokine signaling, and remodels host metabolism to establish a favorable intracellular niche (Krishnan et al., 2023). Consequently, macrophages become dynamic environments where bacterial adaptation and host defense occur simultaneously, and the outcome of this competition largely determines bacterial persistence and disease progression (Samuels et al., 2022).

Recent technological advances have significantly improved understanding of macrophage biology during TB infection. Rather than mounting an immediate pro-inflammatory response, infected alveolar macrophages initially activate a cytoprotective transcriptional program regulated by nuclear factor erythroid 2-related factor 2 (NRF2), which limits early inflammation and inadvertently facilitates bacterial survival (Rothchild et al., 2019). In addition, single-cell transcriptomic studies have revealed remarkable heterogeneity among alveolar macrophages, with distinct subsets exhibiting different capacities to either support or restrict intracellular bacterial growth. Notably, $CD38^{+}$ alveolar macrophages

display enhanced antimicrobial activity and are associated with improved early control of Mtb infection, highlighting the importance of macrophage phenotype and activation state in determining disease outcome (Pisu et al., 2024).

Host metabolism has also emerged as a critical determinant of tuberculosis pathogenesis. During infection, both macrophages and Mtb undergo extensive metabolic reprogramming that influences bacterial persistence, immune activation, and therapeutic response. Activated macrophages adopt distinct metabolic programs that either enhance antimicrobial functions or create nutrient-rich environments favorable for bacterial replication (Huang et al., 2018). Simultaneously, Mtb demonstrates remarkable metabolic flexibility by utilizing diverse host-derived nutrients and adapting to oxidative stress, hypoxia, and nutrient deprivation within granulomatous lesions, thereby promoting long-term persistence and reduced susceptibility to antimicrobial therapy (Ehrt et al., 2018).

Persistent infection is closely associated with the development of drug tolerance, a reversible physiological state that differs from genetically acquired antimicrobial resistance. Host-derived stresses, including cytokine-mediated macrophage activation, oxidative stress, hypoxia, and nutrient limitation, induce bacterial adaptations that reduce susceptibility to first-line anti-tuberculosis drugs without permanent genetic mutations (Datta et al., 2024). Together with efflux pump activation, metabolic remodeling, bacterial heterogeneity, and the protective granuloma microenvironment, these adaptations contribute to prolonged treatment, relapse, and therapeutic failure (Datta et al., 2024). These findings emphasize that effective TB treatment requires strategies targeting both bacterial physiology and the host environment that supports persistence.

Collectively, these discoveries have transformed the understanding of tuberculosis from a disease driven primarily by bacterial virulence into one governed by continuous reciprocal interactions between Mtb and the host immune system. The pathogen's ability to manipulate innate immune recognition, exploit macrophage biology, remodel host metabolism, evade antimicrobial defenses, and establish persistent intracellular infection underscores the complexity of TB pathogenesis (Samuels et al., 2022). Elucidating these molecular interactions is fundamental to developing next-generation vaccines, host-directed therapies, and novel antimicrobial strategies capable of overcoming persistence, immune evasion, and drug tolerance. Accordingly, this review examines current knowledge of host–pathogen interactions in *Mycobacterium tuberculosis*, with particular emphasis on intracellular survival, phagosome maturation arrest, immune modulation, granuloma dynamics, and drug tolerance, and discusses how these insights can inform future approaches to tuberculosis prevention and treatment (Samuels et al., 2022).

Materials and Methods

This mini narrative review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA**)** guidelines. A systematic literature search was performed in four electronic databases: PubMed, Web of Science, Google Scholar**,** and Scopus**.** The search terms used were: ("*Mycobacterium tuberculosis*" OR "tuberculosis") AND ("macrophage" OR "alveolar macrophage") AND ("phagosome" OR "phagosome-lysosome fusion" OR "phagosome maturation") AND ("granuloma" OR "granuloma formation") AND ("latent tuberculosis" OR "active tuberculosis" OR "latency") AND ("drug tolerance" OR "persisters" OR "persistence"). Boolean operators (**AND**, **OR**) were used to combine the search terms.

Inclusion criteria:

1. All original research articles, systematic reviews, meta-analyses, and review articles published between 2016 and 2026;
2. Studies reporting on the molecular and cellular mechanisms of *Mycobacterium tuberculosis* pathogenesis, intracellular survival, host immune interactions, granuloma biology, latency, persistence, and drug tolerance;
3. Only articles published in English language.

Exclusion criteria:

1. Conference abstracts, editorials, commentaries, and opinion articles;
2. Studies focusing primarily on non-tuberculous mycobacteria or unrelated bacterial pathogens;
3. Articles without accessible full-text versions.

Reviewers independently screened article titles and abstracts, followed by full-text assessment of eligible studies. Any disagreements during study selection were resolved through consensus. The methodological quality of the included studies was evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists appropriate for each study design. Relevant data were extracted into a standardized data collection form and synthesized using a narrative review approach.

The second section discusses the molecular basis of host–pathogen interactions, beginning with the initial macrophage encounter, followed by intracellular survival through inhibition of phagosome–lysosome fusion, immune evasion, granuloma formation, host genetic susceptibility, and mechanisms of drug tolerance and persistence.

The third section critically examines the implications of these mechanisms by discussing the dual role of granulomas in disease containment and dissemination, the limitations of current animal models, and the challenges associated with eliminating latent tuberculosis infection.

Finally, the concluding section synthesizes the major findings and presents conclusions and future perspectives, highlighting current knowledge gaps and emerging strategies, including host-directed therapies, biomarker-guided diagnosis, shorter treatment regimens targeting persisters, precision medicine, and improved vaccine development.

In summary, the pathogenesis of tuberculosis involves complex interactions between *Mycobacterium tuberculosis* and the host immune system. A comprehensive understanding of these interconnected mechanisms is essential for developing more accurate diagnostics, more effective therapies, and durable preventive strategies capable of advancing global tuberculosis control.

Results

Initial Infection and Alveolar Macrophage Encounter

The initial encounter between *Mycobacterium tuberculosis* (Mtb) and alveolar macrophages is a critical event in tuberculosis pathogenesis. After inhalation, Mtb bacilli are deposited in the pulmonary alveoli, where resident alveolar macrophages recognize and internalize them. Rather than eliminating the pathogen, these macrophages become the primary intracellular niche in which Mtb establishes infection and determines whether the host clears, contains, or progresses to active disease (Cadena et al., 2016; Queval et al., 2017).

Within the lung microenvironment, alveolar macrophages use multiple pattern-recognition and phagocytic receptors to engulf Mtb. However, the pathogen has evolved mechanisms that exploit this intracellular environment by modulating immune signaling, inflammatory responses, and intracellular trafficking to favor bacterial survival and persistence (Krishnan et al., 2023; Sankar & Mishra, 2023). Recent single-cell transcriptomic studies further demonstrate that alveolar macrophages are functionally heterogeneous, with distinct subsets differing in their ability to support or restrict bacterial growth. Pro-inflammatory $CD38^{+}$ macrophages appear particularly important in early bacterial control, indicating that macrophage phenotype and activation state strongly influence disease outcome (Pisu et al., 2024).

Mechanisms of Intracellular Survival

Following internalization, Mtb employs multiple interconnected mechanisms to evade host antimicrobial defenses and establish persistent infection. These include arresting phagosome maturation, preventing phagosome–lysosome fusion and acidification, suppressing autophagy, neutralizing reactive oxygen and nitrogen species, modulating host cell death pathways, and altering immune signaling. Collectively, these adaptations remodel the intracellular environment, enabling

long-term bacterial survival while disrupting host inflammatory, metabolic, and DNA repair pathways (Chandra et al., 2022; Flynn & Chan, 2022; Bao et al., 2025; Liu et al., 2023).

Phagosome maturation arrest

A major survival strategy of Mtb is the arrest of phagosome maturation. Normally, phagosomes mature through sequential interactions with early and late endosomes before fusing with lysosomes to form acidic, enzyme-rich phagolysosomes capable of destroying pathogens. Mtb disrupts this process by secreting virulence-associated proteins and lipids that interfere with Rab GTPases, phosphatidylinositol signaling, and membrane fusion machinery, thereby maintaining an immature phagosomal compartment that favors bacterial persistence (Carranza & Chavez-Galan, 2019; Bao et al., 2025). This disruption also limits antigen processing and presentation, weakening adaptive immune activation, while acting synergistically with inhibition of autophagy and lysosomal biogenesis to promote persistent infection (Chandra et al., 2022; Flynn & Chan, 2022).

Inhibition of acidification

Mtb also prevents phagosomal acidification, an essential process for activating lysosomal hydrolases and promoting intracellular killing. It inhibits the assembly and retention of vacuolar ATPase (V-ATPase) on phagosomal membranes, reducing proton transport and maintaining a less acidic environment. Queval et al. (2017) showed that Mtb induces GM-CSF production, triggering STAT5-dependent expression of cytokine-inducible SH2-containing protein (CISH), which promotes degradation of the V-ATPase catalytic subunit and enhances bacterial replication. In addition, Mtb possesses intrinsic acid tolerance mechanisms involving intracellular pH regulation, metabolic remodeling, and stress responses. Virulence factors such as ESAT-6, AcpM, and polyphosphate kinase further impair lysosomal acidification and phagosome–lysosome fusion, collectively supporting long-term intracellular persistence (Rai et al., 2022; Bao et al., 2025) (Table 1).

Evasion of reactive oxygen and reactive nitrogen species

Activated macrophages generate reactive oxygen species (ROS) and reactive nitrogen species (RNS) to destroy invading pathogens by damaging bacterial DNA, proteins, lipids, and membranes. To survive, Mycobacterium tuberculosis (Mtb) has evolved multiple strategies to detect, neutralize, and evade oxidative and nitrosative stress while suppressing host antimicrobial responses (Mehta & Singh, 2019).

A key mechanism involves inhibition of ROS production at its source. The secreted PPE2 protein interacts with the NADPH oxidase subunit p67phox, preventing assembly of the oxidase complex and reducing macrophage ROS generation, thereby enhancing intracellular survival (Srivastava et al., 2019). Mtb also employs the redox-sensitive transcription factor WhiB3, which senses oxidative and nitrosative stress through its iron–sulfur cluster and regulates genes involved in redox homeostasis, intracellular survival, and granuloma formation (Mehta & Singh, 2019).

Mtb further promotes persistence by manipulating host stress-response pathways. The host protein Herp suppresses ROS-dependent autophagy through regulation of endoplasmic reticulum stress responses, whereas Herp inhibition increases ROS production, enhances autophagy, and significantly reduces intracellular bacterial survival (Son et al., 2023). Together, these complementary mechanisms enable Mtb to resist oxidative damage while actively suppressing host antimicrobial defenses.

Granuloma formation and function

Granuloma formation is the hallmark of tuberculosis and represents the culmination of interactions between Mtb and the host immune system. Once regarded solely as protective structures that contain infection, granulomas are now recognized as dynamic and heterogeneous microenvironments that both restrict bacterial dissemination and provide niches for persistence (Cohen et al., 2022; Cronan, 2022).

Table 1: Key Virulence Factors of *Mycobacterium tuberculosis* and Their Mechanisms

Virulence Factor	Type	Mechanism of Action	Effect on Host	Clinical/Diagnostic Relevance
ESX-1 (Type VII secretion system)	Secretion system	Exports ESAT-6 and CFP-10; disrupts phagosomal membranes	Cytosolic access, immune modulation, dissemination	ESAT-6/CFP-10 used in IGRA diagnostics; BCG lacks RD1
ESX-3, ESX-5	Secretion systems	ESX-3: Iron acquisition; ESX-5: Immune modulation	Promotes intracellular survival	Potential vaccine targets
Trehalose dimycolate (TDM/Cord factor)	Cell wall glycolipid	Induces granuloma formation, macrophage activation, cytokine production	Inflammatory response, tissue damage	Contributes to "cord" formation; vaccine adjuvant
Phthiocerol dimycocerosates (PDIMs)	Cell wall lipid	Modifies surface properties; promotes phagosome acidification block	Immune evasion, intracellular survival	Essential virulence factor; PDIM-deficient strains are attenuated
Sulfatides (SL-1)	Sulfated glycolipids	Interferes with phagosome-lysosome fusion; modulates inflammatory signaling	Reduced intracellular killing, persistent infection	Potential therapeutic target
Mannose-capped lipoarabinomannan (ManLAM)	Cell wall glycolipid	Suppresses TLR signaling, inhibits macrophage activation, blocks phagosome maturation	Immune suppression, intracellular persistence	Diagnostic antigen; immunomodulatory activity
WhiB3	Redox sensor/transcription factor	Maintains redox homeostasis; regulates oxidative/nitrosative stress responses	Survival under stress conditions	Potential drug target for sterilization
PPE2 protein	Secreted protein	Interacts with p67phox; inhibits NADPH oxidase and ROS production	Reduced oxidative killing	Potential therapeutic target
AcpM	Cell wall biosynthesis enzyme	Disrupts lysosomal acidification and phagosome-lysosome fusion	Enhanced intracellular survival	Potential drug target
Herp (Host factor exploited)	Host protein manipulation	Suppresses ROS-dependent autophagy via ER stress	Reduced autophagic clearance	Host-directed therapy target
DosR regulon	Transcriptional regulatory system	Activates ~50 genes under hypoxia; induces dormancy	Persistence, drug tolerance	Potential target for sterilizing drugs

Their function extends beyond bacterial sequestration to include regulation of immune cell recruitment, inflammatory signaling, angiogenesis, tissue remodeling, metabolism, and antimicrobial activity. Consequently, disease outcome depends on the balance between host immunity and bacterial immune evasion. Well-organized granulomas limit bacterial growth, whereas disorganized lesions characterized by necrosis, hypoxia, and excessive inflammation favor persistence, latency, and disease progression (Jaiswal et al., 2025; Lyu et al., 2024).

Structure

Tuberculous granulomas typically consist of a central core of infected macrophages surrounded by concentric layers of immune cells and connective tissue. However, recent spatial transcriptomic and imaging studies reveal marked structural heterogeneity, with necrotizing granulomas frequently coexisting alongside non-necrotizing immune aggregates that differ in cellular composition and function (Cronan, 2022; Sawyer et al., 2023). Protective granulomas maintain organized architecture that facilitates immune communication and bacterial containment, whereas disorganized lesions exhibit tissue destruction, impaired compartmentalization, and increased bacterial burden (Lyu et al., 2024). As granulomas continuously remodel during infection, their architecture directly influences immune accessibility, antimicrobial penetration, and treatment response (Cronan, 2022; Sawyer et al., 2023).

Cellular composition

Granuloma function depends on its diverse immune cell populations. Macrophages predominate and differentiate into infected, epithelioid, multinucleated giant, and lipid-laden foamy macrophages, each contributing differently to bacterial containment or persistence (Jaiswal et al., 2025). Dendritic cells, neutrophils, natural killer cells, B cells, and $CD4^+$ and $CD8^+$ T lymphocytes coordinate innate and adaptive immunity through antigen presentation, cytokine production, and cytotoxic activity (Flynn & Chan, 2022).

Equally important is the spatial organization of these cells. Effective granulomas maintain coordinated interactions between activated macrophages and T cells, promoting bacterial control through cytokines such as interferon-γ and tumor necrosis factor. In contrast, dysfunctional macrophage polarization, T-cell exhaustion, and altered immune-cell recruitment disrupt granuloma integrity and permit bacterial persistence (Lyu et al., 2024). Single-cell and spatial profiling further demonstrate distinct granuloma ecosystems with unique transcriptional and metabolic programs that shape local immune responses (Krueger et al., 2025).

Caseation

Caseation is a defining feature of advanced granulomas and marks a critical stage in tuberculosis progression. It results in a central acellular, lipid-rich necrotic core produced by macrophage death, extracellular matrix degradation, and immune-mediated tissue destruction (Cronan, 2022). Current evidence indicates that both excessive and insufficient immune responses contribute to caseation, highlighting the importance of balanced immune regulation (Lyu et al., 2024).

Although the caseous core initially restricts bacterial dissemination, it also creates poorly vascularized regions with reduced immune surveillance and limited antibiotic penetration, promoting long-term bacterial persistence (Rao et al., 2019). Progressive liquefaction can ultimately lead to cavitation and transmission of Mtb. Moreover, necrotizing granulomas coexist with surrounding non-necrotizing inflammatory lesions that differ in cellular organization and immune activity, emphasizing the dynamic and heterogeneous nature of tuberculosis pathology (Sawyer et al., 2023). Understanding the molecular mechanisms governing caseation remains essential for developing host-directed therapies that preserve protective granuloma function while limiting tissue damage.

Hypoxia

As granulomas enlarge, restricted vascularization and increased metabolic activity create oxygen

gradients that generate localized hypoxia. This hypoxic microenvironment profoundly influences both host immunity and Mycobacterium tuberculosis (Mtb) physiology, making oxygen availability a key determinant of granuloma function (Krueger et al., 2025). Reduced oxygen tension drives metabolic adaptation in immune cells while inducing slow-growing or non-replicating bacterial states that enhance persistence and antimicrobial tolerance.

Recent spatial analyses show that hypoxia is unevenly distributed within granulomas, forming distinct metabolic niches in the myeloid core. These regions are associated with impaired lymphocyte infiltration, dysfunctional macrophage phenotypes, immune suppression, and increased bacterial burden (McCaffrey et al., 2026). Likewise, hypoxia-inducible factor-1α signaling helps distinguish protective from pathological granulomas, indicating that both insufficient and excessive hypoxic responses can compromise bacterial control (Lyu et al., 2024). Beyond promoting bacterial survival, hypoxia alters cytokine production, angiogenesis, cellular metabolism, and matrix remodeling, reshaping the granuloma microenvironment. Consequently, targeting hypoxia-associated pathways may improve immune function, antimicrobial penetration, and granuloma stability (Krueger et al., 2025).

Latent TB infection

Latent tuberculosis infection (LTBI) represents a clinically asymptomatic state in which Mtb persists despite an effective adaptive immune response. Rather than complete bacterial inactivity, latency reflects a dynamic balance between immune containment and bacterial adaptation. Within granulomas, bacilli are exposed to hypoxia, nutrient limitation, acidic pH, oxidative stress, and sustained immune pressure, leading to metabolic and transcriptional remodeling that supports long-term survival. During this state, Mtb adopts a slow-growing or non-replicating phenotype characterized by reduced metabolism, altered gene expression, and increased drug tolerance. Although most infected individuals remain asymptomatic, disruption of immune homeostasis can trigger bacterial reactivation and progression to active disease. Consequently, LTBI remains the largest reservoir of future tuberculosis cases and a major barrier to disease elimination (Carranza et al., 2020; Palanivel et al., 2023; Salina & Makarov, 2022; Shah & Dorman, 2021).

Dormancy

Dormancy enables Mtb to survive prolonged environmental and immunological stress while retaining the capacity to resume growth when conditions improve. In response to hypoxia, nutrient deprivation, acidic conditions, and immune pressure within granulomas, Mtb shifts from active replication to a non-replicating persistent state with reduced energy expenditure. Lipid metabolism replaces carbohydrate utilization, ATP production declines, and cell envelope remodeling enhances resistance to host defenses and antimicrobial agents. Because many first-line drugs primarily target actively dividing bacilli, dormancy contributes substantially to phenotypic drug tolerance. Importantly, dormant bacilli remain metabolically responsive and can rapidly reactivate following immune compromise, explaining why latent infection may persist for decades before progressing to active disease (Liu et al., 2024; Salina & Makarov, 2022; Stokas et al., 2020; Veatch & Kaushal, 2018; Vilchèze & Jacobs, 2019).

DosR regulon

A central regulator of dormancy is the dormancy survival regulator (DosR) regulon, which enables adaptation to hypoxia, nitric oxide, carbon monoxide, and other granuloma-associated stresses. Activation of the DosR two-component system through DosS and DosT induces approximately 50 genes involved in metabolic downregulation, redox homeostasis, lipid utilization, energy conservation, and protection against oxidative and nitrosative stress. The DosR regulon functions alongside sigma factors, toxin–antitoxin systems, the MprAB pathway, and WhiB proteins to coordinate persistence and stress adaptation. Because DosR activation is reversible, dormant bacilli can rapidly resume active growth when environmental conditions improve. Its essential role in long-term persistence makes the

DosR regulon an attractive target for therapeutics and vaccines aimed at eliminating latent infection (Liu et al., 2024; Salina & Makarov, 2022; Veatch & Kaushal, 2018).

Reactivation risk factors

Although immune responses successfully contain Mtb in most individuals with LTBI, impaired immune function can disrupt this balance and trigger active tuberculosis. HIV infection remains the strongest risk factor because depletion of $CD4^+$ T cells compromises macrophage activation and granuloma integrity. Other contributors include diabetes mellitus, malnutrition, advanced age, chronic kidney disease, smoking, alcohol misuse, silicosis, malignancy, and immunosuppressive therapies such as corticosteroids and TNF-α inhibitors. Reactivation also depends on bacterial regulatory mechanisms that sense improved environmental conditions and initiate resuscitation. Since only a minority of individuals with LTBI develop active disease, identifying biomarkers that predict reactivation remains a major research priority for risk stratification and preventive therapy (Carranza et al., 2020; Gunasekaran et al., 2025; Palanivel et al., 2023; Shah & Dorman, 2021; Veatch & Kaushal, 2018).

Bacterial Factors

The ability of *Mycobacterium tuberculosis* (Mtb) to establish latency and persist within granulomas depends on specialized bacterial determinants, including secretion systems, surface glycolipids, and cell-envelope lipids. These factors act cooperatively to manipulate macrophage signaling, inhibit antimicrobial defenses, remodel intracellular environments, and maintain bacterial viability under host-imposed stress. Understanding these virulence mechanisms provides important targets for novel antimicrobials, vaccines, and host-directed therapies (Ghazaei, 2018; Tiwari et al., 2019).

ESX-1 Secretion System

The ESX-1 (ESAT-6 secretion system-1) Type VII secretion system is a major determinant of Mtb virulence. It exports early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10), which manipulate host immunity and promote bacterial dissemination across the mycobacterial cell envelope (Tiwari et al., 2019). Following phagocytosis, ESX-1 disrupts phagosomal membrane integrity, allowing bacterial products to access the host cytosol and alter innate immune signaling. This activity contributes to intracellular persistence and granuloma formation by stimulating inflammatory responses and immune-cell recruitment. Studies using *Mycobacterium marinum* demonstrate conservation of ESX-1 organization and regulation, supporting its use in studying tuberculosis pathogenesis (Chirakos et al., 2020).

ESAT-6 and CFP-10 are also important diagnostic antigens used in interferon-γ release assays. Furthermore, loss of the RD1 region encoding ESX-1 is a major factor underlying attenuation of the Bacillus Calmette–Guérin (BCG) vaccine, making ESX-1 an important target for improved vaccines and antimicrobial interventions (Krasilnikov et al., 2024; Tiwari et al., 2019).

Cell Wall Lipids – Sulfatides

The lipid-rich Mtb cell envelope is a major interface between the bacterium and host immunity. Sulfatides, particularly sulfolipid-1 (SL-1), contribute to immune evasion by modulating macrophage activation, intracellular trafficking, and phagosome maturation (Queiroz & Riley, 2017). These lipids interfere with phagosome–lysosome fusion, protecting bacilli from acidic conditions and lysosomal enzymes, while dampening excessive innate inflammatory responses. Their expression can also change in response to host-derived stresses, demonstrating the metabolic adaptability of Mtb (Ghazaei, 2018; Queiroz & Riley, 2017).

Mtb lipids function cooperatively by modifying membrane properties, masking pathogen-associated molecular patterns, influencing macrophage receptor engagement, and contributing to granuloma development. This coordinated lipid remodeling supports bacterial persistence during active and latent infection and identifies lipid metabolism as a potential therapeutic target (Radhakrishnan & Sundaramurthy, 2026).

Phthiocerol Dimycocerosates

Phthiocerol dimycocerosates (PDIMs) are major Mtb virulence lipids located within the outer cell envelope. They regulate interactions with host cells, promote bacterial uptake by permissive macrophages, and reduce immune recognition. Loss of PDIMs markedly attenuates Mtb virulence, demonstrating their importance in host colonization and intracellular survival (Rens et al., 2021).

PDIMs also inhibit phagosome acidification and cooperate with ESX-1 to promote phagosomal membrane disruption and bacterial persistence (Rens et al., 2021). Their biosynthesis depends on methylmalonyl-CoA derived partly from host lipids such as cholesterol and odd-chain fatty acids. Propionate supplementation can restore PDIM production under laboratory conditions, demonstrating the relationship between host nutrient availability, bacterial metabolism, and virulence. Consequently, PDIM biosynthetic pathways represent promising therapeutic targets (Mulholland et al., 2024; Rens et al., 2021).

Host genetic susceptibility

TB progression is influenced not only by Mtb virulence but also by host genetic variation. Although approximately one-quarter of the global population is estimated to carry Mtb, only 5–10% of immunocompetent individuals develop active TB during their lifetime, indicating substantial host influence on disease outcome (Abel et al., 2018; Aravindan, 2019). Host genetic susceptibility (Table 2) encompasses inherited variations affecting pathogen recognition, macrophage activation, phagolysosomal maturation, cytokine production, antigen presentation, and vitamin D-mediated antimicrobial responses. These variations influence susceptibility to primary infection, establishment of LTBI, granuloma stability, reactivation, and treatment outcomes (Cai et al., 2019; Jiao et al., 2022).

Current evidence indicates that TB susceptibility is polygenic rather than controlled by a single locus. Genome-wide and candidate-gene studies have identified susceptibility genes involving SLC11A1 (NRAMP1), TLRs, VDR, cytokines, HLA loci, autophagy, and antigen processing. However, the effects of individual polymorphisms vary across populations because of differences in genetic background, environmental exposure, nutritional status, and pathogen diversity. These genes function within interconnected immune pathways that collectively determine whether Mtb is contained or progresses to persistent infection and active disease (Abel et al., 2018; Aravindan, 2019; Jiao et al., 2022).

NRAMP1

Natural resistance-associated macrophage protein 1 (NRAMP1), encoded by *SLC11A1*, is an important host susceptibility gene in tuberculosis. Expressed mainly on macrophage phagolysosomal membranes, NRAMP1 regulates divalent metal ions, particularly iron and manganese. By limiting these essential nutrients, it restricts Mtb replication while enhancing antimicrobial mechanisms such as reactive oxygen and nitrogen species production and pro-inflammatory cytokine responses (Cai et al., 2019; Shahzad et al., 2022).

Polymorphisms in *SLC11A1* have been associated with increased pulmonary TB susceptibility across populations. Reduced NRAMP1 expression weakens phagosomal antimicrobial activity, macrophage activation, and production of TNF-α and IL-12, which are essential for granuloma formation and bacterial containment (Aravindan, 2019; Shahzad et al., 2022). Conversely, increased NRAMP1 expression enhances inflammatory responses, whereas gene knockdown promotes bacterial survival through impaired cytokine production and intracellular killing (Meng et al., 2023). These findings identify NRAMP1 as both a genetic marker of TB susceptibility and a potential target for host-directed therapies (Cai et al., 2019; Meng et al., 2023).

TLRs

Toll-like receptors (TLRs) are important determinants of host susceptibility because they recognize mycobacterial components, including lipoarabinomannan, lipomannan, phosphatidylinositol mannosides, and lipoproteins.

Table 2: Host Genetic Polymorphisms Associated with Tuberculosis Susceptibility

Gene	Protein/Function	Polymorphism(s)	Effect on TB Susceptibility	Population Variation	Key References
SLC11A1 (NRAMP1)	Divalent metal ion transporter; regulates macrophage antimicrobial function	3' UTR (TGTG deletion), INT4, D543N, 5' (GT)n	Increased TB risk with variant alleles	Asian, African, European populations show variation	Cai et al., 2019; Shahzad et al., 2022
TLR2	Toll-like receptor; recognizes lipoarabinomannan and lipoproteins	Arg753Gln, T-16934A	Impaired mycobacterial recognition; increased TB susceptibility	Variable among ethnic groups	Biyikli et al., 2016; Varshney et al., 2022
TLR4	Toll-like receptor; recognizes heat-shock proteins and lipids	Asp299Gly, Thr399Ile	Altered signaling; increased TB risk in some populations	Stronger association in Asian populations	Zhou et al., 2020
TLR8	Toll-like receptor; recognizes ssRNA	-129G/C, Met1Val	Associated with TB susceptibility and LTBI progression	Sex-specific effects possible	Wang et al., 2018
TLR9	Toll-like receptor; recognizes CpG DNA	T-1486C, T-1237C	Associated with TB susceptibility	Population-specific effects	Varshney et al., 2022
VDR (Vitamin D Receptor)	Nuclear transcription factor; regulates antimicrobial peptides (LL-37)	FokI (C/T), BsmI, TaqI, ApaI	FokI polymorphism strongly associated with TB susceptibility (recessive model)	Strongest in Asian populations	Yadav et al., 2021
TNF-α	Pro-inflammatory cytokine; essential for granuloma formation	-308G/A, -238G/A	A allele associated with increased TB risk	Variable; stronger in certain populations	Adane et al., 2021
IFN-γ	Th1 cytokine; activates macrophages	+874T/A (intron 1)	T allele associated with higher production and protection	Population-specific	Adane et al., 2021
IL-10	Anti-inflammatory cytokine	-1082G/A, -819C/T	Associated with altered Th1/Th2 balance	Variable	Aravindan, 2019
HLA Class II	Antigen presentation	HLA-DRB1, DQB1 alleles	Certain alleles associated with protection or susceptibility	Strong ethnic variation	Abel et al., 2018
MBL2	Mannose-binding lectin; complement activation	Codon 54, 57 mutations	Impaired complement-mediated clearance	Associated with TB in some populations	Aravindan, 2019

Their activation through adaptor molecules such as MyD88 stimulates NF-κB and MAPK pathways, promoting TNF-α, IL-12, IFN-γ, and other mediators involved in innate and adaptive immunity (Biyikli et al., 2016). Polymorphisms affecting TLR2, TLR4, TLR8, and TLR9 have been

associated with altered TB susceptibility, although effects vary among populations. Several TLR variants may impair pathogen recognition and downstream signaling, weakening macrophage activation and granuloma formation (Varshney et al., 2022). Experimental evidence further shows that TLR2 deficiency impairs bacterial clearance, granulomatous responses, and production of TNF-α, IFN-γ, and IL-12 following Mtb infection (Biyikli et al., 2016). TLR8 and TLR9 polymorphisms have also been linked to progression from latent to active TB, indicating that TLR signaling influences disease across its spectrum (Biyikli et al., 2018).

Vitamin D Receptor

Vitamin D-mediated immunity is another important determinant of TB resistance. Its biological effects are mediated by the vitamin D receptor (VDR), expressed in macrophages, dendritic cells, and lymphocytes. VDR activation induces antimicrobial peptides such as cathelicidin (LL-37) and β-defensins, promotes phagolysosomal maturation and autophagy, and regulates inflammatory cytokines, thereby enhancing intracellular Mtb killing while limiting tissue damage (Aravindan, 2019; Cai et al., 2019).

VDR polymorphisms, particularly FokI, have been extensively investigated in relation to TB susceptibility. A meta-analysis found that recessive FokI models were significantly associated with increased susceptibility, particularly among Asian populations, although associations varied by ethnicity (Yadav et al., 2021). Thus, genetic variation may influence vitamin D-mediated antimicrobial activity in combination with environmental factors such as vitamin D status, highlighting the importance of integrating genetic and nutritional determinants in TB risk assessment (Abel et al., 2018; Yadav et al., 2021).

Drug tolerance and persistence

Unlike antimicrobial resistance, which results from stable genetic mutations, drug tolerance is a reversible phenotype allowing Mtb to survive prolonged antibiotic exposure without resistance-conferring mutations. Persistence involves a small population of metabolically altered bacilli that withstand bactericidal drug concentrations and resume growth when treatment pressure is removed. These states contribute to prolonged chemotherapy, relapse, and eventual emergence of genetic drug resistance (Goossens et al., 2020; Liebenberg et al., 2022).

Drug tolerance arises through physiological adaptation to hypoxia, nutrient deprivation, oxidative stress, acidic pH, immune pressure, and antibiotics. Mtb responds through reduced replication, metabolic remodeling, altered lipid metabolism, stress-response activation, increased efflux activity, and cell-envelope modification. These adaptations decrease antibiotic effectiveness by reducing metabolic targets and limiting drug susceptibility, thereby supporting persistence within diverse host niches (Chandra et al., 2022; Goossens et al., 2020; Liebenberg et al., 2022).

Non-replicating persisters

Non-replicating persister (NRP) cells represent a well-characterized form of drug tolerance. Although they constitute a small bacterial population, NRPs show substantial tolerance to first-line drugs because these agents preferentially target actively growing organisms. Within granulomas, hypoxia, nutrient and zinc limitation, acidic conditions, and immune pressure promote their formation (Goossens et al., 2020; Li et al., 2021).

NRP formation involves reduced tricarboxylic acid cycle activity, enhanced lipid metabolism, altered redox homeostasis, stress-response activation, and reduced ATP demand. This reversible state facilitates rapid resuscitation following antibiotic withdrawal or immune relaxation, contributing to relapse and treatment failure (Goossens et al., 2020; Li et al., 2021). Targeting persister-specific metabolic pathways and ribosome hibernation may therefore provide strategies for shortening TB treatment and limiting drug resistance.

Biofilm-like cords

Beyond intracellular persistence, *Mycobacterium tuberculosis* (Mtb) survives by forming biofilm-like cords, organized multicellular structures that enhance mechanical stability and antimicrobial tolerance. Unlike conventional bacterial biofilms, these extracellular cords consist of tightly packed

bacilli embedded within lipid-rich matrices that support survival under hostile conditions. Cording is now recognized as an active virulence mechanism that promotes immune evasion, sustained viability, and chronic infection (Mishra et al., 2023).

Biofilm-like cords contribute to persistence by limiting antibiotic penetration, protecting bacilli from phagocytosis, and creating extracellular niches for bacterial growth. Within lung tissues, they compress alveolar cells, suppress innate immune signaling through nuclear deformation, and induce contact-dependent death of infiltrating phagocytes. Importantly, bacilli within cords remain translationally active despite prolonged antibiotic exposure and rapidly resume growth after treatment. Host-derived catecholamines, including epinephrine, further stimulate biofilm formation and antibiotic tolerance through bacterial sensory pathways (Lei et al., 2023; Mishra et al., 2023). These findings identify biofilm-like cords as important contributors to chronic infection and promising therapeutic targets.

Discussion

Tuberculosis pathogenesis results from continuous interactions between bacterial virulence factors, host genetics, and adaptive survival mechanisms. Together, these processes enable Mtb to evade immune defenses, establish persistence, and develop drug tolerance despite robust innate and adaptive immunity. Although advances in molecular microbiology have clarified mechanisms of macrophage manipulation and intracellular survival, host genetic polymorphisms also influence immune responses and disease susceptibility (Abel et al., 2018; Aravindan, 2019; Chandra et al., 2022). However, unresolved questions surrounding granuloma biology, latent infection, and experimental models continue to limit the development of more effective diagnostics, vaccines, and host-directed therapies.

Why granulomas can both contain and spread infection

Granulomas are no longer viewed solely as protective structures but as dynamic microenvironments that simultaneously restrict and support Mtb. While macrophages, T cells, dendritic cells, and neutrophils cooperate to control bacterial replication, Mtb exploits granulomas by inhibiting phagosome maturation, resisting intracellular killing, and adapting to hypoxic, nutrient-limited environments (Chandra et al., 2022; Goossens et al., 2020). Mycobacterial lipids further modulate local immunity, whereas non-replicating persisters withstand prolonged immune and antibiotic pressure. Progressive caseation, liquefaction, and cavitation eventually release bacilli into the airways, facilitating transmission.

Limitations of animal models

Animal models have greatly advanced understanding of TB but cannot fully replicate human disease. Mice rarely develop organized caseating granulomas, cavitary lesions, or heterogeneous latent infection. Although guinea pigs, rabbits, and non-human primates reproduce certain pathological features more closely, differences in immune architecture, genetics, and cost limit their broader use (Chandra et al., 2022). Host genetic diversity and bacterial phenotypes, including biofilm-like cording, persister formation, and drug tolerance, are also difficult to reproduce experimentally (Abel et al., 2018; Cai et al., 2019; Goossens et al., 2020; Mishra et al., 2023). Therefore, animal studies should be complemented with human tissue models, organoids, lung-on-chip systems, and multi-omics approaches.

Challenges in eradicating latent infection

Latent tuberculosis remains a major obstacle because viable bacilli persist for decades in metabolically adapted, non-replicating states. Current diagnostics detect immune sensitization rather than bacterial viability, limiting their ability to predict disease reactivation (Palanivel et al., 2023). Furthermore, persisters, altered lipid metabolism, stress responses, and biofilm-like communities reduce antibiotic efficacy and increase relapse risk (Bi et al., 2022; Goossens et al., 2020). Consequently, host-directed therapies that enhance autophagy are shown in table 3.

Table 3: Therapeutic Strategies Targeting Host-Pathogen Interactions in TB

Strategy	Target/Mechanism	Examples	Stage of Development	Advantages	Challenges/Limitations
Host-Directed Therapies (HDTs)	Enhance protective immunity; reduce inflammation	Metformin, statins, vitamin D, corticosteroids, IL-1 antagonists	Clinical trials and preclinical studies	Adjunct to antibiotics; reduces tissue damage; no resistance	Patient variability; optimal dosing not established
Autophagy Enhancers	Promote autophagic clearance of Mtb	Rapamycin, everolimus, carbamazepine	Preclinicals ome clinical trials	Targets intracellular bacilli; enhances immune function	Safety concerns with immunosuppression
Anti-inflammatory HDTs	Reduce excessive inflammation and caseation	Corticosteroids, TNF-α inhibitors, IL-1 receptor antagonists	Clinical use (corticosteroids); investigational for biologics	Reduces lung damage; improves outcomes in severe TB	Risk of reactivation with TNF inhibitors
Persister-Targeting Drugs	Kill non-replicating drug-tolerant bacilli	Nitroimidazoles (pretomanid, delamanid), bedaquiline, clofazimine	Approved/ Clinical use	Shortens treatment duration; targets dormant bacilli	Toxicity concerns; resistance development
Efflux Pump Inhibitors	Enhance antibiotic accumulation	Verapamil, reserpine, CCCP	Preclinical	Overcomes drug tolerance; enhances existing drugs	Toxicity; limited clinical data
Vaccines Targeting Persistence	Induce immunity against dormant antigens	H56:IC31 (Ag85B-ESAT-6-Rv2660c), M72/AS01E, MTBVAC	Clinical trials (Phase II/III)	Targets latent and active infection	Variable efficacy; complex trial design
Granuloma-Penetrating Formulations	Improve antibiotic delivery into granulomas	Liposomal formulations, nanoparticle delivery	Preclinical	Improves drug penetration into necrotic cores	Manufacturing complexity; cost
Immunometabolic Modulators	Reprogram macrophage metabolism	Metformin, mTOR inhibitors, HIF-1α modulators	Preclinical and clinical trials	Enhances antibacterial responses; reduces inflammation	Complexity of metabolic pathways
Biomarker-Guided Therapy	Stratify LTBI reactivation risk	Multiplex cytokine profiling, transcriptomic signatures	Translational research	Personalized treatment; reduces overtreatment	Validation needed; implementation challenges
Gene Therapy	Correct host genetic susceptibility	CRISPR-mediated gene editing	Preclinical (research stage)	Potential permanent correction	Safety; delivery challenges; ethical concerns

These therapies regulate inflammation, and improve intracellular bacterial killing, together with advances in biomarkers, vaccines, and persistence-targeted therapeutics, offer promising strategies for TB elimination (Goossens et al., 2025).

Conclusions and Future Perspectives

This review demonstrates that tuberculosis is driven by continuous host–pathogen interactions rather than bacterial virulence alone. From macrophage invasion and intracellular survival to granuloma formation, host genetics, biofilm-like cording, and drug-tolerant persisters, Mtb employs complementary mechanisms that sustain long-term persistence despite effective immunity and antimicrobial therapy (Chandra et al., 2022).

Host genetic polymorphisms involving NRAMP1, Toll-like receptors, vitamin D receptor, TNF-α, and IFN-γ further influence disease susceptibility, while granulomas simultaneously restrict bacterial dissemination and provide protective niches for dormancy and drug tolerance (Adane et al., 2021; Jiao et al., 2022; Varshney et al., 2022). Although substantial progress has been made, knowledge gaps remain regarding persistence, granuloma heterogeneity, and biomarkers capable of predicting disease progression (Palanivel et al., 2023).

Future TB control will depend on integrating host-directed therapies, persister-targeted regimens, precision medicine, improved biomarkers, novel vaccines, and individualized treatment strategies (Jeong et al., 2022; Kaufmann, 2023; Meserve et al., 2025; Singh, 2024; Thomas et al., 2024; Velayutham, 2025). Equally important is the development of human-based experimental models that better capture host–pathogen interactions and granuloma complexity. A deeper understanding of these mechanisms will facilitate more accurate diagnostics, shorter and more effective therapies, and durable preventive strategies capable of accelerating progress toward global tuberculosis elimination.

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Competing Interest

The author declares no competing interests regarding the publication of this manuscript.

Author Contribution

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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