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Review Article

POST-ADAPTIVE SURVIVAL MECHANISMS IN *MYCOBACTERIUM TUBERCULOSIS*: A COMPREHENSIVE REVIEW

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ABSTRACT

Mycobacterium tuberculosis (MTB) survives hostile host environments by activating complex post-adaptive survival mechanisms that enable long-term persistence and drug tolerance. Under conditions of nutrient deprivation, hypoxia, oxidative stress, and immune pressure, MTB activates metabolic reprogramming, cell wall remodeling, and regulatory networks. These responses contribute to phenotypic drug tolerance and complicate tuberculosis (TB) treatment outcomes. This review summarizes molecular, metabolic, and phenotypic post-adaptive mechanisms employed by MTB, with particular emphasis on post-translational modifications, stress-responsive pathways, and dormancy-associated processes. In addition, the clinical relevance of these adaptive strategies, including their impact on drug efficacy, treatment duration, and therapeutic failure, is critically discussed. A deeper understanding of post-adaptive survival mechanisms may facilitate the development of improved therapeutic strategies targeting persistent and drug-tolerant TB.

Keywords: *Mycobacterium tuberculosis*, Post-adaptation, PhoPR, Post-translational modifications, Metabolic reprogramming, Phenotypic drug tolerance, Persistence, Host stress adaptation.

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INTRODUCTION

Mycobacterium tuberculosis (MTB) is a highly adapted intracellular pathogen responsible for tuberculosis (TB), which remains one of the leading causes of mortality from infectious diseases worldwide [1]. Its capacity to establish long-term infection and persist within host macrophages depends largely on sophisticated post-adaptive survival mechanisms. Following phagocytic uptake, MTB encounters multiple hostile conditions, including acidic environments, oxidative and nitrosative stress, limited nutrient availability, hypoxia, and exposure to antimicrobial compounds. Rather than relying solely on early infection strategies, MTB initiates a series of coordinated regulatory, metabolic, and structural adaptations that enable survival under these adverse conditions. These post-adaptive responses include sensing environmental stress signals, post-translational modification (PTM) of key proteins, development of phenotypic heterogeneity that supports non-replicative persistence, and extensive metabolic remodeling to optimize energy utilization and stress tolerance. Together, these mechanisms facilitate immune evasion, promote tolerance to anti-tubercular drugs, and support a dormant physiological state, ultimately contributing to latent infection and complicating effective therapeutic intervention [2-4]. This review explores the various mechanisms of adaptability that MTB employs in response to host stresses, highlighting key regulatory systems, biochemical modifications, and metabolic shifts that support its survival and pathogenicity [5]. Unlike previous reviews that primarily focus on isolated stress responses or genetic resistance mechanisms, the present review integrates molecular, metabolic, and phenotypic post-adaptive survival strategies of MTB. This work uniquely emphasizes the transition from adaptive stress tolerance to clinically relevant drug tolerance and persistence, incorporating PTMs, phenotypic reservoirs, and a critical analysis of recent trials such as Nix-TB and ZeNix, thereby updating the field with a translational perspective on TB pathogenesis and therapeutic challenges. MTB encounters multiple hostile conditions within the host, including acidic pH, oxidative and nitrosative stress, nutrient deprivation, hypoxia, and antimicrobial pressure. In response, the pathogen activates coordinated post-adaptive survival strategies involving stress sensing, regulatory system activation, metabolic reprogramming, cell wall remodeling, and phenotypic heterogeneity. Together, these integrated responses promote long-term persistence, phenotypic drug tolerance, and survival under prolonged host and drug-induced stress (Fig. 1).

MTB employs various post-adaptation mechanisms to survive hostile conditions within the host, including antibiotic pressure and immune responses. These adaptations involve metabolic shifts, cell wall remodeling, transcriptional regulation, and phenotypic drug tolerance, which help it persist and become less susceptible to drugs. Understanding how these adaptive responses relate to the drug's targeting MTB is essential for improving treatment strategies and combating drug-resistant TB. The following table summarizes key post-adaptation mechanisms of MTB along with representative medications that target these bacterial processes, highlighting their modes of action and clinical significance. The major post-adaptive survival mechanisms used by MTB under host-induced stress and highlights representative drugs that target these pathways. Table 1 shows how metabolic remodeling, cell wall modifications, redox balance, and DNA damage responses contribute to bacterial persistence and drug tolerance.

SENSING AND RESPONDING TO HOST-RELATED STRESSORS

MTB faces several adverse conditions during host infection, mainly within macrophage phagosomes. The stressors include acidic pH, oxidative and nitrosative stress from reactive oxygen and nitrogen species, hypoxia caused by granuloma formation, nutritional deficiency due to sequestration, and immune system pressures. The bacteria have developed sophisticated sensing and response mechanisms to detect and adapt to these hostile environments, which are crucial for their intracellular survival and persistence [11].

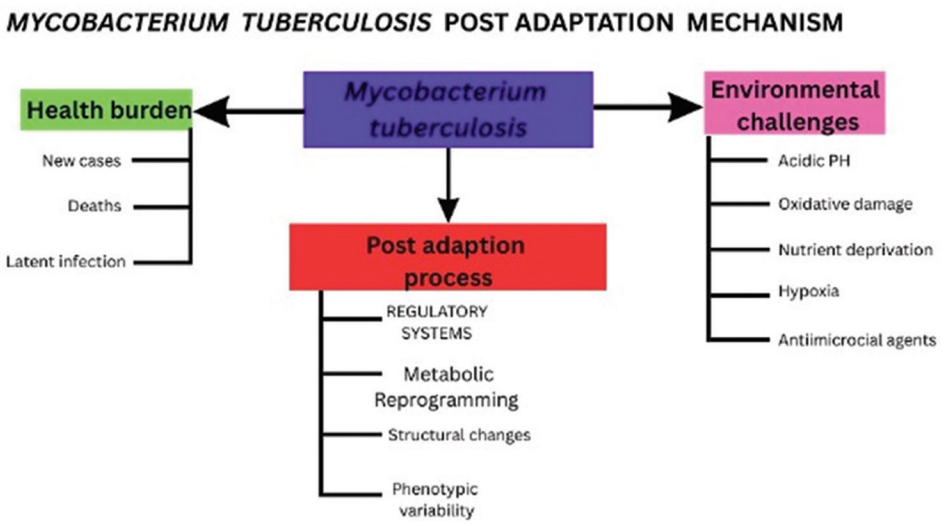

Fig. 1: Post-adaptation survival mechanisms of *Mycobacterium tuberculosis*

Table 1: Post-adaptation mechanisms in *Mycobacterium tuberculosis* and corresponding drug targets

Post-adaptation mechanism	Description	Representative drug	Drug action/target	References
Metabolic adaptation	Shift toward lipid metabolism; growth arrest	Isoniazid	Inhibition of mycolic acid synthesis	[6]
Cell wall modification	Cell wall thickening; efflux activation	Ethambutol	Inhibition of arabinosyl transferase	[7]
Transcriptional regulation	Stress-response gene upregulation	Rifampicin	Inhibition of DNA-dependent RNA polymerase	[8]
Drug tolerance and persistence	Reduced metabolic rate; persister states	Bedaquiline	Inhibition of adenosine triphosphate synthase	[9]
Efflux pumps and resistance	Overexpression of efflux systems	Moxifloxacin	Inhibition of DNA gyrase	[10]

Chemical structures and molecular formulas of the listed anti-tuberculosis drugs are provided in Supplementary Table S1

DETECTION OF ENVIRONMENTAL STRESSORS

Acidic pH

Within the phagosome compartment, MTB encounters acidic conditions that serve as a major stressor [2]. The bacteria detect pH changes mainly through specialized two-component sensory systems, especially the Two-component regulatory system PhoP/PhoR (acid and chloride stress sensing) (PhoPR) system, which controls downstream gene expression vital for acid adaptation and virulence [12].

Oxidative and nitrosative stress

MTB detects reactive oxygen species (ROS) and reactive nitrogen intermediates produced by the host's immune defenses. These molecules cause oxidative damage, prompting MTB to activate detoxification enzymes and repair mechanisms to neutralize reactive species [13,14].

Hypoxia

Granuloma development and limited vascular supply can considerably decrease oxygen levels, causing MTB to detect hypoxic conditions mainly through oxygen-sensing regulatory systems like the dormancy survival regulator (DosR) regulon, which triggers metabolic shifts toward dormancy [15].

Nutrient Limitation

MTB detects a lack of essential nutrients such as carbon sources, iron, and amino acids inside the host, leading to the activation of nutrient acquisition systems and metabolic reprogramming [16,17].

Immune pressures

MTB senses and responds to host-derived immune effectors, including antimicrobial peptides and cellular signaling molecules, by altering cell wall components and regulatory pathways. Adaptive responses to detected stress: On sensing these stressors, MTB initiates multi-layered adaptive strategies [18,19]

Modulation of growth rate

MTB might slow down or stop replication (dormancy or non-replicating persistence [NRP]) as a survival tactic that reduces metabolic needs and susceptibility to antibiotics [20,21].

Induction of stress response genes

The activation of regulons, including PhoPR and DosR, increases the expression of genes involved in detoxification, repair, lipid metabolism, and cell wall remodeling [22,23].

Cell wall remodeling

Modifications to the *mycobacterial* cell membrane enhance resistance to adverse influences and decrease permeability to detrimental substances [24,25].

Metabolic shifts

MTB adjusts its metabolic pathways to improve survival during low oxygen levels, nutrient shortages, and redox stress by switching from aerobic respiration to alternative mechanisms such as cytochrome bd oxidase-dependent processes. These integrated sensing and response systems allow MTB to endure the challenging intracellular environment, evade immune responses, develop phenotypic drug resistance, and persist throughout prolonged infection.

REGULATORY SYSTEMS IN ADAPTATION

MTB employs various interconnected regulatory systems to detect environmental stress and control gene expression changes that improve survival, virulence, and persistence. This includes two-component regulatory systems, transcription factors (TFs), sigma factors, and protein phosphorylation signaling pathways [26].

Two-component regulatory systems

Two-component systems (TCSs) consist of a sensor histidine kinase and a response regulator. They recognize specific environmental signals and trigger precise gene expression responses. PhoPR detects acidic pH and chloride stress [27]. PhoR (sensor kinase) autophosphorylates in response to low pH and then transfers the phosphate group to PhoP (response regulator) [22]. phoP activates genes related to lipid production, secretion mechanisms, and virulence factors [28]. It is essential for intracellular survival; mutations lead to reduced pathogenicity [29]. Transcriptional Regulatory Protein A (PrrA)/ Sensor Histidine Kinase B (PrrB) respond to hypoxia, redox shifts, and oxidative stress. PrrB detects oxygen and redox signals, phosphorylates PrrA, which then activates hypoxia-survival genes and the alternative respiratory pathway. The PhoPR two-component regulatory system plays a central role in phenotypic adaptation and drug stress responses of MTB by sensing acidic and chloride stress within host phagosomes, as illustrated in (Fig. 2). PhoR, the membrane-bound sensor kinase, becomes activated under acidic conditions and undergoes autophosphorylation, followed by transfer of the phosphate group to the response regulator PhoP. Activated PhoP subsequently induces the transcription of genes involved in lipid metabolism, secretion systems, and virulence-associated functions. These PhoP-regulated genes contribute to intracellular survival, stress adaptation, and maintenance of pathogenicity under hostile host conditions. Disruption or mutation of the PhoPR system significantly attenuates bacterial virulence and impairs survival within macrophages, highlighting its importance in environmental sensing and adaptive regulation.

In addition to TCSs, MTB uses other TFs and sigma factors to control gene expression [30]. WhiB Family: Iron-sulfur cluster proteins that serve as redox-responsive TFs (WhiB1–WhiB7) [31]. They sense oxidative and nitrosative stress and regulate genes involved in antioxidant defenses, DNA repair, and redox balance [32]. Some factors (e.g., WhiB7) activate internal antibiotic resistance genes [33]. Alternative sigma factor E: Activated in response to cell envelope stress and oxidative damage [34,35]. It directs RNA polymerase (RNAP) to genes encoding enzymes that alter the cell wall, chaperones, and stress detoxification proteins. cAMP receptor protein: Responds to cyclic adenosine monophosphate signaling, modulating central metabolism, virulence genes, and adaptability to nutrient levels. Phenotypic non-replicating persistence (NRP) adaptations that enable MTB to survive hostile host environments and tolerate antibiotic pressure without acquiring genetic resistance. Major regulatory systems contributing to phenotypic adaptation, drug tolerance, and persistence in MTB are summarized in (Table 2).

PTMS

The major PTMs involved in stress adaptation and survival of MTB are summarized in (Table 3). PTMs are essential for MTB adaptability, as they alter protein function, stability, localization, and interactions after synthesis. These modifications enable MTB to quickly adapt cellular processes in response to external stress without requiring the production of new proteins [39]. After exposure to stress, MTB develops several post-adaptation mechanisms that help it survive within the host. The bacterium can escape from the phagosome using the ESAT-6 Secretion System-1 (Early Secretory Antigenic Target-6 Secretion System-1) (ESX-1) secretion system and phthiocerol dimycocerosates (PDIMs), while mycolic acids in the cell wall provide resilience and protection. It resists oxidative stress by neutralizing reactive oxygen and nitrogen species through enzymes such as catalase-peroxidase enzyme (KatG). For intracellular maintenance, *MTB* uses proteasomes and regulates autophagy to ensure its survival. Key intracellular survival and persistence mechanisms employed by MTB following host adaptation, including phagosomal escape, oxidative and nitrosative stress neutralization, and proteasome-mediated protein quality control, are illustrated (Fig. 3). Following phagocytic uptake by macrophages, the bacterium promotes phagosomal escape through the ESX-1 secretion system and PDIMs, enabling access to a more permissive intracellular niche. Enhanced cell-wall resilience mediated by mycolic acids further strengthens resistance to hostile intracellular conditions. Oxidative and nitrosative stress generated by host immune defenses is counteracted by antioxidant enzymes such as catalase-peroxidase (KatG), alkyl hydroperoxide reductase (AhpC), and superoxide dismutase (SOD), protecting the bacillus from reactive oxygen and nitrogen species. In addition, proteasome-dependent degradation of damaged or misfolded proteins supports intracellular homeostasis, allowing sustained survival during persistent infection.

PTMs play a central role in regulating protein function and cellular adaptation in MTB. By introducing reversible chemical modifications, PTMs enable rapid modulation of signaling pathways, metabolic activity, and protein stability in response to host-induced stresses, including nutrient deprivation, hypoxia, oxidative stress, and antimicrobial pressure. Collectively, these modifications contribute to

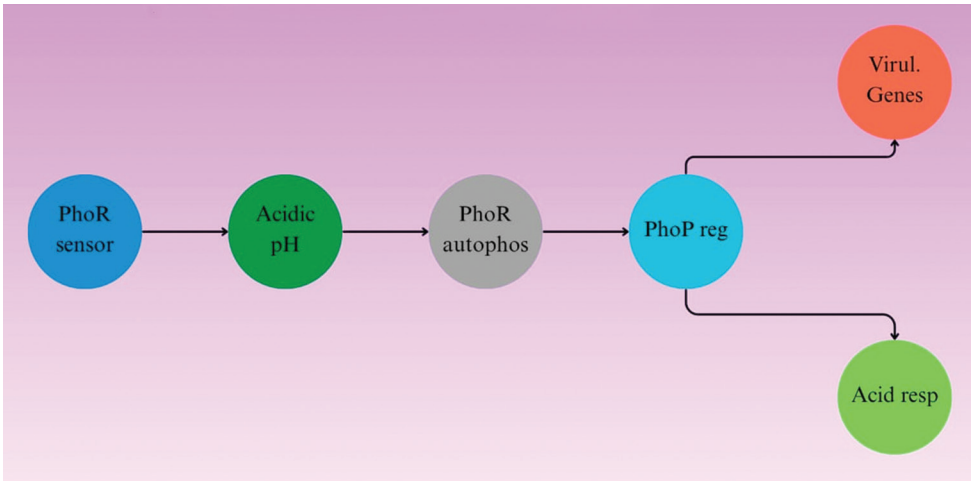

Fig. 2: PhoPR-mediated signaling pathway regulating phenotypic adaptation and drug stress responses in *Mycobacterium tuberculosis*

Table 2: Phenotypic adaptations contributing to drug tolerance and persistence in *Mycobacterium tuberculosis*

Subsystem	Type	Key functions	Stress adaptation role	REFERENCES
Two-component regulatory system PhoP/PhoR (acid and chloride stress sensing)	Two-component system	Acid and chloride stress sensing; virulence regulation	Crucial for intracellular survival	[36]
PrrA/PrrB	Two-component system	Hypoxia, redox stress genes	Survival in granuloma hypoxia	[37]
TcrXY	Two-component system	Chloride, oxidative stress adaptation	Ionic and oxidative tolerance	[38]
WhiB family	Redox-responsive transcription factors (TFs)	Antioxidant, DNA repair, redox control	Survival under reactive oxygen species/reactive nitrogen species attack	
Alternative sigma factor E	Alternative sigma	Cell wall and oxidative stress response	Reinforces barrier function	
cAMP receptor protein	cAMP-responsive TF	Metabolic reprogramming	Nutrient adaptation	
Serine/threonine protein kinases A and B	STPK	Cell wall synthesis, division	Morphological adaptation	
Serine/threonine protein kinase G	STPK	Anti-phagosomal fusion, metabolism	Immune evasion	

Table 3: Common post-translational modifications in *Mycobacterium tuberculosis*

PTM type	Example enzymes	Primary targets	Functional impact	Role in adaptation	References
Phosphorylation	Serine/threonine protein kinases A and B, serine/threonine protein kinase G	Metabolic enzymes, regulators	Alters activity and signaling	Controls metabolism, division, and stress response	[40]
Acetylation	Lysine acetyltransferases	Glycolytic enzymes, transcription factors	Modulates activity/stability	Nutrient and energy adaptation	[41]
Methylation	Methyltransferases	RNA polymerase, DNA	Alters transcription regulation	Fine-tunes gene expression	
Pupylation	prokaryotic ubiquitin-like protein ligase	Misfolded proteins	Marks for proteasomal degradation	Removes damaged proteins during stress	[42]
Glycosylation	Mannosyl transferases	Adhesion protein Apa, Mannosylated lipoprotein LpqH, Superoxide dismutase C	Immune evasion, adhesion	Host immune modulation	[43]
Lipidation	Lipoprotein acyltransferases	Surface proteins	Anchors to membranes	Enhances signaling and nutrient uptake	[44]

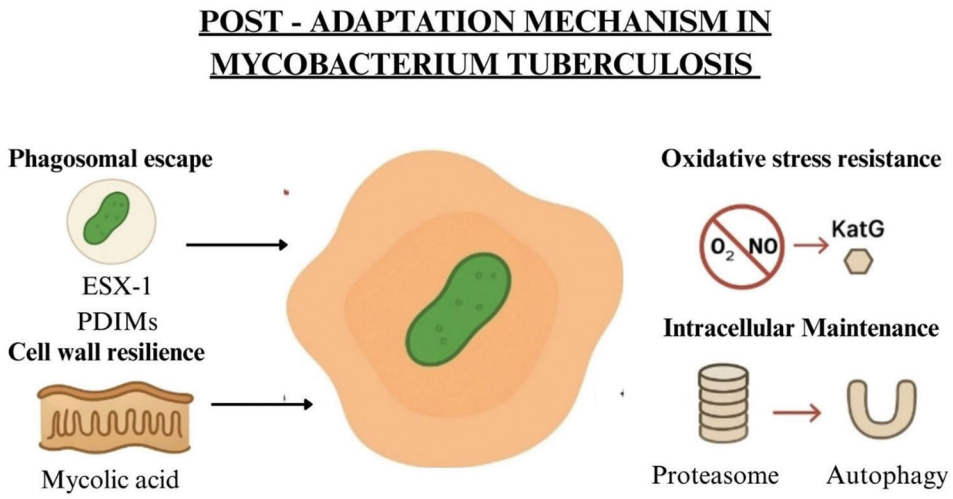

Fig. 3: Intracellular survival and persistence mechanisms of *Mycobacterium tuberculosis* following host adaptation

bacterial survival, persistence, and phenotypic drug tolerance during infection.

Phosphorylation events regulate protein acetylation by modulating acetyltransferases, while pupylation interacts with glycosylation to maintain surface protein homeostasis under stress. This crosstalk

creates an integrated regulatory network enabling rapid adaptation to multiple simultaneous host stressors. Pupylation of PanB (3-methyl-2-oxobutanoate hydroxymethyltransferase) enhances bacterial survival under hypoxic conditions by targeting damaged metabolic enzymes for proteasomal degradation, maintaining essential pathway functionality [45].

Phosphorylation

Phosphorylation of serine, threonine, or tyrosine residues, mediated by serine/threonine protein kinases such as Serine/Threonine Protein Kinases A and B (Pkn A, B), and serine/threonine protein kinase G, as well as tyrosine kinases, plays a crucial role in regulating cellular processes. This modification influences signaling pathways, enzymatic activity, TFs, and structural proteins. In stress adaptation, phosphorylation coordinates essential functions like cell division, peptidoglycan synthesis, energy management, and defense against oxidative stress, thereby enhancing bacterial survival in harsh conditions. [46].

Acetylation and methylation

Acetylation

Acetylation occurs at lysine residues and affects enzyme activity, protein stability, and the DNA-binding ability of transcription factors (TFs) [47,48]. It is linked to regulating central metabolism during times of nutritional scarcity. Methylation can modify proteins and nucleic acids, altering RNAP subunits and impacting transcription output [49-51].

Pupylation (prokaryotic ubiquitin-like modification)

The small protein prokaryotic ubiquitin-like protein (Pup) attaches to target proteins, signaling them for degradation by the proteasome. This process is essential for maintaining protein quality control during oxidative and nutritional stress by removing damaged or unnecessary proteins [45,52,53].

Glycosylation and lipidation

Glycosylation, particularly O-mannosylation, modifies surface and secreted proteins such as adhesion protein Apa, Mannosylated lipoprotein LpqH, and SOD C, enhancing immune evasion by altering antigen recognition and influencing host–pathogen interactions and adhesion. Lipidation involves fatty acid modifications that anchor proteins to membranes, thereby affecting nutrient transport and signal transduction [54].

ADAPTATION MECHANISMS OF MTB TO DRUG STRESS

Phenotypic adaptation and persistence

Phenotypic adaptation enables MTB to survive extended exposure to host immune responses and antimicrobial agents by adopting altered physiological states [55]. These changes result from reversible phenotypic shifts rather than permanent genetic mutations, forming subpopulations with varying stress tolerance levels. MTB adapts to drugs through phenotypic tolerance and genetic resistance. Tolerant bacterial populations serve as evolutionary reservoirs, enabling subpopulations to accumulate mutations under drug pressure. This facilitates the transition from reversible phenotypic tolerance to heritable genetic resistance, explaining why incomplete treatment regimens promote the emergence of multidrug-resistant-TB (MDR)-TB. Phenotypic tolerance is reversible and non-genetic, involving strategies such as metabolic slowdown, efflux pumps, cell wall thickening, biofilm formation, and stress responses, which help the bacteria survive during treatment. In contrast, genetic resistance is irreversible and caused by mutations or gene transfer, leading to modifications like target alteration, drug inactivation, and changes in permeability [47].

Genetic drug resistance (irreversible, mutation-driven)

Genetic drug resistance results from permanent changes in bacterial DNA, either through chromosomal mutations or horizontal gene transfer, which gives bacteria a survival advantage under antibiotic pressure [56].

Key mechanisms include

- Target modification: Alteration of drug-binding sites prevents effective antibiotic action.
- Drug inactivation: Enzymatic breakdown or modification of the antibiotic.
- Cell wall permeability changes: Reduced drug entry into the bacterial cell.

This form of resistance leads to MDR-TB, where MTB becomes resistant to at least rifampicin and isoniazid, the two most potent first-line anti-TB drugs [57]. Together, these mechanisms contribute to MDR-TB, which is characterized by resistance to rifampicin and isoniazid. MTB adapts to prolonged antibiotic exposure through reversible phenotypic drug tolerance and irreversible genetic resistance. Phenotypically tolerant subpopulations survive drug pressure by metabolic slowdown, efflux pump activation, and cell wall remodeling, thereby acting as an evolutionary reservoir for resistance-conferring mutations. Continued antibiotic exposure facilitates the transition from reversible phenotypic tolerance to irreversible, mutation-driven genetic resistance, leading to MDR-TB (Fig. 4).

NRP definition

A reversible state marked by metabolic downregulation with little to no bacterial proliferation arises in response to stimuli such as hypoxia within granulomas, nutrient limitation, acidic pH, and reactive

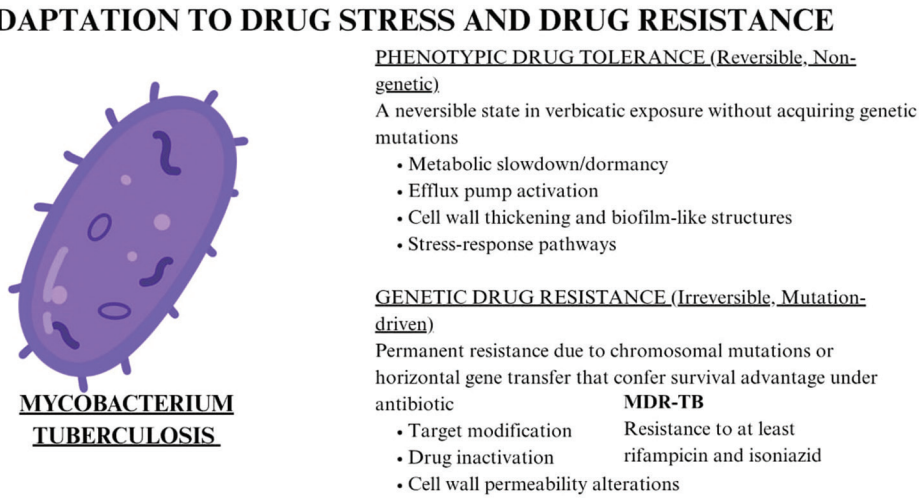

Fig. 4: Evolutionary transition from phenotypic drug tolerance to mutation-driven genetic drug resistance in *Mycobacterium tuberculosis*

oxygen or nitrogen species. This condition is characterized by reduced transcription and translation, suppression of growth-related genes, and increased expression of stress-response regulons like DosR/DosS. Importantly, NRP bacilli display tolerance to many first-line TB drugs that act on actively dividing cells [58-63].

Morphological and cellular envelope modifications, colony morphology

Stress can alter the surface structure and texture of colonies on solid media, reflecting changes in the cell wall. Under such conditions, bacterial cells may show size variation, appearing either smaller or elongated. In addition, the cell wall often thickens through the addition of extra lipid layers, like mycolic acids, which reduce permeability to antimicrobial agents and host immune defences [45].

Biofilm development and aggregation

Biofilms are structured microbial communities embedded within an extracellular matrix that enhance resistance to antibiotics and oxidative stress. Within granulomas, bacteria often form dense aggregates, creating protective clusters that shield inner bacilli from immune attack and limit drug penetration [54].

Respiratory adaptations

During hypoxia or nitric oxide stress, MTB shifts to alternative respiration through the induction of cytochrome bd oxidase, enabling continued adenosine triphosphate (ATP) production when conventional respiration is compromised. At the same time, energy conservation strategies such as reducing the proton motive force and slowing overall metabolism prolong survival under host-induced stress conditions [64]. These adaptive responses of Mycobacterium tuberculosis to host-induced stresses and their clinical consequences are summarized as follows. NRP induced by hypoxia, nutrient limitation, and acidic conditions contributes to drug tolerance and long-term survival during latent infection. Morphological changes and cell wall thickening reduce immune recognition and drug permeability, complicating treatment efficacy. Biofilm formation under prolonged nutrient deprivation provides collective protection to bacterial communities, further enhancing tolerance to antimicrobials. Respiratory shifts under hypoxia and nitric oxide stress maintain ATP production in low-oxygen environments, supporting bacterial survival within granulomas and underscoring the need for therapies targeting these adaptive states (Table 4).

METABOLIC REPROGRAMMING

Metabolic reprogramming of MTB is a key survival tactic that allows the pathogen to withstand nutritional scarcity, hypoxia, acidic pH, oxidative damage, and drug exposure. By altering its metabolic pathways, MTB boosts energy production, conserves resources, and maintains redox balance during prolonged stress conditions.

Alteration in carbon metabolism activation of the glyoxylate shunt

Catalyzed by isocitrate lyase and malate synthase, this process facilitates the use of fatty acids and cholesterol as carbon sources. It bypasses CO_2-producing stages of the TCA cycle to conserve carbon. The Methyl citrate cycle metabolizes propionyl-CoA derived from cholesterol and odd-chain fatty acids, preventing the buildup of harmful intermediates. As a result, it promotes prolonged survival in lipid-rich environments, such as those found within granulomas [69].

Alternative respiratory pathways: Cytochrome bd oxidase

MTB sustains respiration under hypoxic or nitric oxide stress through a pathway that, although less energy efficient, confers strong resistance to oxidative damage. Under nutrient-limited conditions, the bacterium suppresses energy-intensive processes and increasingly relies on alternative anaerobic electron acceptors to maintain ATP production when oxygen is scarce [70].

Maintenance of redox balance in antioxidant systems

Enhanced expression of antioxidant enzymes such as SOD, catalase-peroxidase (KatG), and AhpC helps neutralize reactive oxygen and nitrogen species. Low-molecular-weight thiols, including mycothiol and ergothioneine, further protect the cell by mitigating oxidative and nitrosative stress. In addition, modulation of the Nicotinamide adenine dinucleotide (reduced/oxidized forms) ratio supports metabolic flexibility, allowing the bacterium to maintain cofactor balance and redox homeostasis under adverse conditions [71].

ENERGY STORAGE AND UTILISATION

During non-replicative persistence, triacylglycerol (TAG) accumulates in cytoplasmic lipid inclusions, serving as an energy reservoir that supports eventual reactivation. At the same time, the bacterium conserves ATP by downregulating energy-intensive processes, thereby enhancing long-term survival under stress conditions [72]. The major diagnostic challenges associated with identifying adaptive and phenotypically drug-tolerant states of MTB highlight the gap between molecular understanding and routine clinical detection.

Metabolic shift in carbon utilization pathways of MTB

MTB undergoes extensive metabolic reprogramming to sustain survival under nutrient-limited and hypoxic intracellular conditions. Activation of the glyoxylate shunt, mediated by isocitrate lyase and malate synthase, enables efficient utilization of fatty acids and cholesterol while conserving carbon by bypassing CO_2-generating steps of the tricarboxylic acid cycle. Simultaneously, the methylcitrate cycle detoxifies propionyl-CoA derived from cholesterol and odd-chain fatty acids, preventing accumulation of toxic intermediates. In addition, alternative respiratory pathways such as cytochrome bd oxidase support energy generation under hypoxia and nitric oxide stress, while antioxidant systems, including KatG, AhpC, and SOD, maintain redox balance. TAG accumulation further provides an energy reserve during dormancy and non-replicative persistence (Fig. 5). Adaptive mechanisms employed by MTB to survive hostile host environments. Activation of the glyoxylate shunt and methylcitrate cycle enables efficient lipid utilization and detoxification of propionyl-CoA during intracellular growth. Alternative respiratory pathways such as cytochrome bd oxidase support energy generation under hypoxia and nitric oxide stress. Antioxidant enzymes, including KatG, AhpC, and SOD, protect against reactive oxygen and nitrogen species, while thiol redox buffers, such as mycothiol and ergothioneine, maintain intracellular redox balance. Additionally, TAG storage provides an energy reservoir that supports bacterial persistence during dormancy and nutrient limitation.

DIAGNOSTIC CHALLENGES IN DETECTING ADAPTIVE STATES

Despite advances in molecular diagnostics, current tools primarily detect genetic resistance and often fail to identify phenotypically drug-

Table 4: Clinical implications of adaptive survival mechanisms and emerging anti-tuberculosis treatment strategies

Adaptation type	Trigger (s)	Benefit to *Mycobacterium tuberculosis*	References
Non-replicating persistence	Hypoxia, nutrient, and pH stress	Drug tolerance; survival during latency	[65]
Morphological changes	General stress	Reduced immune detection; altered permeability	[66]
Cell wall thickening	Acidic and oxidative stress	Barrier to drugs and host effectors	[67]
Biofilm formation	Long-term nutrient limitation	Collective protection in the extracellular matrix	[68]
Respiratory shifts	Hypoxia, NO stress	Maintain adenosine triphosphate synthesis under limited O_2.	[4]

tolerant and non-replicating populations of MTB. Rapid molecular assays such as GeneXpert focus on canonical resistance-conferring mutations but do not capture metabolic, transcriptional, or physiological adaptations associated with persistence. As a result, adaptive bacterial subpopulations may remain undetected during treatment, contributing to delayed clearance, relapse, and therapeutic failure. These diagnostic limitations highlight the need for biomarkers capable of identifying stress-adapted and tolerant MTB states, as summarized in (Table 5).

Global transcriptional reprogramming

Hypoxia response (DosR regulon): Activation of about 50 genes under low-oxygen conditions. These include genes related to nitrate respiration, lipid metabolism, and dormancy survival [4]. Genes linked to acid and nutrient stress: Increased expression of phosphate acquisition systems, ion transporters, and stress-related chaperones. A reduction in growth-related genes, such as ribosomal proteins and DNA replication enzymes, helps conserve resources. Response to Drug Exposure: Drug-induced stress triggers efflux pumps (for example, Gene encoding an efflux pump protein contributing to drug tolerance [Rv1258c]), genes involved in oxidative stress defense, and enzymes that remodel lipids [79].

Proteomic remodeing

Changes in protein levels: Shift toward enzymes involved in the glyoxylate cycle, methylcitrate pathway, and antioxidant processes. Stress-specific protein isoforms: PTMs create protein variants that are more adaptable under stress conditions. Phosphorylated metabolic enzymes change flow patterns. Lower ribosomal protein levels correspond with decreased metabolic activity during persistence [80].

INTEGRATION OF TRANSCRIPTOMIC AND PROTEOMIC DATA

Multi-omics studies show that not all changes in messenger RNA are visible at the protein level, emphasizing selective translation and regulation of protein stability. Regulatory coordination among transcriptional activators (DosR, PhoP, and WhiB) and PTMs that affect protein degradation ensures precise adaptation. Adaptation to pharmacological stress and drug resistance describes the ability of Mycobacterium tuberculosis to endure prolonged antibiotic exposure through phenotypic drug tolerance and genetic resistance mechanisms. MTB has developed the capacity to endure extended antibiotic exposure through phenotypic drug tolerance (reversible, non-genetic) and genetic resistance. Phenotypes facilitate the establishment of MDR and extensively drug-resistant (XDR) bacteria [81,82].

Phenotypic drug tolerance

Antibiotic tolerance is a temporary state in which bacteria survive drug exposure without acquiring resistance mutations. In MTB, this involves a shift to NRP with reduced metabolic activity, thereby limiting drug–target interactions. Tolerance is further supported by the upregulation of efflux pumps such as Efflux pump protein (MmpL7) and Rv1258c, which actively expel antibiotics, along with cell wall thickening and increased mycolic acid content that hinder drug penetration. In addition, the production of drug-modifying enzymes, including acetyltransferases, contributes to reduced drug efficacy. This adaptive state enables the pathogen to withstand treatment and provides a reservoir from which resistant variants may eventually emerge [83].

Stress responses during drug exposure

Exposure to drugs such as isoniazid (INH), a first-line anti-tuberculosis drug, and rifampicin triggers oxidative stress through the accumulation of reactive oxygen species triggers oxidative stress through the accumulation of ROS, which in turn induces the expression of antioxidant defenses, including KatG, AhpC, and enzymes responsible for monothiol biosynthesis. To adapt, MTB undergoes metabolic transitions, shifting toward more energy-efficient pathways, increasing reliance on fatty acids and lipids as carbon sources, and downregulating

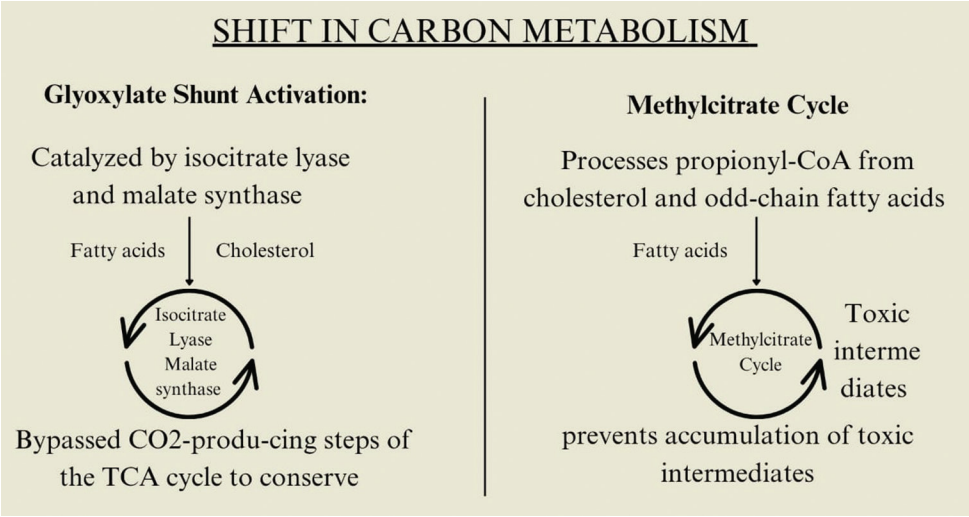

Fig. 5: Major metabolic adaptations supporting survival and persistence of *Mycobacterium tuberculosis* under nutrient limitation and hypoxic stress

Table 5: Diagnostic challenges in detecting adaptive and phenotypically drug-tolerant states in *Mycobacterium tuberculosis* (MTB)

Adaptation strategy	Key pathways/enzymes	Benefit to MTB	References
Glyoxylate shunt	Isocitrate lyase, malate synthase	Lipid utilization; carbon conservation	[73]
Methyl citrate cycle	Methyl citrate synthase	Detoxifies propionyl-CoA	[74]
Alternative respiration	Cytochrome bd oxidase	Energy generation under hypoxia/NO stress	[75]
Antioxidant systems	Catalase-peroxidase enzyme, alkyl hydroperoxide reductase, superoxide dismutase	Neutralize reactive oxygen species/reactive nitrogen species	[76]
Thiol redox buffers	Mycothiol, ergothioneine	Maintain redox homeostasis	[77]
TAG storage	Triacylglycerol synthase	Energy reserve in dormancy	[78]

translation and replication machinery. In parallel, a fraction of the bacterial population differentiates into persister cells, a dormant state in which antibiotic targets are inactive or absent, thereby promoting survival under prolonged drug pressure [84].

Genetic drug resistance mechanism: Persistent genetic changes that prevent drug binding or activate alternative pathways

Mutations in specific genes cause resistance to key TB drugs. Changes in katG disrupt the production of the catalase-peroxidase enzyme needed for isoniazid activation, leading to isoniazid resistance. Alterations in rpoB modify the β-subunit of RNAP, providing rifampicin resistance, while mutations in gene coding for arabinosyl transferase interfere with arabinosyl transferase activity, resulting in ethambutol resistance. These genetic changes are driven by selection pressures from incomplete or prolonged treatment, combined with bacterial DNA repair systems that allow mutation-prone groups to survive and adapt under difficult conditions [85].

Correlation between phenotypic tolerance and genetic resistance

Resilient, tolerant cells endure the early antibiotic assaults, serving as a reservoir for resistance mutations. This event elucidates the necessity of prolonged TB treatment regimens to completely eradicate the infection and the potential for relapse [86]. These adaptive responses enhance bacterial survival, facilitate persistence, and contribute to drug tolerance under stress conditions (Table 6).

Therapeutic implications and future directions understanding the adaptation processes of MTB provides a foundation for developing new techniques to shorten treatment duration, improve drug effectiveness, and prevent resistance development. Targeting these pathways could weaken the bacterium's ability to survive, making it more susceptible to the immune system and antimicrobial treatments [90].

TARGETING REGULATORY FRAMEWORKS: INHIBITION OF PHOPR MAY HINDER ACID STRESS ADAPTATION AND THE PRODUCTION OF VIRULENCE GENES

Disruption of WhiB family proteins compromises redox sensing, weakening the bacterium's ability to withstand oxidative stress. Similarly, inhibiting the serine/threonine protein kinases PknA and PknB interferes with cell wall biosynthesis and cell division, impairing survival under stress conditions [91].

Targeting enzymes of PTMs

Inhibiting Pup ligase may block proteasome-mediated protein breakdown, leading to the accumulation of harmful proteins under stress conditions. Inhibiting O-mannosyltransferases or key phosphorylation enzymes may interfere with immune evasion and metabolic balance [92].

Disrupting phenotypic persistence strategies involve pharmaceuticals that reactivate latent, non-replicating bacilli, rendering them susceptible to current antibiotics

Compounds that inhibit biofilm development or cell wall thickening may improve medication penetration [51].

Metabolic susceptibilities

Inhibiting isocitrate lyase (glyoxylate shunt) or enzymes in the methylcitrate pathway may obstruct lipid utilisation critical for prolonged survival. Focusing on antioxidant systems like mycothiol or ergothioneine pathways may enhance MTB's susceptibility to oxidative stress induced by the host and pharmaceuticals [93].

Host-directed therapies (HDTs)

Altering the pH, ion concentration, or metabolism of host macrophages can destabilize the favorable environment for Mycobacterium tuberculosis, while enhancing host autophagy or the formation of bactericidal reactive oxygen and nitrogen species further promotes bacterial clearance [11].

FUTURE RESEARCH IMPERATIVES

Integration of multi-omics (genomics, transcriptomics, proteomics, metabolomics) to thoroughly map adaptation processes. Single-cell investigations to elucidate heterogeneity in MTB populations throughout infection and therapy. Pharmaceutical combination approaches that concurrently address both active and latent bacterial subpopulations. Molecular targets involved in MTB stress adaptation and persistence that can be exploited for therapeutic intervention. Regulatory systems such as PhoPR, WhiB, and PknA/PknB control environmental sensing and adaptive responses, making them attractive drug targets. Enzymes involved in PTMs, including Pup ligase and kinases, regulate protein turnover and immune evasion. Persistence mechanisms such as biofilm formation and dormancy contribute to drug tolerance, and their disruption can expose hidden bacterial subpopulations. Targeting metabolic adaptations, such as the glyoxylate shunt and the methylcitrate cycle, can starve bacteria of essential nutrients, while inhibiting antioxidant defenses increases susceptibility to oxidative stress. HDTs further enhance treatment outcomes by modulating host pathways, such as autophagy and intracellular pH, to create an unfavorable environment for bacterial survival (Table 7).

Table 6: Future perspectives and research gaps in targeting adaptive survival mechanisms of *Mycobacterium tuberculosis* (MTB)

Adaptation type	Example mechanisms	Benefit to MTB	References
Phenotypic tolerance	Dormancy, efflux pumps, and cell wall thickening	Survival during drug exposure	[87]
Oxidative stress response	Catalase-Peroxidase enzyme (KatG), alkyl hydroperoxide reductase, mycothiol production	Detoxify reactive oxygen species generated by drugs	[88]
Metabolic shift	Lipid utilization, slowdown of replication	Energy conservation under stress	[11]
Genetic Resistance	katG, rpoB, gene coding for arabinosyl transferase mutations	Permanent insensitivity to the drug	[89]

Table 7: Potential therapeutic targets in *Mycobacterium tuberculosis* (MTB) adaptation pathways

Target type	Example targets	Rationale	References
Regulatory systems	PhoPR, WhiB, Serine/threonine protein kinases A and B	Block stress sensing/adaptation	[94]
PTM enzymes	Pup ligase, kinases, glycosyltransferases	Disrupt protein regulation & immune evasion	[46]
Persistence mechanisms	Biofilm disruptors, dormancy breakers	Expose hidden bacterial subpopulations	[95]
Metabolic adaptations	Isocitrate lyase, methylcitrate enzymes	Starve bacteria of key nutrients	[96]
Antioxidant defenses	Mycothiol, ergothioneine enzymes	Increase reactive oxygen species/reactive nitrogen species damage	[97]
Host- directed therapies	Autophagy inducers, pH modifiers	Alter the host environment to MTB's disadvantage	[8]

CLINICAL CONTEXT AND RECENT THERAPEUTIC ADVANCES TARGETING MTB ADAPTATION

Challenges in treating TB

TB, caused by MTB, remains a major global health challenge, aggravated by the emergence of MDR and XDR strains [90]. Recent clinical trials demonstrate variable success. The Nix-TB trial reported 89% treatment success for the bedaquiline–pretomanid–linezolid (BPaL) regimen in XDR-TB patients, but was limited by an 18-month follow-up and exclusion of extensively pre-treated cases. The ZeNix trial showed that 6-month BPaL was superior to longer regimens, yet 14% experienced significant linezolid toxicity. BPaL regimen faces significant challenges, including peripheral neuropathy. MDR-TB strains show resistance primarily to rifampicin and isoniazid, the cornerstone drugs of standard therapy [98]. XDR-TB further resists fluoroquinolones and at least one second-line injectable drug. These resistant phenotypes often arise from inadequate treatment adherence, incomplete regimens, or innate bacterial mechanisms of persistence [99].

Treatment of drug-sensitive TB necessitates prolonged multidrug regimens lasting 6 months or more, due to the presence of metabolically adaptable subpopulations of MTB, including dormant, non-replicating persisters, which exhibit phenotypic drug tolerance [100]. This prolongs therapy, increases toxicity risks, and facilitates resistance development. Therefore, targeting MTB's adaptive and persistence mechanisms are crucial to improve treatment outcomes and shorten therapy duration [101].

DIAGNOSTIC CHALLENGES IN DETECTING ADAPTIVE STATES

Current diagnostics (GeneXpert, LJ culture) detect genetic resistance but fail to identify phenotypically tolerant persisters and non-replicating MTB subpopulations [102]. PCR-based methods target canonical resistance mutations (rpoB, katG) but miss metabolic shifts and DosR regulon activation characteristic of persistence [103]. Novel approaches, including metabolic probes (Alamar Blue), transcriptomic biomarkers (whiB7, icl1), and flow cytometry-based viability staining, show promise but lack clinical validation and widespread availability. This diagnostic gap delays initiation of persistence-targeting regimens, allowing adaptive subpopulations to expand during standard therapy [104].

THERAPEUTIC STRATEGIES TARGETING MTB ADAPTATION MECHANISMS

Inhibition of regulatory kinases (Pkn A and Pknb)

PknA and PknB play vital roles in MTB adaptive responses, regulating cell wall biosynthesis, cell division, and metabolism through phosphorylation of key substrates [105].

- Drug targeting: Small-molecule inhibitors of PknA/PknB have been identified and are under preclinical evaluation. These inhibitors disrupt phosphorylation-mediated signaling pathways essential for MTB survival under stress, leading to impaired cell division and vulnerability to antibiotics. For example, several imidazopyridine derivatives have demonstrated efficacy in inhibiting PknB activity and MTB growth [106].
- Clinical relevance: Targeting kinases involved in adaptation may overcome phenotypic tolerance and enhance killing of both replicating and persistent MTB populations [107].

Inhibition of pupylation pathway

The pupylation system, a prokaryotic analogue of ubiquitination, tags damaged or regulatory proteins for degradation via the proteasome, enabling MTB to survive host-induced stress [108]

- Drug targeting: Pup ligase inhibitors interfere with tagging of proteins for degradation, resulting in accumulation of damaged proteins and impaired stress responses. Compounds targeting this pathway have shown bactericidal activity in non-replicating MTB models [47].
- Potential outcome: Inhibitors of pupylation could sensitize MTB to oxidative stress and antibiotic pressure, reducing persistence and resistance development [109].

HDTs

Given MTB's intracellular lifestyle and adaptability, HDTs aim to modulate host immune responses to enhance bacterial clearance and reduce inflammation-associated pathology [110];

- Enhancing autophagy: Agents like rapamycin and metformin induce autophagy pathways in macrophages, promoting the degradation of intracellular MTB. HDTs can shift macrophage metabolism to less hospitable states for MTB [111].
- Modulating host redox environment: Drugs that modulate reactive oxygen and nitrogen species (ROS, reactive nitrogen species [RNS]) levels impact MTB survival, as oxidative and nitrosative stresses are key bacterial pressures [111].
- Adjusting phagosomal pH: Compounds altering phagosomal acidification may disrupt MTB's preferred vacuolar environment [112].
- Clinical trials: HDTs are being evaluated in combination with standard antimicrobials to shorten therapy and improve treatment success [113].

Novel drug candidates targeting dormant and persistent mtb

MTB persistence in a non-replicative state contributes significantly to treatment failure and relapse. New drugs targeting metabolic and respiratory adaptations in dormant MTB have been approved or are under trial [114]:

- Bedaquiline: A diarylquinoline that inhibits ATP synthase, disrupting energy generation, especially effective against both active and dormant MTB [115].
- Pretomanid: A nitroimidazo-oxazine that generates RNS under hypoxic conditions, targeting dormant bacilli, approved as part of combination regimens for MDR and XDR-TB [116].
- Delamanid: Another nitroimidazole with similar activity against non-replicating MTB [117].
- Other investigational agents: Compounds targeting the glyoxylate shunt (isocitrate lyase inhibitors), cytochrome bd oxidase (alternative respiration), and lipid metabolism pathways aim to overcome MTB's metabolic plasticity [118].

IN SILICO APPROACHES IN ANTI-TB DRUG DISCOVERY

In silico approaches have become powerful tools in accelerating anti-TB drug discovery by enabling rapid screening and prioritization of potential inhibitors. Virtual screening and molecular docking studies have successfully identified natural products targeting the InhA and EthR proteins of MTB, demonstrating strong binding affinities and inhibitory potential against these key enzymes involved in mycolic acid biosynthesis and the ethionamide activation pathway [119,120]. Similarly, molecular docking and molecular dynamics simulations have been applied to screen FDA-approved drugs against enoyl-acyl carrier protein reductase (InhA), revealing stable ligand–protein interactions and promising inhibitory candidates [121]. These studies highlight the value of computational approaches in reducing experimental burden and guiding rational lead identification for anti-TB drug development.

Clinical evidence from recent TB trials

In this context, recent clinical trials further highlight both progress and unresolved challenges in the management of drug-resistant TB. The Nix-TB trial demonstrated high treatment success using the BPaL regimen in XDR TB; however, limited patient heterogeneity and short follow-up periods constrain the generalizability of these findings. The subsequent ZeNix trial evaluated modified linezolid dosing to improve safety, revealing that although efficacy was largely preserved, linezolid-associated toxicities, particularly peripheral neuropathy and myelosuppression, remained significant concerns. These outcomes emphasize that although current regimens improve cure rates, they do not adequately address phenotypically tolerant and persistent MTB populations, underscoring the need for safer, more targeted therapeutic strategies.

INTEGRATING NEW THERAPIES INTO CLINICAL PRACTICE

- Treatment duration: Novel agents with activity against persisters and resistant strains have enabled shorter regimens in recent WHO

guidelines, e.g., the 6-month BPaL regimen for MDR/XDR-TB [122].
- Combination approaches: Regimens combining conventional antibiotics with host-directed and metabolic inhibitors hold promise for overcoming adaptation-driven persistence [123].
- Challenges: Emergence of resistance against new drugs, toxicity profiles, and variable host immune status remain obstacles needing continued research [124].

RECENT AND ONGOING CLINICAL TRIALS

1. Nix-TB trial: Evaluated BPaL regimen showing high efficacy and treatment shortening in XDR-TB patients [125].
2. Pan-TB trials: Investigate bedaquiline and pretomanid combinations in drug-sensitive TB, aiming to shorten therapy [126].
3. HDT trials: Studies assessing metformin, statins, and immune modulators as adjunct TB therapies to enhance host clearance [127].

CASE STUDIES AND EXAMPLES OF RESISTANCE EMERGENCE IN MTB

Clinical isolates and genetic mutations conferring drug resistance

- katG mutations and isoniazid resistance: The *katG* gene encodes catalase-peroxidase required for activating isoniazid (INH), a frontline TB drug. Mutations, especially the S315T substitution, are commonly found in INH-resistant clinical isolates worldwide. These mutations impair catalase-peroxidase activity, preventing conversion of INH into its active form and thereby conferring resistance [128].
- rpoB mutations and rifampicin resistance: Rifampicin acts by targeting the β-subunit of RNAP, encoded by *rpoB*. Mutations in the rifampicin resistance-determining region of *rpoB*, such as S531L or H526Y, reduce drug binding affinity. These mutations are prevalent in rifampicin-resistant MTB strains, which often constitute a major component of MDR-TB [129].

Persistence and relapse due to phenotypic heterogeneity

- Persister cell populations: MTB exhibits phenotypic heterogeneity, where subpopulations enter a non-replicating, dormant state (persisters) that survive antibiotic treatment without genetic resistance. These persisters evade drug killing due to slowed metabolism and altered target availability. Clinical relapse has been linked to survival of such persistent populations even after extended therapy [51].
- Case example: Studies in high TB burden regions have demonstrated that treatment failure and relapse often involve isolates lacking classic resistance mutations but manifesting drug tolerance attributed to persister phenotypes. Advanced molecular techniques reveal these persisters' ability to survive in granulomatous lesions and resuscitate under favorable conditions [130].

Epidemiological tracking of MDR and XDR strains

- TB can present with severe and fatal outcomes, particularly in immunocompromised individuals. Reported a fatal case of disseminated TB in a 24-year-old male patient with Crohn's disease, emphasizing the increased risk of widespread mycobacterial infection in patients receiving immunosuppressive therapy. This case highlights the diagnostic challenges, rapid disease progression, and the critical importance of early detection and timely antitubercular intervention in high-risk populations [131].
- Spread of MDR/XDR-TB: Molecular epidemiology shows the clonal expansion of MDR and XDR MTB strains, often associated with distinct lineages such as the Beijing genotype in East Asia, linking specific resistance-conferring mutations with regional outbreaks [132].
- Global trends: WHO reports indicate that MDR-TB accounts for approximately 5% of new and 18% of previously treated TB cases globally, with XDR-TB cases raising concern due to limited treatment options. Surveillance data from multiple countries reveal the geographic spread correlating with socio-economic factors and healthcare infrastructure gaps [133]. In this context, understanding the interplay between HIV and TB is critical. This cross-sectional study at Wangaya Hospital in Denpasar, Bali, Indonesia, examined the association of WHO clinical stages and various risk factors with the occurrence of pulmonary TB among people living with HIV/AIDS. It found that advanced HIV clinical stages and specific risk factors significantly increase the likelihood of developing pulmonary TB. Early identification and management of these factors are essential to reduce TB incidence among HIV-positive patients [134].

Molecular mechanisms linked to clinical phenotypes

- Efflux pump upregulation and treatment failure: Overexpression of efflux pumps like Rv1258c and MmpL7 in MTB reduces intracellular drug concentrations, contributing to low-level drug resistance and treatment failure. Clinical isolates with elevated efflux activity demonstrate decreased susceptibility to INH, rifampicin, and fluoroquinolones, highlighting efflux as a key non-mutational resistance mechanism [135].
- Cell wall thickening and drug penetration: MTB adapts to host stresses by modifying its cell envelope, increasing the thickness and hydrophobicity via enhanced mycolic acid production. Clinical isolates from patients failing therapy often exhibit these altered cell wall phenotypes, which reduce permeability to antibiotics and immune effectors, contributing to persistence and drug tolerance.

CONCLUSION AND PERSPECTIVES

MTB possesses a unique ability to modify itself down to the cellular and molecular level to survive and remain dormant in the most antagonistic environments, and in this case, the host. MTB adjusts to a variety of challenging alterations, including but not limited to a reduced pH, oxidative and nitrosative damage, and a lack of nutrients. MTB then alters its metabolism, cellular architecture, and genetic regulation. Adaptability is regulated by a complex system of PhoPR and DosR, PTMs, non-dividing persistence, and, most importantly, adaptations to metabolism to survive for extended periods of time. These processes, in combination, defeat the challenges presented by a host and cause the MTB to enter a dormant state far less susceptible to numerous drugs. Final outcomes of these adaptations include difficult-to-treat and drug-resistant infections. These difficult-to-treat infections are a front row to the meridian of genetic modification and drug resistance. Knowledge of what has been presented here has a direct impact on how and what drug-resistant MTB infections will be treated.

Future strategies for TB control should move beyond the exclusive use of conventional antimicrobials and adopt an integrated approach that also targets the adaptive mechanisms of MTB. Combining these therapies with host-directed interventions that fine-tune the immune response may significantly enhance treatment outcomes. Such a comprehensive framework has the potential to shorten therapy duration, counteract drug resistance, and substantially reduce the worldwide impact of TB. In conclusion, a deeper understanding of the post-adaptive biology of MTB is essential for the development of more precise, effective, and long-lasting therapeutic strategies, ultimately advancing global efforts toward TB elimination.

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AUTHORS' CONTRIBUTIONS

Prasanthi Tulasi handled conceptualization and drafted the manuscript. Shobha Singarapalle managed data curation and validation. Manal NK Hamem focused on visualization and methodology. Murali Krishna Kumar Muthyala oversaw supervision, edited the manuscript, and provided final approval. All authors reviewed and approved the final version.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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