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Original Research Article

Tuberculosis Therapeutics and Drug Resistance: Mechanisms, Challenges, and Emerging Solutions

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Abstract:
Tuberculosis remains a leading cause of infectious disease mortality worldwide. The effectiveness of tuberculosis control programs is increasingly undermined by the emergence of multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*. A clear understanding of anti-tuberculosis drugs, their molecular targets, and resistance mechanisms is essential for guiding treatment strategies and drug development. This review summarizes current tuberculosis treatment regimens and provides a comprehensive overview of first-line, second-line, and newer anti-tuberculosis drugs, with emphasis on their mechanisms of action and genetic determinants of resistance. Relevant peer-reviewed literature, World Health Organization reports, and experimental studies were reviewed to synthesize current knowledge on tuberculosis therapeutics and resistance mechanisms. First-line drugs primarily target cell wall synthesis, transcription, and protein synthesis, while second-line and newer agents expand activity to energy metabolism and dormant bacilli. Drug resistance arises through target gene mutations, enzymatic drug modification, altered drug activation, efflux mechanisms, and intrinsic cell wall barriers. Resistance to newer drugs such as bedaquiline and delamanid is increasingly reported, often involving alternative genetic pathways beyond classical targets. Sustained effectiveness of tuberculosis treatment requires integration of molecular diagnostics, rational drug use, and continued surveillance of resistance patterns. Advances in newer therapeutics offer promise, but careful stewardship is essential to prevent rapid resistance emergence.
Keywords: Drug Resistance, Mechanisms of Actions, Mycobacterium tuberculosis, Newer Drugs, Tuberculosis Therapeutics

Introduction

Tuberculosis continues to pose a major global health burden despite the availability of effective chemotherapy [1]. The rise of multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis strains threatens progress toward global elimination targets [2]. Anti-tuberculosis drugs act on diverse bacterial pathways, including cell wall biosynthesis, transcription, translation, and energy metabolism [3]. However, the adaptive capacity of MTB has led to widespread resistance, necessitating prolonged and complex treatment regimens. This review examines tuberculosis therapeutics and the molecular basis of

resistance, with focus on clinically relevant drug classes and emerging agents.

Tuberculosis Therapeutics: Actions and Drug Mechanisms

Treatment Regimens for Tuberculosis

Drug-Sensitive Tuberculosis:

Standard treatment for drug-sensitive TB consists of an intensive phase lasting eight weeks, during which rifampicin, isoniazid, ethambutol, and pyrazinamide are administered daily based on body weight. This is followed by a continuation phase of sixteen weeks using rifampicin, isoniazid, and ethambutol. In patients with previous TB treatment, the intensive phase is extended to twelve weeks and includes streptomycin for the first eight weeks, followed by a twenty-week continuation phase with isoniazid, rifampicin, and ethambutol [4, 5].

Multidrug-Resistant and Rifampicin-Resistant Tuberculosis:

Treatment of MDR or rifampicin-resistant TB involves a prolonged and complex regimen. The intensive phase lasts six to nine months and typically includes ethionamide, isoniazid, kanamycin, pyrazinamide, ethambutol, levofloxacin, and cycloserine. This is followed by an eighteen-month continuation phase under strict supervision, comprising ethionamide, cycloserine, isoniazid, levofloxacin, and ethambutol [5, 6]. In 2019, the World Health Organisation approved a fully oral nine-month treatment course that includes bedaquiline for managing MDR/RR-TB in patients whose disease remains susceptible to fluoroquinolones [7].

Extensively Drug-Resistant Tuberculosis:

XDR-TB treatment requires individualized regimens with second-line and newer drugs. The intensive phase spans six to twelve months and includes para-aminosalicylic acid, moxifloxacin, capreomycin, high-dose isoniazid, co-amoxiclav, linezolid, and clofazimine. The continuation phase extends for eighteen months, maintaining all drugs except injectable agents [5, 8].

Anti-Tuberculosis Drugs

First-Line Drugs

Isoniazid:

Isoniazid, introduced in 1952, exhibits bactericidal and bacteriostatic activity against rapidly and slowly growing MTB. It penetrates the mycobacterial cell membrane and targets the katG and inhA genes. Activation by the catalase-peroxidase enzyme encoded by katG produces reactive intermediates that inhibit mycolic acid synthesis through inhA-encoded enoyl-ACP reductase [9, 10]. High-level resistance is commonly associated with katG mutations, particularly S315T, while promoter mutations upstream of inhA confer low-level resistance [11].

Rifampicin:

Rifampicin, derived from Streptomyces mediterranei, inhibits DNA-dependent RNA polymerase by binding to the beta subunit encoded by rpoB. Resistance is primarily caused by mutations within the rifampicin resistance-determining region, although rare mutations outside this region have also been reported [11, 12].

Ethambutol:

Ethambutol inhibits arabinosyl transferases encoded by the embCAB operon, disrupting arabinogalactan and lipoarabinomannan synthesis in the cell wall. Resistance has been linked to mutations in embB, particularly at codons 306, 406, and 497 [13].

Pyrazinamide:

Pyrazinamide is active under acidic and hypoxic conditions. It is converted to pyrazinoic acid by the enzyme encoded by pncA. The drug disrupts membrane energetics and interferes with protein synthesis and energy metabolism through targets including rpsA, panD, and clpC1 [14]. Resistance is most frequently associated with diverse mutations in pncA.

Streptomycin:

Streptomycin, the first effective anti-TB antibiotic, inhibits protein synthesis by binding to the 30S ribosomal subunit. Resistance arises from mutations in rpsL and rrs, affecting ribosomal protein S12 and 16S rRNA, respectively [15, 16].

Second-Line Drugs

Para-Aminosalicylic Acid:

Para-aminosalicylic acid interferes with folate metabolism by inhibiting dihydropteroate synthase and dihydrofolate synthase, while also impairing mycobactin-mediated iron uptake [17].

Ethionamide:

Ethionamide is a prodrug activated by EthA monooxygenase, regulated by EthR. It inhibits mycolic acid synthesis through formation of an NAD adduct that inactivates InhA [18].

Cycloserine:

Cycloserine disrupts cell wall synthesis by inhibiting alanine racemase, an enzyme essential for D-alanine production and peptidoglycan assembly [19].

Fluoroquinolones:

Fluoroquinolones inhibit DNA gyrase by targeting gyrA and gyrB. Resistance is associated with mutations at specific codons within these genes, particularly A90 and D94 in gyrA [20].

Aminoglycosides and Polypeptides:

Aminoglycosides and polypeptides inhibit protein synthesis by binding to ribosomal RNA. Resistance mechanisms include rRNA mutations and enzymatic drug modification [21].

Linezolid:

Linezolid binds to the 23S rRNA of the 50S ribosomal subunit, preventing initiation of protein synthesis. Resistance is linked to mutations in rplC and rrl [22].

Newer Anti-Tuberculosis Drugs

Bedaquiline:

Bedaquiline inhibits the ATP synthase proton pump, leading to energy depletion in active and dormant MTB. Resistance is sometimes associated with mutations in atpE, although alternative mechanisms have been reported [23, 24].

Delamanid:

Delamanid is activated by deazaflavin-dependent nitroreductase encoded by Rv3547. It inhibits synthesis of methoxy and keto mycolic acids, essential components of the cell wall [25].

PA-824:

PA-824 disrupts mycolic acid synthesis and energy metabolism through mechanisms that differ between replicating and non-replicating bacilli. Resistance is linked to deficiencies in F420 cofactor pathways [26].

SQ-109:

SQ-109 targets the MmpL3 transporter, blocking trehalose monomycolate transport and mycolic acid assembly [27].

Mechanism of Drug-Resistant Mycobacterium tuberculosis

Species belonging to Mycobacterium genus are known for intrinsic resistance due to their atypical lipid-laden cellular wall thickness. Antibiotics may be altered structurally or enzymatically cleaved within the cell membrane, contributing to drug ineffectiveness. Efflux systems in Mycobacterium tuberculosis remain a subject of controversy, potentially playing a role in high-level drug resistance under specific conditions [28].

Innate Drug Resistance in MTB:

The inherent resistance correlates with the unique makeup and arrangement of the mycobacterial cell wall barrier, influencing drug penetration. The thick and hydrophobic cell wall hinders diffusion of non-water-soluble molecules, such as certain antibiotics like macrolides, rifamycins, fluoroquinolones, and

tetracyclines. Studies with lipid synthesis-defective mutants demonstrate susceptibility to drugs the wild-type strain resists [29].

Inactivation of Drugs in MTB:

Upon entering the cellular wall, antibiotics may undergo enzymatic cleavage, such as the hydrolysis by β-lactamases on β-lactam containing drugs. Mycobacterium tuberculosis possesses a broad-spectrum β-lactamase, BlaC, which irreversibly inhibits clavulanate. Interest in using β-lactam drugs against MDR/XDR strains has resurged, showing promising outcomes in various regimens [30].

Besides cleavage, antibiotics can be modified, like methylation or acetylation. Eis protein acetylates and inactivates aminoglycoside antibiotics in Mycobacterium tuberculosis [31].

Enzymatic Drug Target Modification:

Mycobacterium tuberculosis employs mechanisms conserved in bacteria producing antibiotics. Erm methyltransferase monomethylates residues between 2057 and 2059 of the Ribosomal RNA 23S, imparting resistance to different macrolide antibiotics [32].

Mechanism due Drug Efflux of Drugs in MTB:

Efflux mechanisms, crucial in bacterial physiology, are encoded by various genes in Mycobacterium tuberculosis, with controversial roles in clinically significant drug resistance. Efflux pumps can expel a range of structurally unrelated compounds, including anti-tuberculosis drugs [33].

Drug Resistance Mechanism against Newer Drugs

Bedaquiline:

The predominant mutation in mutants showing resistance to bedaquiline involves the A63P alteration in gene coding for the atpE, with the I66M mutation also identified. I66M introduces modifications that disrupt the effective bedaquiline's attachment towards its target site [34]. However, a report examining resistance mechanisms of bedaquiline drug in MTB revealed Out of the 8 resistant mutants, only 4 showed alterations in gene atpE, while the remaining 230 isolates did not have genetic variations in either atpE, suggesting the existence of alternative resistance mechanisms [35].

Delamanid:

Delamanid's activity depends on reductive activation by MTB. In Mycobacteria rendered delamanid-resistant through experimental induction, researchers found a genetic mutation within the Rv3547 gene, indicating its participation in the drug activation process [36].

PA-824:

Resistance to PA-824 is mainly linked to the absence of a particular G6PD (FGD1) or the F420 dezaflavin cofactor. Furthermore, a protein specific to nitroimidazo-oxazine recently discovered introduces slight structural modifications in the drug [37].

Factors Influencing the Emergence of Drug-Resistant Tuberculosis

The misuse and overuse of antimicrobials have accelerated drug resistance development, leading to several problems. In line with CDC assessments, one-third of outpatient antibacterial prescriptions are unnecessary, contributing to resistance and unnecessary expenses. Patients' failure to complete antimicrobial courses as prescribed and incorrect drug usage in developing countries further exacerbate the issue. Inappropriate monotherapies, disregarding WHO guidelines, hinder effective treatments. Moreover, the consumption of falsified or counterfeit medication with no active drug component, wrong drugs, or incorrect doses also promotes resistance [38]. Addressing these problems is crucial to combat drug resistance, ensure effective treatments, and protect public health.

Conclusion

Understanding the mechanisms of action of anti-tuberculosis drugs and the molecular basis of resistance is central to effective TB control. While newer drugs offer hope for MDR and

XDR TB, resistance can emerge rapidly without proper stewardship. Integrating molecular diagnostics, optimized treatment regimens, and strong public health interventions remains critical for achieving sustainable TB elimination.

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