Literature Review

Immunology of Drug-Resistant Tuberculosis (DR-TB): A Literature Review

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Abstract

Drug-resistant tuberculosis (DR-TB) poses significant challenges to control efforts due to its complex pathogenesis and limited treatment options. DR-TB arises through primary infection with resistant strains or secondary resistance during the course of treatment. Secondary resistance is divided into intrinsic and acquired. In intrinsic resistance, infection is caused by TB germs that have evolved, causing resistance through several mechanisms, namely reducing cell membrane permeability, drug reflux, degradation and target modification, while acquired resistance is caused by chromosomal mutations in target genes during the treatment process. Resistance is driven by chromosomal mutations in key genes such as rpoB, katG, inhA, pncA, emb, gyrA/gyrB, rrs and others, leading to reduced drug susceptibility. This review summarizes immunological mechanisms relevant to resistance and current treatment approaches.

Keywords: drug-resistant, immunological mechanism, tuberculosis

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INTRODUCTION

Tuberculosis (TB) remains a major health concern. The World Health Organization (WHO) reported in 2023 that TB causes about twice as many deaths as Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS). With an estimated 1,060,000 cases, Indonesia is the second-largest source of TB cases worldwide after India.[1] In 2021, there were 7,876 detected cases of drug-resistant TB. Rifampicin-resistant TB/Multidrug-resistant TB (RR-TB/MDR-TB) notifications reached 12,531 cases in 2024.[2,3] The management of Drug-Resistant TB (DR-TB) presents more complex challenges. Several elements may contribute to an increased risk of drug resistance.

Resistance may be primary or secondary. Primary resistance arises from an infection with a drug-resistant strain, whereas secondary resistance develops during the course of treatment.[4] Drug updates as a therapeutic regimen have been widely carried out. In 2022, the WHO conducted a clinical trial of non-injectable Anti-Tuberculosis Drugs (ATD) with a treatment duration of 6 months and is currently used in the treatment of DR-TB. This effort aimed to shorten the treatment duration, thereby reducing cases of treatment failure.[5,6] To support better care, this review focuses on immunological mechanisms that contribute to resistance and treatment response in DR TB.

DRUG-RESISTANT TUBERCULOSIS (DR-TB)

Drug-Resistant TB complicates TB control and requires advanced diagnostics and treatment.[7] Resistance emerges when *Mycobacterium tuberculosis* acquires mutations that reduce susceptibility to rifampicin, isoniazid, fluoroquinolones, and Group A agents such as bedaquiline and linezolid.[8] Resistance occurs in new patients through transmission or in previously treated patients through reinfection or selection under therapy. In new cases, resistance is caused by infection with TB bacteria from patients with DR-TB (primary resistance).[4]

Conversely, in patients with a prior history of ATD, resistance may arise from direct infection by patients with DR-TB or as a result of the treatment process (secondary resistance).[4] Secondary resistance is often linked to nonadherence, malabsorption, inappropriate regimens or treatment delays. Irregular and repeated administration of ATD can also cause mutations in the chromosomes of TB bacteria, resulting in resistance.[5,6] Table 1 shows anti-tuberculosis drug groups used in DR-TB according to the WHO in 2018.[8]

Table 1. ATD classification in drug-resistant TB

Group	Drugs	Abbreviation
Group A	Levofloxacin / Moxifloxacin	Lfx/Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B	Clofazimine	Cfz
	Cycloserine or	Cs
	Terizidone	Trd
Group C	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or	Ipm-Cln
	Meropenem	Mpm
	Amikacin or	Amk
	Streptomycin	S
	Ethionamide or	Eto
	Prothionamide	Pto
	P-aminosalicylic acidi	PAS

The course of Drug-Susceptible TB (DS-TB) infection is similar to primary-resistant DR-TB, the difference being the type of bacterial strain that infects. Meanwhile, in DR-TB with secondary resistance, several intrinsic mechanisms or mutations cause differences in the immunological mechanisms and course of infection.[4,9]

Multidrug-resistant TB denotes resistance to both rifampicin and isoniazid, with or without other drugs. Pre-Extensively Drug-Resistant TB (Pre XDR TB) is MDR TB that is also resistant to one of the fluoroquinolone ATDs (levofloxacin or moxifloxacin). Meanwhile, XDR TB occurs if TB bacteria are also resistant to other group A ATDs (bedaquiline or linezolid).[8]

Drugs for TB management work effectively to eliminate bacteria in several ways, including increasing the metabolic process, reducing the thickness of the cell wall in TB bacteria and increasing the activity of transporter proteins. The cell wall of TB bacteria functions as a defence barrier. Some drugs can interfere with the synthesis of the cell wall so that it becomes thinner and making it easier for drugs to penetrate the bacteria. In addition, several classes of drugs are effective in increasing the activity of transporter proteins that help carry antibiotics into cells without reflux.[10]

TYPES OF DRUG-RESISTANT TUBERCULOSIS (DR-TB)

Monoresistance TB

Monoresistance of *Mycobacterium tuberculosis* refers to resistance to a single first-line anti-TB drug, such as isoniazid (INH) or rifampicin (RIF).[11] It is caused by specific mutations. For INH, mutations in the katG gene, particularly S315T and promoter mutations in inhA, are common. On the other hand, resistance to RIF is most commonly caused by mutations in the 81-bp region of rpoB. Resistance levels can vary depending on the type of mutation.[12,13]

The World Health Organization recommends tailored first-line regimens including rifampicin and companion drugs for INH resistance. Additionally, RR-TB is managed as MDR using standardized all-oral regimens. Early detection of RR prompts a switch to second-line regimens to prevent further resistance.[5] Recent WHO updates have expanded shorter all-oral treatment options for MDR/RR cases.[14]

Polyresistant TB

Resistance to more than one first-line anti-TB drug, excluding the combination of isoniazid and rifampicin at the same time, is defined as polyresistance.[11] It reflects the accumulation of multiple single-drug resistance mutations (e.g., katG + other targets).[15] Treatment must be individualized based on resistance patterns, as polyresistance can lead to ineffective standard regimens and potential progression to MDR if not managed properly.[11]

Multidrug-resistant TB (MDR-TB)

Multi-drug resistant TB is characterized by resistance to isoniazid and rifampicin, the two primary first-line medications.[11] MDR results from the co-occurrence of katG/inhA and rpoB mutations, or from sequential acquisition under inadequate therapy/transmission of MDR strains.[15] MDR-TB poses a significant global health challenge with a persistent high burden, leading to poorer outcomes compared to drug-susceptible TB and necessitating more complex, expensive and toxic treatment regimens.[16] Recent WHO guidelines advocate for all-oral regimens, prioritizing individualized treatments based on drug susceptibility tests to enhance tolerability and prevent further resistance development.[14]

Pre-extensively drug-resistant TB (pre-XDR)

Rifampicin-resistant TB/Multidrug-resistant TB with additional fluoroquinolone (FQ) resistance, referred to as pre-XDR, is characterized by specific mutations in gyrA and gyrB.[11,17] Pre-XDR cases typically experience worse outcomes than MDR without FQ resistance and necessitate the incorporation of novel agents like bedaquiline, linezolid and pretomanid, as per WHO recommendations for individualized treatment approaches.[5,18]

Extensively drug-resistant TB (XDR-TB)

Extensively drug-resistant TB is now defined as MDR-TB/RR-TB that is additionally resistant to any fluoroquinolone and at least one key Group A drug (bedaquiline or linezolid).[11] Resistance mechanisms include gyrA/gyrB mutations for fluoroquinolone resistance and variations in genes affecting bedaquiline and linezolid resistance.[19,20] Comprehensive diagnostics, including molecular assays and WGS, are required for detection.[5] XDR-TB poses significant treatment challenges, leading to lower cure rates and higher mortality.[21] Current strategies emphasize rapid patient identification, all-oral regimens, and ongoing updates to treatment protocols based on emerging evidence.[14]

PRIMARY DRUG-RESISTANT TUBERCULOSIS (DR-TB)

The immunological mechanism of DR-TB is similar to that of DS-TB. TB bacteria spread through droplets, inhaled into the respiratory tract to reach the alveoli, phagocytosed by alveolar macrophages and form granulomas to limit the spread. As long as the bacteria are in the granuloma, the host does not show symptoms (asymptomatic) and the TB bacteria can be eliminated or enter a latent phase.[22]

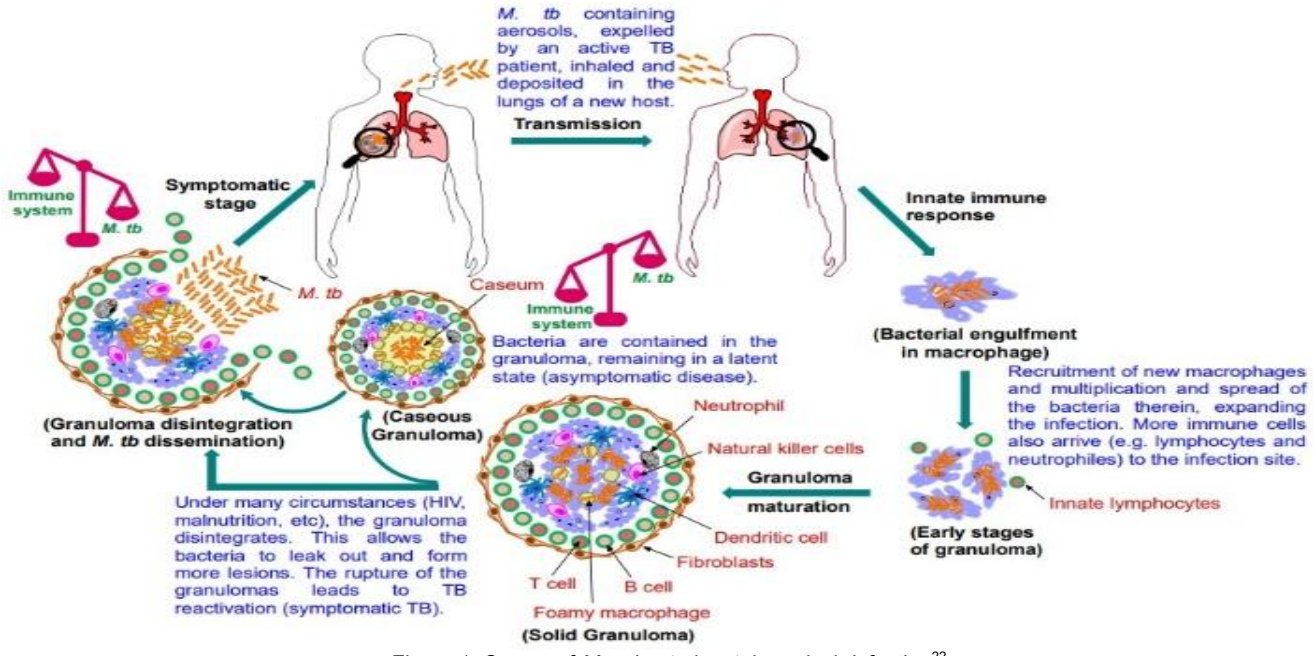

Figure 1. Course of *Mycobacterium tuberculosis* infection[22]

The body's ability to eliminate TB bacteria through innate and adaptive immune mechanisms greatly affects the course of the disease. The course of *Mycobacterium tuberculosis* infection is shown in Figure 1.[22] However, if macrophages fail to destroy acid-fast bacilli (AFB) bacteria, the infection cycle will continue.[22,23] Macrophages will release lipid content, leading to caseation and the decay of the granuloma. At that point, the TB bacteria will exit the granuloma, leading to dissemination in the lungs and respiratory system.[22,24]

The body's immune response to TB infection begins when the bacteria enter the respiratory tract. Respiratory epithelial cells detect bacteria via Pattern Recognition Receptors (PRRs), activate Antigen Presenting Cells (APCs), and trigger an immune response by altering the composition of the fluid lining the respiratory tract, thereby enhancing its antimicrobial function. In addition, PRR activation also causes the production of pro-inflammatory cytokines and activation of T cells in the mucosa that stimulate the production of Interferon (IFN)-γ and Tumor Necrosis Factor (TNF)-α.[25,26]

After passing through the respiratory tract and reaching the alveoli, the alveolar macrophages begin to phagocytose TB bacteria with the help of IFN-γ and TNF-α (Fig. 2).[27] *Mycobacterium tuberculosis* will remain in the phagosome. The phagosome will undergo maturation, acidification and increase the production of pro-inflammatory cytokines to eliminate TB bacteria from the host body. However, TB bacteria can fight innate immunity by inhibiting phagosome maturation, phagosome-lysosome fusion and the production of pro-inflammatory cytokines.[28]

Innate immunity by alveolar macrophages begins within the first 12 hours after *Mycobacterium tuberculosis* enters the alveoli. If bacilli survive, they replicate, lyse macrophages and spread to epithelium and endothelium, then disseminate hematogenously and via lymphatics to lung apices and other vascular organs.[29]

Other innate immune cells that play a role in the course of TB infection are neutrophils and Natural Killer (NK) cells. Neutrophils express Programmed Death-Ligand 1 (PD-L1), which increases lymphocyte death, resulting in an increase in the number of neutrophils with PD-L1 in TB patients, while NK cells recognize and lyse infected macrophages.[30–32]

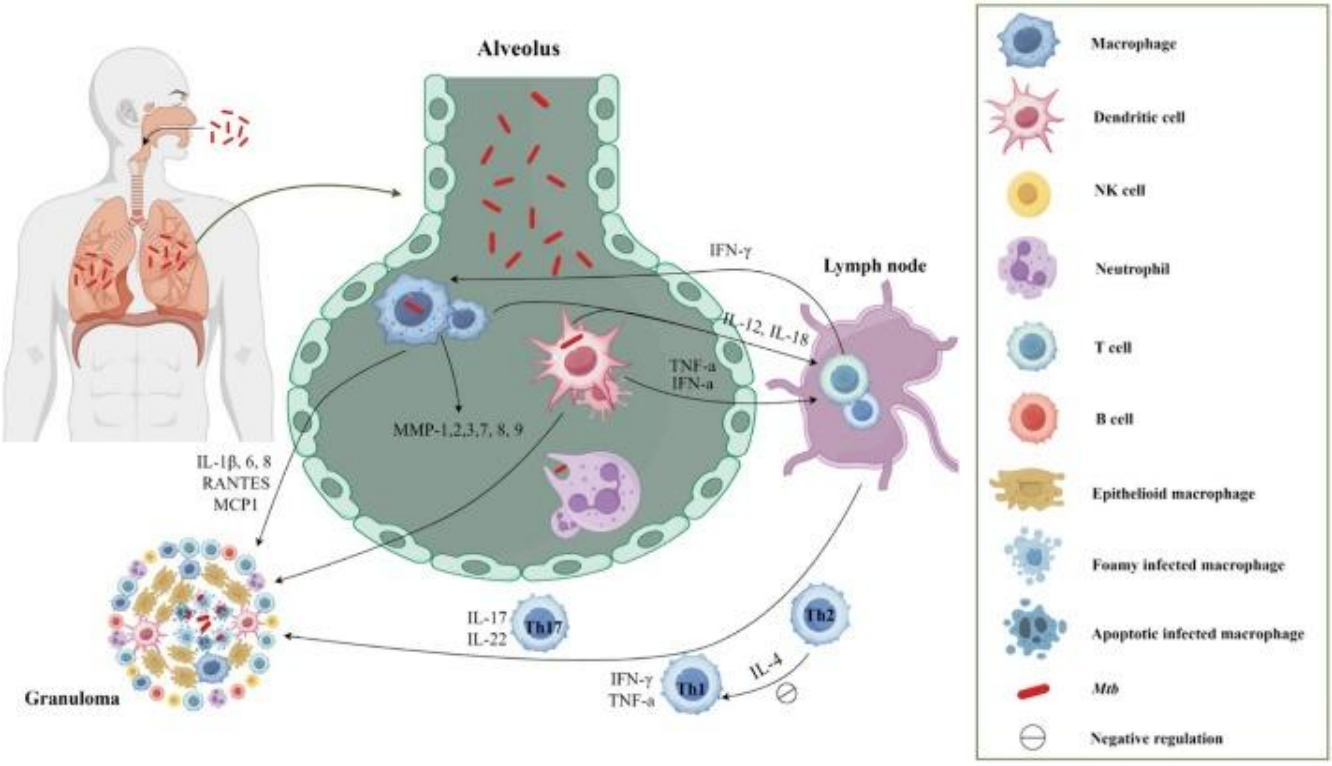

Figure 2. Immune system response to *Mycobacterium tuberculosis* infection[27]

Dendritic cells play a role in innate and adaptive immunity by presenting antigens.[33] *Mycobacterium tuberculosis* enters dendritic cells through the CD209 receptor, which binds to *Mycobacterium tuberculosis* lipoarabinomannan mannose (ManLAM), penetrates the cell, disrupts dendritic cell activity, increases production of IL-10 (anti-inflammatory cytokine) and decreases IL-12 (pro-inflammatory cytokine), thereby suppressing T cell activity.[34]

The adaptive immune response begins when antigens that have been phagocytosed by APCs migrate to the lymph nodes within 1-3 days. APCs then present antigens through Major Histocompatibility Complex Class II (MHC Class II) to activate naive CD4+ T cells and MHC Class I for naive CD8+ T cells. Furthermore, naive CD4+ and CD8+ T cells will be activated and differentiate into T helper (Th)-1, Th-2, Th-17 and T regulator (Treg).[35]

Th-1, Th-2, Th-17 and Treg cells will migrate back to the lungs, activating macrophages through IFN-γ in 14-17 days.[36] IFN-γ stimulates phagolysosome maturation in infected macrophages, stimulates the production of Nitric Oxide (NO), defensins and autophagy, but requires the help of IL-6, IL-1 and TNF-α.[37]

The interaction of innate and adaptive immunity forms granulomas (Ghon focus), which limit infection by isolating the bacteria in cellular compartments. IFN-γ and TNF-α maintain the bacteria in a dormant state in the granuloma, resulting in Latent Tuberculosis Infection (LTBI). However, if the dominance of IL-4 and TGF-β in inhibiting macrophages is greater than the role of IFN-γ and TNF-α in inducing and activating macrophages, then the TB bacteria will be active and replicate again. Next, necrosis occurs and active bacteria are released into the lung tissue and respiratory tract.[32,34]

SECONDARY DRUG-RESISTANT TUBERCULOSIS (DR-TB)

Mycobacterium tuberculosis infection secondary resistance mechanisms are classified as either intrinsic or acquired. Intrinsic resistance reflects bacterial traits that reduce drug efficacy, including decreased cell envelope permeability, drug efflux, drug inactivation and target modification. This makes TB more difficult to eliminate.[38]

The wall structure of *Mycobacterium tuberculosis* consists of a cell envelope, cell wall and cell membrane.[39] The capsule consists of protein, glucan and lipid, while the cell wall consists of mycolic acid, arabinogalactan (AB) and peptidoglycan (PG). The high lipid content causes the envelope of TB bacteria to become thicker, more hydrophobic and impermeable, thus inhibiting the diffusion of drugs even though they are hydrophobic, such as rifampicin, macrolides, fluoroquinolones and tetracyclines.[38,39] The components that make up the cell wall of TB bacteria are shown in Figure 3.[39]

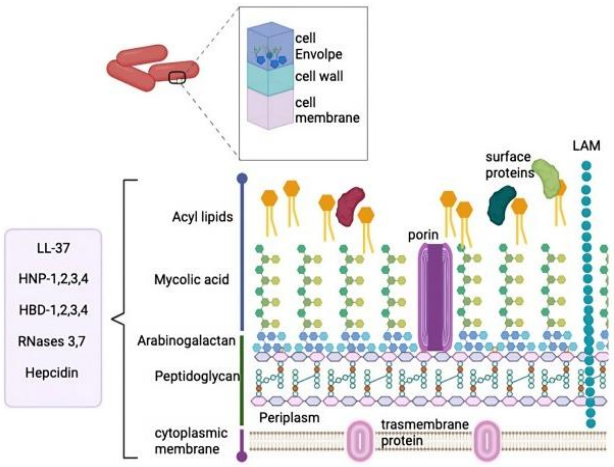

Figure 3. Mycobacterium tuberculosis cell wall[39]

Mutations in transporter proteins can cause resistance to fluoroquinolones, tetracyclines and aminoglycosides.[40] These proteins contribute to the transportation of drugs, nutrients and metabolic substances. Hence, mutations that impair their function lead to drug efflux, which reduces the effectiveness of therapy.[41,42]

In addition, a physiological adaptation of TB bacteria also triggers resistance. The β-lactamase enzyme encoded by the blaC gene can degrade β-lactam antibiotics such as meropenem and clavulanic acid to inhibit.[43,44] Modifications of other enzymes can trigger resistance to aminoglycosides through the process of methylation and acetylation of antibiotics.[38]

Tuberculosis bacteria can also modify drug targets, preventing antibiotics such as macrolides, streptomycin and fluoroquinolones from binding to their receptors. MfpA production by TB bacteria inhibits the action of fluoroquinolones by preventing their interaction with DNA gyrase, allowing the bacteria to survive despite antibiotic treatment.[45]

Acquired resistance arises from selection under inadequate exposure, including irregular or suboptimal dosing and poor regimens. This encourages adaptation and mutation of TB bacteria, making them increasingly intolerant to treatment and more contagious.[38] Before treatment, the body of a TB patient contains sensitive and resistant bacteria from the beginning. Monotherapy removes susceptible bacilli and allows resistant subpopulations to expand; combination therapy suppresses this selection.[46] Therefore, a combination of drugs is needed to prevent the dominance of resistant bacteria.[47] The mechanism of action of first-line TB drugs and mutations that cause resistance are shown in Figure 4.[47]

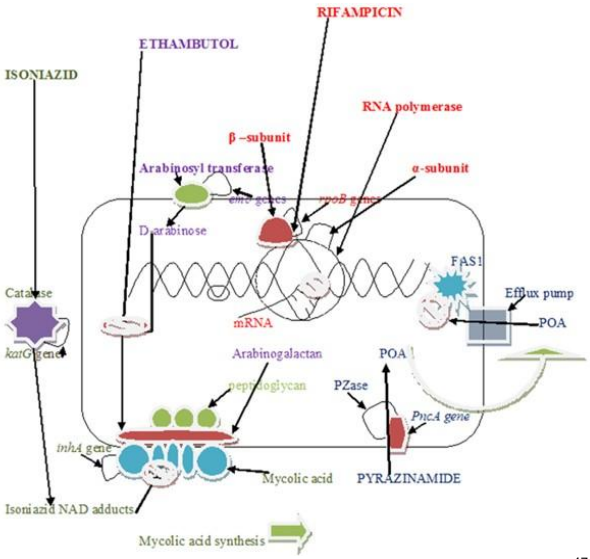

Figure 4. Mechanism of action and resistance on first-line ATD[47]

Rifampicin inhibits RNA synthesis by attaching itself to the beta subunit of RNA polymerase (rpoB), which causes transcriptional disruption and bacterial death. However, mutations in the rpoB gene, especially in the Rifampicin Resistance Determining Region (RRDR) hot-spot region especially at codons 516, 526, and 531), make TB bacteria resistant, so that rifampicin is no longer effective in killing them.[48,49]

Isoniazid is encoded by the katG gene and is activated by the catalase/peroxidase enzyme. Isoniazid functions by preventing the production of mycolic acid, a crucial part of the TB cell wall. This drug is only effective against metabolically active bacteria. The main resistance occurs due to missense mutations in codon 315 of KatG (S315T), which cause 60–95% of resistance cases. Another mechanism is overexpression of the inhA gene due to c-15t mutations in fabG1-inhA, which is the second most common cause of resistance.[50]

Pyrazinamide works by disrupting the metabolism of TB cell membranes after being activated by the pyrazinamidase enzyme (PZase) encoded by the pncA gene. Its active form is pyrazinoic acid (POA), which will increase the acidity of the cytoplasm, inhibit energy production and disrupt cell transport. This drug is important in first-line TB therapy because it can kill persistent bacteria. Mutations in the pncA gene that cause loss of PZase function are the main cause of resistance to pyrazinamide.[47,51]

Ethambutol works by inhibiting the arabinosyltransferase enzyme encoded by the emb gene, which plays a role in the biosynthesis of arabinogalactan in the TB cell wall.[47] Mutations in the emb gene can reduce the effectiveness of ethambutol, causing resistance. In addition, mutations in the ubiA gene encoding the enzyme decaprenyl-phosphate 5-phosphoribosyltransferase (DPPR synthase) also contribute to resistance, especially when occurring together with emb mutations.[47,52]

Fluoroquinolones can kill dormant and replicating *Mycobacterium tuberculosis* by inhibiting the enzyme topoisomerase II (DNA gyrase), which plays a role in DNA transcription and replication.[47] The main mechanism of fluoroquinolone resistance is mutation in DNA gyrase (gyrA and gyrB), especially in gyrA. Mutations that occur in the gyrA gene codons 94, 90 and 88 will cause a higher risk of resistance. In addition, excessive expression of the pstB transporter protein can accelerate resistance.

Resistance to fluoroquinolones can cause Pre-XDR TB.[53] The mechanism of action of second-line TB drugs and mutations that cause resistance are shown in Figure 5.[47]

Amikacin, kanamycin, capreomycin and viomycin can be options in the therapy of DR-TB. Amikacin and kanamycin inhibit the 16S rRNA enzyme encoded by the rrs gene, thereby disrupting protein synthesis. Mutations in the rrs gene cause resistance to both drugs by altering the ribosomal binding site of these aminoglycosides, thereby reducing drug affinity and preventing inhibition of protein synthesis. The most frequent mutation, A1401G, is strongly associated with high-level resistance to both drugs.[54,55]

Capreomycin and viomycin are affected by ribosomal RNA methylation, which is encoded by the TlyA gene. Mutations in TlyA, which encodes a 2′-O-methyltransferase that acts on both 16S rRNA and 23S rRNA, lead to the loss of these methylations and thereby disrupt the proper binding interface for capreomycin and viomycin across the ribosomal subunit interface. As a result, these antibiotics cannot bind effectively and inhibit translation.[56]

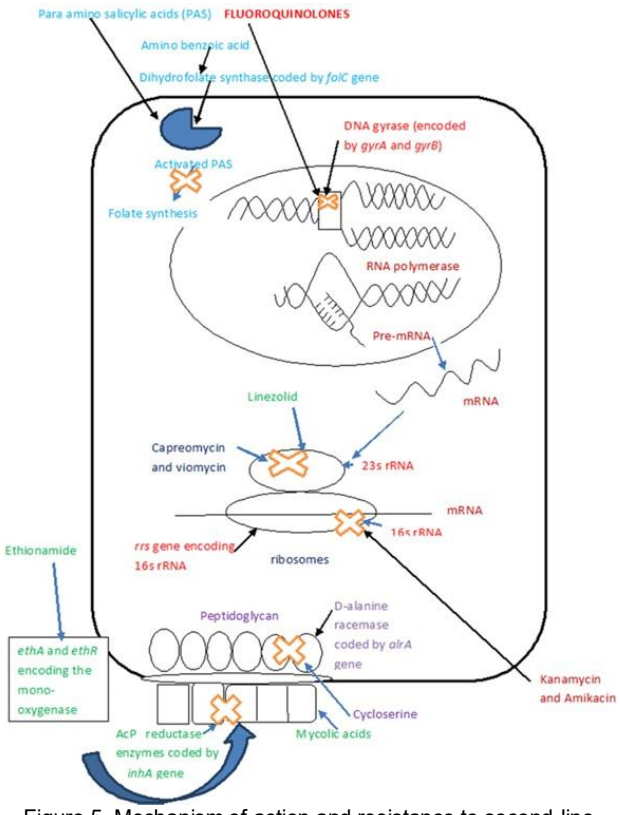

Figure 5. Mechanism of action and resistance to second-line ATD[47]

Ethionamide is an isonicotidic acid derivative similar to isoniazid. This drug is activated by the enzyme monooxygenase, then inhibits the formation of NAD and enoyl-ACP reductase, thereby disrupting the synthesis of mycolic acid. Resistance occurs due to mutations in the etaA/ethA, ethR and inhA genes. The InhA gene also plays a role in isoniazid resistance, so isoniazid and ethionamide resistance can occur simultaneously.[57]

P-aminosalicylate is an amino benzoic acid analog that interferes with folate synthesis by activating the enzyme dihydrofolate synthase encoded by the folC gene. Mutations in the folC gene confer resistance. Cycloserine is an alanine analog that inhibits cell wall peptidoglycan biosynthesis by inhibiting the enzyme D-alanine racemase, preventing the conversion of L-alanine to D-alanine. The mechanism of resistance is uncertain, but overexpression of the D-alanine racemase encoded by the alrA gene is thought to be the cause of resistance.[58,59]

Ethionamide is an isonicotidic acid derivative that is structurally similar to Isoniazid. Linezolid, from the oxazolidinone group, can inhibit protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit (*rrl* gene) so that fusion between the 50S and 30S subunits does not occur. Resistance occurs due to mutations in the 23S rRNA so that the drug cannot bind to its receptor.[50] Clofazimine disrupts the expression of mycobacterial genes and prevents mycobacterial integration host factor (mIHF) from attaching to DNA.[60] Clofazimine resistance is linked to mutations in the transcriptional repressor Rv0678 (mmpL5), which upregulates the efflux protein Mmpl5.[50]

Bedaquiline works by damaging cell membranes and interfering with ATP synthesis by disrupting the flow of proton pumps through binding to ATP synthase subunit C. Resistance occurs due to mutations in the AtpE gene encoding the subunit C. Delamanid is a nitroimidazole derivative, activated by the nitro reductase enzyme encoded by the ddn gene and inhibits mycolic acid synthesis. Mutations in fgd1 and ddn cause resistance. Protonamide also requires

the ddn enzyme for activation and loss of glucose-6-phosphate dehydrogenase causes resistance.[61]

THE RELATIONSHIP BETWEEN IMMUNE RESPONSE AND DRUG-RESISTANT TUBERCULOSIS (DR-TB)

The immune response in DR-TB is different from DS-TB. DR-TB has fewer CD4+ Th1 T cells, which play a role in IFNγ activation, but more CD4+ Th17 T cells (producing IL-17, IL-22) and regulatory T cells (producing IL-10). CD8+ T cells and NK cells in DR-TB also show decreased production of lytic and cytotoxic mediators compared to DS-TB. The number of Arginase 1+ (Arg 1+) alveolar macrophages is higher in DR-TB, while iNos+ is higher in SO-TB. Until now, the differences in immune responses in DS-TB and DR-TB patients still require further research.[62]

In immunocompromised conditions such as HIV, there is a significant decrease in CD4+ T cells, which weakens macrophage activation and granuloma formation, leading to caseous necrosis and dissemination of *Mycobacterium tuberculosis*. HIV patients are more susceptible to drug-resistant TB, even without a history of TB treatment, due to weakened immunity and more frequent hospitalizations, increasing exposure to resistant bacteria.[63]

BPALM AND BPAL MANAGEMENT

The principal strategy for the treatment of MDR-TB/RR-TB in the absence of contraindications is BPaLM (bedaquiline, prothionamide, linezolid and moxifloxacin). This regimen is effective in suppressing bacterial growth, exhibits a sterilizing effect and helps to prevent relapse, as shown in RCT studies by the WHO.[5] This combination consists of two core drugs that kill TB bacteria in each phase and two additional drugs that increase effectiveness and prevent resistance.[5,64]

Bedaquiline inhibits the production of ATP needed by TB bacteria to survive. Protionamide inhibits the synthesis of mycolic acids that form cell walls in both aerobic and anaerobic conditions. Linezolid has the advantage of being able to penetrate cavities with an early bactericidal effect on rapidly replicating TB bacteria, while moxifloxacin has a high bactericidal effect and remains effective even if there is resistance to other fluoroquinolones.[65]

CONCLUSION

Resistance to *Mycobacterium tuberculosis* infection is classified into two types of mechanisms, primary and secondary. Primary resistance occurs due to infection by strains that are already resistant to drugs, while secondary resistance can be intrinsic or acquired. The intrinsic resistance mechanism occurs due to the evolution of TB bacteria that cause biological changes, such as reducing cell membrane permeability, disrupting transporter proteins, producing enzymes that inactivate drugs and modifying drug targets. Meanwhile, acquired resistance occurs due to chromosomal mutations in target genes during the treatment process. Some genes involved in acquired resistance include rpoB (rifampicin), katG and inhA (isoniazid), pncA (pyrazinamide), emb (ethambutol), gyrA and gyrB (fluoroquinolones), rrs (amikacin and kanamycin), tylA and rrs (capreomycin and viomycin), etaA/ethA, ethR and inhA (ethionamide), folc (p-aminosalicylate), rrl (linezolid), Rv 0678 (clofazimine), AtpE (bedaquiline) and ddn (delamanid and protionamide)

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CONFLICT OF INTEREST

None.

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