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Declined Drug Susceptibility Mechanisms against Mycobacterium Tuberculosis

Abstract

Anti-microbial treatment is extensively used in conventional tuberculosis treatment, leading to resistance development. In this review, we summarized the mode of action and susceptibility protocols of anti-Tubercular drugs. An effort to elucidate the role of genetic variations, cell membrane adaptions, and efflux pump modalities in treatment failure will be an asset in devising prospective strategies.

Key Words: Tuberculosis, Drug resistance, Mechanism of Action, Mutations

Introduction

Despite being a preventable and curable disease, TB remains on top of the infectious killing disease, claiming 1.5 million lives every year. Young people between the ages of 15-34 are carrying the heaviest burden of this disease. Tuberculosis is the principal reason for anti-microbial resistance and fatalities among people suffering from HIV. In 2020, WHO reveals the 30% global decline in deaths caused by Tuberculosis, which shifts its place from 7th to 13th in 2019. But still, this communicable disease is a major challenge in developing countries. Several treatment regimens have been implicated against Tuberculosis and MDRTB. XDRTB is treated with repurposed drugs like Phenothiazines and Novel drugs, including Bedaquiline, Delamanid, or Pretomanid. Mainly genetic mutation confers to resistance and now has also been shown by Novel drugs, indicating an alarming situation that needs utmost attention.

First-Line Drug Resistance

Isoniazid

Isoniazid (INH) was presented in 1952 (Johnnson *et al.*, 1997) and is deemed to be one of the potent prodrugs (Zhang and Yew, 2009) that exist as first-line antibiotics (Raghunandanan *et al.,* 2018). It is triggered by the catalase/peroxidase *katG* enzyme (Boellela *et al.,* 2016) and becomes a robust bacteriostatic agent (Kendler *et al.,* 2018) against *Mycobacterium Tuberculosis (Mtb)* (Lentz *et al.,* 2018). It produces its activity by impeding mycolic acid production in the bacterial outer membrane while obstructing reductase enzymes, which is encoded by *inhA* (Rawat *et al.,* 2003) and has MIC of [0.02microg/ml to 0.06microg/ml] (Lempens *et al.,* 2018).

The missense, mutation, implantation, redundancy, or even complete omission of genes (Vilcheze and Jacobs, 2007) can originate in *ndh, kasA, katG,* along with *ahpC* and *inhA* (Almeida and Palomino, 2011; Larsen *et al.,* 2002*).* As previously discussed, it most frequently happens in S315T of *katG*, evolving substantial decrease or permanent failure of catalase/peroxidase function (Zhang *et al.,* 1992). Structural reforms of the active domain and genetic variation in 215CT promoter region emerges in *inhA* (Leung *et al.,* 2006), whereas hyper-expression of *ahpC* (Sherman *et al.,* 1996) and silent genetic changes of *mabAg609a (*Ando *et al.,* 2014*)* confers to resistance (Seifert *et al.,* 2015). 64% *katG* S315T mutation have a significant decrease in susceptibility with MIC >1microgram/ml, while 19 % mutation in *inhA* promoter has mild resistance with MIC <

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1microgram/ml (Riviere *et al.,* 2020; Ayanwale *et al.,* 2020). Scientific investigations have revealed a 2-fold increase in resistance by inhibition of dihydrofolate reductase in *Mtb* due to the INH-NADP 4R isomer (Wang *et al.,* 2010).

Rifampicin

Rifampicin, amongst the broad-spectrum antibiotics, is used against bacterial pathogens (Sensi *et al.,* 1960). Rifampicin, possessing exceptional sterilizing activity (Rattan and Musser, 1998). RIF adheres to RNA polymerase enzyme, in turn, hinders mRNA production resulting in organism destruction.

Resistance in rifampicin is correlated with a minimum of 10 genetic mutations (Sensi, 1983). The amino acid substitution in the rpoB gene is the major cause of resistance of RIF (Herrera *et al.,* 2003). The 51 bp RRDR of the rpoB gene mainly contributes to mutations in codon 516, 526, and 531 (Ramaswamy, 1998; Herrera, 2003). Non-compliance drug resistance occurs. The modifications in several codons contribute to minor drug resistance (Heil and Zillig, 1970). Primary codon positions include 511,516 along with 518. Various factors not limited to age, HIV infection prevalence, and geography may also account for resistance. Despite the rare occurrence of RIF resistance, studies have deduced concomitant resistance in RIF and isoniazid (Cohn *et al,* 1997).

Ethambutol

Introduced in the 1960s (Lee and Neguyen, 2020), Ethambutol (EMB) is a first-Line Drug (Sreevatsan *et al.,* 1997) with bacteriostatic action (Thomas *et al.,* 1961), prescribed for the treatment of Tuberculosis since 1966 (Goude, 2009), only effective D-form (Lee and Neguyen, 2020). EMB is not given on its own, but in Quadruple following combinational therapy (Jeong *et al.,* 2015) generating its effect by more than just interfering with the core polymer, Arabinogalactan AG (Takayama and Kilburn, 1989), but also hindering the synthesis of lipoarabinomannan LAM of *the Mycobacterium* cell wall (Dengg *et al.,* 1995). Scholars demonstrated enhanced action of INH when it binds to transcriptional regulator *TerR* (Zhy, 2018).

Almost 4% of the clinical isolates displayed resistance (Wright and Zignol, 2008) mainly driven by genetic substitution in Rv3806c and Rv3792 (pathway genes), decaprenylphosphoryl-B-D-arabinose (DPA) (Safi *et al.,* 2013), arabinosyl transferase *emb* operon counting *embB* codon 289, 292 and 306 (Lety, 1997; Starks *et al.,* 2019*).* Moreover, *embC* and *embA* (Ramaswamy *et al.,* 2000) interferes with outer membranes permeability (Bakula *et al.,* 2013). Current reviews managed to show no mutagenesis in *embB*, raising the question of having other mechanisms involved (Zhang and Yew, 2009). Analyses of the allelic exchange implied substitution of the amino acid (Sreevatsan *et al.,* 1997) in which the most common shift was Gly406Ala at nucleotide position 1217 by the transformation of G →C (Bakula *et al.,* 2013) Mild, moderate, and major-level substitution have EMB MIC 20, 100, and >256microgram/ml respectively (Telanti *et al.,* 1997).

Pyrazinamide

Pyrazinamide, like isoniazid and ethionamide, is a prodrug that requires mycobacterial enzyme pyrazinamidase for its conversion to pyrazinoic acid (Konno *et al.,* 1967; Scorpio and zhang, 1996). Pyrazinamide introduction has shortened the TB treatment to 6 months (Mitchison, 1985). Various novel drug candidates are used together with pyrazinamide, in the mouse TB infection model, for optimal efficacy (K. Andries *et al.,* 2005; Nuermberger *et al.,* 2008). Postulated PAO action mechanism includes retardation in the kinetics of membrane, inhibition of membrane transmission, the production of Co-enzyme A, and increase in acidity of cell plasma (Zhang *et al.,* 2003; Njire *et al.,* 2016). Various studies propose fatty-acid synthase enzyme Type-I as a Pyrazinamide target (Zimhony *et al.,* 2007; Zimhony *et al.,* 2000). Pyrazinamide encoding *pncA* gene mutation is majorly linked to decreased PZA susceptibility (Scorpio *et al.,* 1997; Palomino *et al.,* 2014). Unlike isoniazid, the domain for mutation of PZA is significant (Pym *et al.,* 2002). However, few PZA resistant strains possess no *pncA* mutations (Cheng *et al.,* 2000; Smith *et al.,* 2013), which hints at an alternative mechanism. Several studies reveal the overexpression of the *rpsA* gene accounts for PZA resistance (Shi *et al.,* 2011). Detailed analysis of *rpsA* gene, in resistant strains without *pncA*, indicated deletion of 3 base pairs GCC, leading to the exit of Ala 438 (Boni *et al.,* 2000). Concerns exist over the contribution of *rpsA* in PZA resistance, which may conclude, need for further studies.

Streptomycin

Streptomycin, classified as a glycoside anti-microbial agent, was the initial curative agent for TB (Tasha *et al.,* 2013), introduced in 1942 (Dookie *et al.,* 2018).

Streptomycin adheres irreversibly to s12 protein in ribosomes and 16s rRNA (Moazed and Noller 1987; Finken *et al.,* 1993), leading to inhibition of translation (Ruusala and Kurland, 1984), and interference with ribosomal proofreading (Winder, 1982). Initially, *mycobacterium tuberculosis* was susceptible to SM. Gradually, resistance evolved due to mono drug therapy (Crofton and Mitchison, 1948). Mutations in *rrs* or *rpsL* genes account majorly for SM resistance. Simultaneous genetic variation in *rrs* or *rpsL* genes are rarely observed. Predominantly, *rpsL* gene alterations were at codon 43 and 88 while, codon 513 and 516 were observed for *rrs* gene (Betzaida *et al.,* 2013). Investigation deduced the participation of *gidB* gene, in mild resistance (Verma *et al.,* 2014; Spies *et al.,* 2008; Okamoto *et al.,* 2007). Further, mechanisms, including efflux pumps and cell membrane disruptions, may also confer resistance.

Second-Line Drugs

Injectables Aminoglycosides

WHO (World Health Organization) reported 480,000 cases of MDR (Multi-Drug Resistance) Tuberculosis across the globe in 2014 (Zulma *et al.,* 2015). Currently, Aminoglycoside Injectables KAN, AMK, (Johansen et al., 2006) and Tuberactinomycin CAP and viomycin (Akbergenov *et al.,* 2011) are being used as potential drugs against MDRT (Reeves *et al.,* 2013). Therapy through these medications is complicated, expensive, and hazardous due to its lengthy timeframe (Quenard *et al.,* 2017; Zimen *et al.,* 2013).

Kanamycin (KAN) was discovered in 1957 and clinically used in 1958 (WHO, 2009), producing its remarkable bactericidal effects (Hota *et al.,* 2018; WHO, 2009). The action mechanism of aminoglycoside includes hampering of protein synthesis when it adheres with the 30S subunit in the ribosomes (Zaunbrecher *et al.,* 2009). A research study found three *rss* gene mutations appearing in A140G, G1484T and C1402T (Jugheli *et al.,* 2009; Maus *et al.,* 2005) inevitably results in cross-resistance amongst Capreomycin, Kanamycin and Amykacin (Campbell *et al.,* 2011). Further investigations reported conformational changes and mutation in *eis* gene, resulting in accelerated expression of *eis*, which inactivates the KAN (Reeves *et al.,* 2013; Abraham *et al.,* 2020) but not AMK (Zaunbrecher *et al.,* 2009). The same author suggests substitution in *whiB7* of transcriptional activator provoking enhanced *whiB7* transcripts, which ultimately leads to increased expressions of *eis* (Rv2416c) and *tap* (Rv1258c) (Reeves *et al.,* 2013).

Capreomycin (CAP) is being extensively used against XDRT since 2006 after replacing KAN and AMK (Georghiou *et al.,* 2012). CAP and Viomycin are bacteriostatic anti-microbial agents that bind to 50S subunits interfering with the translation process through intersubunit bridge *B2a* (Stanley *et al.,* 2010) but do not interfere with mRNA (Tsukamura, 1969). Resistance transpired due to genetic variation in *the tlyA* gene (Brossier *et al.*, 2017), causing the absence of the methylation process in rRNA (Johansen *et al.,* 2006).

Fluoroquinolones

Fluoroquinolones, possessing robust bactericidal activity, are classified amongst second-line drug therapy for TB (Almeida *et al.,* 2011). Nalidixic acid derivatives include ciprofloxacin, ofloxacin, and a few novel compounds such as gatifloxacin and moxifloxacin (Dookie *et al.,* 2018). Majorly FQ's inhibit topoisomerase II (Aubry *et. al* 2004) and IV (Zhang and Yew, 2005; Bernard *et al.,* 2015), resulting in DNA breakdown and microbial fatality (Andriole, 2005). FQ's decrease susceptibility is associated with aminoacid switching of *gyrA* and *gyrB* genes (Takiff *et al.,* 1994; Che *et al.,* 2017; Smith *et al.,* 2013). Studies reveal the predominant role *gyrA* gene over *gyrB* (Smith *et al.,* 2013). Alanine 90 and Aspartate 94 account majorly in *gyrA* gene mutation (Sun *et al.,* 2008). Contrarily, codon 74, 88, and 91 role is limited (Maruri *et al.,* 2012; Aubry *et al.,* 2006; Matrat *et al.,* 2006). For significant FQ's resistance, double amino acid substitution in *gyrA* or co-occurring mutations in *gyr A* and *gyr B* are prerequisites (Takiff *et al.,* 1994; Kocagöz *et al.*, 1996). Alteration in cell membrane permeability to the drug (Almeida *et al.,* 2011) and efflux-pump is significant in mediating resistance (Escribano *et al.,* 2007; Takiff *et al.,* 1996; Cambau *et al.,* 1996; Jarlier and Nikaido 1994). Further, MfpA protein, homologous to DNA structure, binds to topoisomerase II and inturn inhibits its action (Hegde *et al.,* 2005), resulting in minor resistance (Smith *et al.,* 2013; Ginsburg *et al.,* 2003).

Ethionamide

Ethionamide, a second line structural analogue of isoniazid, is mainly utilized in multi-drug resistant tuberculosis therapy (Engohang-Ndong *et al.,* 2004). Similar to isoniazid, ETH is a prodrug and possesses

a common pathway, which may result in cross-resistance (Morlock *et al.,* 2003). ETH may get activated by enzymatic action and bacterial metabolism (alian *et al*., 2017). Obstruction in the production of mycolic acid results in the breakdown of cell wall biosynthesis by activated drug (Morlock *et al.,* 2003).

ETH resistance may result from *ethA* and *inhA* mutations (Jacob *et al.,* 1994; Clifton *et al*., 2000). Structural variations in C15–T of *inhA* are predominantly responsible for reduced susceptibility to ethionamide (Vannelli *et al.,* 2002). Additionally, *inhA*-based ETH resistance may also conform to the cross-resistance of isoniazid (Diana *et al*., 2013). Studies demonstrate *ethA* expression is opposed by neighboring *ethR* gene (Engohang-Ndong *et al.,* 2004).

Para-Amino Salicylic Acid

In combinational therapy against Tuberculosis, second-line Para aminosalicylic acid (PAS) has been functioning since 1940 (Sumit *et al*., 2013; Lehmann, 1946; Dye *et al*., 2002). Being less tolerated and toxic, its consumption was decreased dramatically (Iwainsky, 1988).

Constrained growth of tubercle bacilli, attributed to the bacteriostatic drug disposition, is expected to be driven through impeding the synthesis of folic acid (Dye *et al*., 2002) and cell wall component mycobactin. (Vanessa *et al*., 2009).

The primary explanation for the susceptibility against PAS takes place on account of mutagenesis of *thyA* and *drfA* coding region, pertaining to the biosynthesis of thymine nucleotide (Pablo *et al.,* 2009; Mitnick *et al.* 2003; sumit Chakraborty *et al*., 2013). Maximum gene variations in *thyA* were recorded in TB patients from China (Bharti *et al*., 2019).

Novel or Repurposed Drugs

Bedaquiline

Bedaquiline, a diarylquinoline drug, seems to possess an unorthodox action mechanism against TB (Hendrik *et al.,* 2014). WHO warned of deliberate drug administration, encouraging the emergence of resistance (Kenny *et al.,* 2014). BDQ resistance, typically attributed to the mutations in *atpE*, *Rv0678*, intergenic region between *Rv0678* and *Rv0677c,* and *pepQ* (*Rv2435c*) genes (N. Engyl *et al.,* 2015; Kenny *et al*., 2014). In addition, the substitution of *Rv0678* gene, acting as an inhibitor of the efflux pump, results in minute resistance (Amber, 2017). Polymorphisms in the Rv1979c and PepQ (Rv2535c) genome is affiliated with concomitant resistance in clofazimine (CFZ) (Deepak *et al*., 2016).

Nitroimidazole

Nitroimidazole antibiotics were discovered in the late 1950s (Ang *et. al.,* 2017). New prodrugs, Delamanid and Pretomanid, require bioactivation of nitro group to exert its bactericidal action, against both replication and hypoxic nonreplicating Tuberculosis, by decreased production of mycolic acid during outer membrane formation (Matsumoto *et al*., 2006; Samuelson, 1999), and nitric oxide release (Lamprecht *et al.,* 2016; Singh *et al.,* 2008), causing respiratory poisoning respectively. Resistance occurs by decreased activity/expression or mutation of reductive enzyme *Ddn* (Haver *et al.,* 2015), which catalyzes menaquinone, only present in *Mycobacterium Tuberculosis* (Ang *et al.,* 2017). *Ddn* enzyme is $F_{420}H_2$-Dependent (Gurumurthy *et al.,* 2013). Genomic sequence study showed 46 no-synonymous substitutions, among which several mutants were unable to activate the drug 2 and deletion of *Ddn* quinone reductase(Jing *et al.,* 2019). Variation in three binding sites (S78, Y130, Y136) and polymorphism (SNP) of genes of *Ddn* affect the nitroimidazole activating activity and confer to the resistance of the drug (Mohamed *et al.,* 2016; Haver *et al.,* 2015). The study has also shown the difference of activity between two drugs against resistant mutant. Out of 75 mutants studied, 65 did not reduce the Delamanid, while 50 were unable to decrease Pretomanid (Lee *et al.,* 2020; Cellitti *et al.,* 2012; Mohamed *et al.,* 2016). It was also revealed that Mutations in *Ddn* also cause the transmission of disease (Ai *et al.,* 2016).

Phenothiazine (Chloramphenicol and Thioridazine)

Phenothiazines discovered in 1883 (Masie, 1954) are tricyclic, anti-psychotic, "Non-Antibiotic" anti-microbial agents expecting broad-spectrum intervention that modifies the cell permeability, illustrating synergistic effect along with other anti-microbial agents (Amaral and Molnar, 1991; Kristiansen and Amaral, 1997; Amaral *et al.,* 2001). Phenothiazine compounds such as Chlorpromazine (CPZ) and Thioridazine (TDZ), share the same potential activity against MDRTB and XDRTB (Ordway *et al.,* 2003; Amaral *et al.* 2004; Viveiros and Amaral, 2001).

CPZ was formulated in 1950 as an anti-psychotic agent along with many nasty consequences (BMA. 2010), but reconsidered as a potential anti-MDRTB (Alsaad *et al.,* 2014). The concentration used 15-20mg/L is higher than the clinically indicated value for a chronic patient (Molnar *et al.,* 1997). CPZ produces its effect by preventing the growth and killing *Mtb* (Amaral and Viveiros, 2012).

TDZ being less noxious, replaced the CPZ (Amaral *et al.,* 1996). When given in combination at a dose of 200mg/day, it contributes by interfering with gene expression, inhibition of efflux pump, suppression of replication, and retardation of Ca++ and K+ transport process that leads to complete extrusion and killing of bacteria (Amaral and Viveiros, 2012; Amaral and Mornal, 2012).

According to an electronic database study, other anti-microbial agents that could be used against XDRTB include doxycycline, and Co-trimoxazole, and metronidazole which are not on the WHO list (Alsaad *et al.,* 2014).

SQ109 (Ethambutol Analogue)

SQ109 is a potent anti-MDRTB agent (Onajole *et al.,* 2010) having a bactericidal activity (Boeree, 2017) that entered as an improved analogue of ethambutol in the clinical trials (Lee *et al.,* 2003). SQ109 reported low bioavailability due to the first-pass effect and boosted up to 91.4% by administering as a prodrug (Meng *et al.,* 2009). It targets the mycobacterial cell wall by lessening the mycolic acid concentration (Tetli *et al.,* 2020); conversely, it acts as an inhibitor of the efflux pump (Te Brake *et al.,* 2016). Moreover, it is also associated with MmpL3 inhibition (Tetli *et al.,* 2020).

Susceptibility in SQ109 tends to happen by mutagenesis in MmpL3 (Umumararargu *et al.,* 2020). Recent research indicates impaired menaquinone synthesis, ATP synthesis, and cellular respiration on the cytoplasmic membrane (Tetli *et al.,* 2020). The activity of SQ109 is concentration-dependent as complete extrusion happens at a concentration of 256mg/L and kills 99% *Mtb* when exposed to 64mg/mL within one day (de Knegt *et al.,* 2017). Synergistic effects are seen when SQ109 is combined along with isoniazid, rifampicin, and Bediquline, while augmented effects are noted with Streptomycin and Suetozid (PNU-100480) in in-*vitro* studies (Umumararargu *et al.,* 2020).

Linezolid

Linezolid, the member of oxazolidinones, possesses considerable in vivo and in vitro action against TB (Alcala *et al.,* 2003; Cynamon *et al.,* 1999). LZD inhibits the initial phase in protein formation by binding to 50s ribosomal subunit (Zhang, 2005; Escribano *et al.,* 2007). G2572T and G2061T genetic variations in the *rrl*, leads to Anti-TB drug's resistance (Navisha Dookie, 2018). Resistance results in elevation of MIC of 4–8 mg/L to 16–32 mg/L range (Hillemann *et al.,* 2008).C154R mutation in the *rplC* gene also impart LZD resistance (Bloemberg *et al.,* 2015). The role of efflux mechanisms or other non-ribosomal modifications cannot be neglected.

Clofazimine

Clofazimine is a drug known as riminophenazine, specifically developed for tuberculosis treatment in 1950 (Arbiser and Moschella, 1995). The precise action mechanism is uncertain, but neutrophil and monocyte appear to be the principal location of an operation where it prohibits the inflammatory action by scavenging hypochloric acid while preventing chlorination (Arbiser and Moschella, 1995). Also, bactericidal effect is produced by redox cycling of Clofazimine (Xu *et al.,* 2017), shortening the therapy timeframe (Zhang *et al.,* 2015)

Genetic variation in transcriptional repressor *Rv0678* linked with mmpS5 and mmpL5 genes is correlated with the upregulation of efflux pumps, which tends to result in resistant strains (Yew *et al.,* 2017; iu *et al.,* 2020). Mutation involves the insertion and revocation of nucleotide G at 193 positions (Zhang *et al.,* 2015). Further investigations revealed that *Rv1979c* involved in the transport of amino acids and, *Rv2535c* which encodes a proline aminopeptidase peptidase PepQ was spotted to be the risk factors of developing drug susceptibility (Zhang *et al.,* 2015; Xu *et al.*, 2017; Van *et al.,* 2020). PepQ *Rv3525c* gene suggests mild resistance (Ameida *et al.*, 2016; Xu *et al.*, 2017). Research work reported 1.2microgram/ml MIC for Clofazimine. Adequate interventions can be made by constructing the MIC data to mitigate the transmission of resistant strains (Xu *et al.*, 2017). Improved genetic knowledge can help in molecular diagnosis and monitoring of drug resistance (Kadura *et al.*, 2020).

NAS 91 & NAS 21

In recent times, NAS 21 & NAS 91 exhibited promising anti-mycobacterial activity (Pedro, 2011). Being a dominant pharmacophore, NAS-91 acts as a candidate for future inhibitors (Choi *et al.,* 2000).

According to *M. bovis* BCG examination, FAS-II dehydratase coded by Rv0636 developed the main the variation in oleic acid production, occurs as a consequence of upregulated Rv0636 gene analogue. The oleic acid synthesis was inhibited, as demonstrated by an assay (Eduardo *et al.*, 2011).

Benzothiazinone

Benzothiazinone is classified amongst potential tuberculosis treatment therapies (Variam *et al.,* 2017). DprE1 enzyme and its inhibitors are a member of newly introduced TB medications. (Inshad *et al.,* 2016). DprE1 and DprE2 speed up the conversion of DPR to its epimer DPA. Mycobacterial outer membrane production is modulated by DPA (Inshad *et al.*, 2016). Mechanistic studies revealed the importance of the NO_2 and Sulfur groups for anti-TB target for resistance (Veemal, 2009). Partial obstruction of mycolic acid biosynthesis, as well as activity at position 8 and 1, respectively. Further, Trifluoromethyl significant role was also highlighted against Tuberculosis (Monika *et al.*, 2016).

Conclusion

Decreased anti-microbial drug susceptibility against *M. Tuberculosis* presents a great challenge to human health globally. The inception of resistance to anti-tubercular drugs is restricting the treatment options, which tends to be a great threat to human life, especially in developing countries. New therapy regimens, surveillance studies, and strategies for early diagnosis of declined drug susceptibility deemed mandatory.

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