Biological Times

Volume No. 2 | Issue No. 9 | Pages 27-28

Antibiotic Resistance in *Mycobacterium tuberculosis*: a Global Threat to Humans

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ABSTRACT

The effectiveness of practically all available medicines has decreased due to the rising prevalence of drug resistance in *Mycobacterium tuberculosis* (TB), hampering efforts to stop the spread of this global health threat. To increase treatment efficacy and stop the emergence of antibiotic resistance, optimal drug combinations are required in addition to the discovery of new medications. Antibiotic resistance often results in decreased sensitivity, but occasionally, drug resistance evolution can result in increased sensitivity to unrelated medicines. Collateral sensitivity in *M. tuberculosis* is mainly unstudied, although it suggested alternate approaches to fight drug-resistant forms that are resistant to present treatments. Here, the mechanism of resistance in *M. tuberculosis* and a combination of therapy against this particular pathogen has been explained.

Key Words: *M. tuberculosis,* Resistance, Drugs.

Introduction:

The gram-positive bacteria *Mycobacterium tuberculosis* is responsible for the deadly disease tuberculosis (TB). This infectious disease is causing millions of causalities each year, particularly in third generation countries, TB is one of the comments diseases [1]. Treatment of *M. tuberculosis* is a big challenge around the world because treatment of this requires second-line drugs which are less expensive and less toxic. Global prevalence has decreased over the past few years, and almost ten million new cases have been reported in 2015, of which half a million were brought on by *M. tuberculosis* strains classified as multi-resistance drugs (rifampicin and isoniazid) cases [2]. Tuberculosis treatment through rifampicin and isoniazid is not very effective in controlling the infection. To achieve better results against *M. tuberculosis* fluoroquinolones or other injectable aminoglycoside can be given along with multi-resistance drugs [3]. Streptomycin, the first successful antituberculosis medicine, was found in 1944. The newly found drug began treating TB patients quite successfully. When different TB patients were treated with streptomycin, it showed excellent results and patients showed improvements in their health during the first few months of medication [4]. But with the passage of time, their condition go downhill again. It was soon realized that this was caused by the emergence of *M. tuberculosis* serotypes that were resistant to streptomycin, rendering it useless. then combined therapy was initiated and Para-aminosalicylic acid was given with streptomycin [5]. Numerous new antituberculosis drugs were manufactured throughout the later years. The use of rifampicin drug in the treatment of tuberculosis after its discovery changed the game by reducing treatment time from 18 months to just 9 months [6]. The World Health Organization opted for the current, six-month standard treatment plan which includes 2 months of treatment with 4 therapeutic drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) followed by 4 months of isoniazid and rifampicin treatment. Continuous use of a single medicine or more than one medicine for an extended period has an impact on the development of drug resistance, that is why to attain good results and to avoid resistance one must require a short duration of therapy and a reduction in unpleasant drug effects [7]. Drug-resistant pathogenic strains of *M. tuberculosis* strains continued to emerge until the combination of different drugs was used for the treatment of tuberculosis patients, exhibiting high efficacy and less repetition. Variants of Multiple drug resistance *M. tuberculosis* developed on numerous occasions in various regions of the world [8]. A further factor in the development of this pathogenic bacterium is the variations and the uneven distribution of development rates of drug-resistant variants around the world that we see today in differences in the quality of public health systems. In the absence of a reliable vaccine, it is urgently necessary to develop new treatment protocols, medications, and diagnostic tools in order to slow the emergence of drug resistance, prevent the spread of resistant variants, and improve the treatment outcomes for patients infected with *M. tuberculosis* serotypes.

Mechanism of drug resistance in *M. tuberculosis* :

Mycobacterium members are well known for having built-in resistance to a variety of antibiotics. This resistance is primarily explained by the nature of the cell envelope i.e., abnormally thick and lipid-rich structure [9]. Some antibiotics may undergo structural or enzymatic cleavage after entering the cell membrane, rendering them useless. A variety of pathways for efflux have also been discovered in *M. tuberculosis*, however, it is unclear whether they contribute to the development of clinically significant levels of drug resistance [10]. A further peculiarity about *M. tuberculosis* is that there doesn't seem to be any continuous horizontal gene transfer. Horizontal gene transfer has been observed in different species of genus *Mycobacterium*, but studies showed that is not the major factor in the development of resistance. Other factors include Chromosomal mutations, genetic components, and structural changes. Due to the frequently reduced pathogenicity/biosafety requirements and faster growth characteristics of these *Mycobacteria* compared to *M. tuberculosis*, numerous studies have been carried out to investigate the causes of treatment resistance [11].

Structural involvement in drug resistance

Bacterial cell wall and drug penetration:

The peculiar behavior, shapes and configuration of the mycobacterium cell membrane have frequently been blamed for the resistance against antibiotics. The structural differences of the genus *Mycobacterium* are more dominant as they have thicker and hydrophobic cell walls and cell membranes than other gram-positive bacteria because their membranes contain more contents such as lipids and mycolic acids [12]. Numerous studies carried out on various mycobacterial species have shown that the low porin intensity and the framework of the cell envelope have a key role in the low compound permeability of the cell membrane [13]. A layer of lipids that is covalently joined to the peptidoglycan barrier by arabinogalactan makes up a significant portion of the cell wall. Additionally, immunogenic glycolipids are "extractable" from the cell wall. The cell wall's lipid-rich composition makes it hydrophobic and blocks the passage of water-soluble substances. It is believed that only water-filled porins may allow tiny hydrophilic substances to pass through the cell membrane, including several medications that are effective against *M. tuberculosis* [14] Reports on the existence of protein porins in *M. tuberculosis*, however, were missing but for other *mycobacterium* species, these porins are true. Specific protein abbreviated as CpnT (outer membrane channel protein) showed sensitivity to antibiotics in *M. bovis* (BCG) and *M. tuberculosis*. In different serotypes of *M. tuberculosis*, CpnT appears to be under positive selection, because of mutations in the CpnT gene [15]. However, the investigations support the existence of porins and their function in the uptake of tiny hydrophilic. It is also thought that the fluidity of the membrane is constrained by the physical arrangement of the lipids in the cell wall. The research showed that *M. smegmatis* has the lowest membrane fluidity of all the actinobacteria [16]. The length and presence of functional groups in mycolic acid are thought to affect this. It's interesting to note that ethambutol increases the fluidity of the membrane and the diffusion of substances across the cell membrane when *M. smegmatis* is exposed to subinhibitory concentrations of the drug.

To cite this article: Shahood SA, MZU Abidin, ZH Malik, AMA Khan & MR Mishra, 2023. Antibiotic Resistance in Mycobacterium tuberculosis: a Global Threat to Humans. Biological Times, 2(9):27-28.

The specific characteristics of the mycobacterial cell wall restrict water-insoluble compounds including the different groups of antibiotics, such as macrolide, tetracycline, and fluoroquinolone groups, from diffusing freely [17]. The rate of diffusion does, however, appear to be somewhat influenced by the hydrophobicity of the molecules, because hydrophobic molecules migrate more easily through bacterial cell envelope. Different studies showed that mutation in the structure of the cell membrane (lipid synthesis) of *Mycobacterium* may lead to resistance and it is a key factor in the intrinsic resistance of mycobacteria to many hydrophobic antibiotics [18].

***Mycobacterium tuberculosis* drug inactivation**

Antibiotics can be cleaved with the help of enzymes when they made an entry through the cell wall. For example, when β-lactam drugs gain entry into the bacterial cell, the β -lactamases enzymes are released which denature the β-lactam rings [19]. *M. tuberculosis* is inherently resistant to this class of antibiotics, according to early experiments using penicillin. One class beta-lactamase, designated BlaC, is encoded by the *M. tuberculosis* genome. BlaC is restricted to periplasmatic space and is either detached or anchored to the lipoprotein on the plasma membrane [20]. These enzymes of *M. tuberculosis* showed specificity in a broader way and it is β-lactamase which shows broad substrate specificity and is a well-thought-out broad-spectrum β-lactamase.

Antibiotics can also be rendered inactive by methylation or acetylation in addition to drug breakdown. To present, the increased intracellular survival protein's acetylation of a number of aminoglycosides used to treat drug resistance bacteria is an excellent method of drug inactivation by chemical alteration in *M. tuberculosis* [21] These have been shown to acetylate and inactivate the cyclic peptide antibiotic capreomycin and kanamycin A. The overexpression of intracellular proteins caused by mutations found in *M. tuberculosis* gives low-level resistance to kanamycin A.

In *M. tuberculosis*, a brand-new drug inactivation mechanism has just been identified. The pyrido-benzimidazole compound '14' has strong bactericidal activity against aerobically developing *M. tuberculosis.* A previously unidentified methyltransferase that is encoded by the gene Rv0560c may N-methylate compound 14. The decaprenyl phosphoryl-D-ribose 2-oxidase (DprE1), a key enzyme in the synthesis of arabinogalactan, is not susceptible to inhibition by the methylated molecule 14 [22]. Although *M. tuberculosis* and bacteria in general use this unique drug resistance mechanism, it has not yet been associated with any recognized clinical implications.

Conclusions

Antibiotic resistance nowadays has become a global problem. Doctors and scientists are using combinations of antibiotics against certain infections and drug-resistant strains of bacteria, particularly *Mycobacterium tuberculosis*. In the future, the focus is to determine the exact mechanisms of a drug and to prepare on drug that will overcome the resistance strains of the genus *Mycobacterium*.

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