Short Commentry

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Structural Analysis of Mycobacterium Tuberculosis Mutations to Investigate the Role in Antibiotic Drug Resistance

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Abstract:

Multidrug-resistant tuberculosis (MDR-TB) is among the most troubling component of the pandemic of anti-microbial resistance since TB patients that fail treatment have a high peril of death. Extensively drug-resistant tuberculosis (XDR-TB) has emerged as a major public health problem worldwide. Multidrug-resistant (MDR) Mycobacterium tuberculosis strains are resistant to at least the first-line antituberculotic drugs, rifampin (RIF) and isoniazid (INH), which are the mainstay of short-course chemotherapy for tuberculosis. Drug resistance arises when mutations, or chromosomal replication errors, occur in genes that encode sedate targets or drug metabolism mechanisms and effect the adequacy of hostile to tuberculosis treatments M. tuberculosis uses various mechanisms, including mutations in genes that code for drug target genes and become resistant to drugs and therefore, better comprehension of the molecular mechanism and genetic basis of development of resistance to drugs used in chemotherapy is required. Thus, in this study structural analysis of Mycobacterium Tuberculosis mutations is done to study protein-ligand interactions and thus highlight binding trends. Several mutations in different mycobacterium tuberculosis strains has been reported from different regions around the world. Mutations associated with multi/extensive drug resistance has been identified from literature and "The Comprehensive Antibiotic Resistance Database". Table 1 elaborated the data of some of the most frequent mutations.

Table 1; Summary of the mutations associated with First- and Second-line drug resistance

GENE	MUTATIONS	Resistance	Target
rpoB **(codon 513, 516, 522, 526, 531 and 533)**	V176F, S531L, H526W, D516V, D516F (Kazakhstan) D516Y	Rifampicin /rifampin	RNA polymerase
katG **(codon 315),** inhA **(promoter -15 nucleotide)**	S315T, S315R, S315N, C15T	Isoniazid	Catalase-peroxidase enzyme
embB	D240H, D311H, L239P, M306I, M306L, M306V, Y319C	Ethambutol	EmbB
rpsL rrs gidB	K43R, K88Q, K88R, T40I, A514C, C491T, A513T, A513C, C516T, V77G, A10P, A205A, L16R, E92D	Streptomycin resistant genes	Ribosomal S12 Protein

The current research aims to investigate the role of mutations for four first line antibiotics Rifampicin, Isoniazid, Streptomycin and Ethambutol that cause resistance in mycobacterium tuberculosis thus rendering TB untreatable. To accomplish the task, a ligand dataset of these four drugs have been created and their respective targets that include rpoB, katG, rpsL and embB genes are identified. A detailed analysis has been followed up to gather the reported mutations for these proteins. Moreover, structural analysis of mutated proteins has been carried out in comparison with normal proteins to measure the impact of mutations on secondary and tertiary structures. This information further helps in understanding the interactions of the antibiotic drugs in normal and mutated proteins to study the resistance pattern in first line antituberculotic drugs.

From the analysis of secondary structure of mycobacterium tuberculosis proteins, it had been found that secondary structure of normal rpsL gene proteins contained 2 helices, 6 strands and 9 loops and coils whereas mutated protein K43R has 5 strands, K88R has 1 helix and 8 loops/coils. While other two mutated proteins K88Q and T40I has same number of helices, strands and loops/coils as the normal protein. rpoB gene protein models has 38 helices both in normal and mutated protein structures. T508N has 34 strands/ sheaths while all other proteins including normal one has 35 strands. Number of loops/ coils vary in all proteins. Similarly, katG gene normal protein has 41 helices, 5 strands and 44 loops/coils. Whereas, 11 mutated proteins have 40, 43, 45 and 46 helices and 43, 45, 46, 47, 48, 49 loops/coils in their structures. Number of strands is 5 in both normal and mutated proteins. embB gene proteins has 10 helices, 12 strands in both normal and mutated structures and number of loops/coils vary i.e. 19 in normal protein and 20 and 21 in mutated proteins. These changes in secondary structure of mycobacterium tuberculosis normal and mutated proteins is due to the point mutations. This change can cause change in the binding site for the antituberculotic drugs thus causing resistance against respective first line drugs. Tertiary structure of all the four proteins of rpoB, katG, rpsL and embB shows little variation in structure of normal and mutated protein models. Single amino acid mutations slightly change the structure which affects the binding of the ligand i.e. drugs to the target protein.

Docking analysis and study of protein-ligand interaction shows that the ligand (drug) binds to a different residue in mutant proteins as compared to proposed binding active site residue in normal or wild type proteins. For example, in rpsL wild type or normal protein shows ligand interaction with His77 with one hydrogen bond and Val33 with two external bonds whereas drug binds to different residues in mutated proteins. rpoB proteins shows ligand interactions with normal protein at residue Val637 with one hydrogen bond. In mutated protein D516F drug/ligand binds to residue Arg63 with two hydrogen bonds. katG normal protein shows ligand interaction with residues Asn701 with one hydrogen bond and Leu43 with two hydrogen bonds. A93T shows interactions at residue Tyr608 with one hydrogen bond and Leu43 with one hydrogen bond. embB normal protein has ligand interactions at residue Val1048 with external bond. D240H has interactions at residue His1047, Pro834, Val1048, Tyr835, Arg1045 with one hydrogen bond. Thus, mutations cause change in the active site due to change in structure at secondary and tertiary level result in causing resistance.

The study concludes that overall change in secondary structure of proteins and thus tertiary structure would render the interactions of ligands basically first-line anti-TB drugs to change thus conferring resistance. Due to mutation, the target site has acquired change in structure that alter the binding site for the drug and resulted in development of drug resistance in mycobacterium tuberculosis.