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In-silico analysis of rifampicin resistance in *Mycobacterium tuberculosis*

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Rifampicin (RIF) is an important drug in the anti-tuberculosis therapy. Although rare, resistance to RIF is increasing because of its widespread application. RIF binds to the β subunit of DNA-dependent RNA polymerase (RNAP), close to the RNA/DNA channel and acts early in transcription and physically blocks the elongation of the growing RNA chain after 2-3 nucleotides have been added. The majority of mutations responsible for RIF resistance have been mapped to three distinct loci near the centre of the *rpoB* gene which codes for β subunit. The genetic basis for RIF resistance in approximately 95% of the cases is due to mutations in an 81-bp RIF resistance-determining region (RRDR) of the *rpoB* gene, corresponding to codons 507 to 533 which encodes for 27 amino acids based on *E. coli* numbering system. Mutations at positions 521, 526, 531 and 533 have been reported to be the most commonly involved codons. These mutants are generally associated with high-level RIF resistance (MIC<32 µg/ml) and are absent in susceptible organisms. Therefore, it is of interest to study the interactions between the clinical mutants (MTs) of RpoB and RIF which are responsible for mediating RIF resistance in MTB, using *in silico* approaches. In this direction, homology model of wild type (WT) of RpoB of MTB was generated using crystal structure of 2A68 (3 domains structure), which is considered as template and WT, and for MTs (H526D and L521M) substitutions were done at the respective positions with the help of MODELLER software. Followed by which, docking of WT and MTs of RpoB proteins with RIF was carried out by software-GOLD. The docking of RIF with WT and MTs showed higher values with WT compared to MTs. The high score in WT is may be due to lack of unfavorable substitutions which are present in the MTs. Molecular dynamics (MD) simulation is done for 4 nano-seconds with RIF which has shown the binding energy of -22.88 kcal/mol for the WT, while in case of MT such as H526D, the energy was found to be higher (-45.8 kcal/mol). For the MT-L521M, the bound RIF molecule after simulation has moved out from the active site of the target protein. These results suggest that substitutions have pronounced effect on the conformation of the MT proteins and eventually upon the RIF binding interactions leading to the cause of resistance. To our knowledge, this is the first *in silico* based evidence for clinical mutants of RIF resistance.

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