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Mycobacterial Diseases

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Perspective

Influence of Mycobacterial gene mutations on Rifampicin-Specific Phenotypic Resistance (RSPR)

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DESCRIPTION

Antibiotic tolerance refers to genetically susceptible bacterial subpopulations that die at a slower rate than the general population. Antibiotic tolerance is associated with a variety of phenotypes. Non-replicating persistence is the most studied, as non-or slowly-replicating bacteria are typically multi-drug tolerant. However, there is evidence that particularly in mycobacteria, the which are actively replicating bacteria can also be highly drug tolerant. This study focuses to discuss about tolerance to the first-line anti-tuberculous antibiotic rifampicin, which inhibits RNA Polymerase (RNAP), in actively growing cells that are called as Rifampicin-Specific Phenotypic Resistance (RSPR). It is well-known that mycobacteria can survive, but also actively grow in bulk-lethal rifampicin concentrations. Both specific translational errors involving the indirect tRNA, aminoacylation pathway and a paradoxical up regulation of rpoB in response to rifampicin-mediated RSPR have been identified through previous studies. Importantly, both RSPR mechanisms were confirmed in clinical isolates of *Mycobacterium tuberculosis*, confirming the clinical relevance of this type of antibiotic tolerance. Tn-Seq (Transposon Insertion Sequencing) has proven to be an effective tool for forward genetics in bacteria. Although Tnseq has been extensively used for identifying genetic factors involved in bacterial physiology, host-pathogen interactions, and antibiotic resistance. Tnseq can be used to identify the genetic factors involved in both hyper tolerance and hyper susceptibility against rifampicin in two models of rifampicin tolerance in *Mycobacterium smegmatis* (Msm). Deletion of the putative translation elongation factor in LepA mediates RSPR by disrupting the physiological transcriptional response of rpoB, and the mutations in lepA found to mediate rifampicin tolerance. Because these mutations are in conserved sites between *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, their phenotypes are likely to be conserved.

Insertion and deletion mutations in lepA gene

Transposon insertion in lepA was found to be a cause of increased rifampicin tolerance under all experimental conditions, and thus it is crucial to focus on lepA deletion for further investigation. For this, a strain of *Mycobacterium smegmatis* in which the lepA gene was deleted *via* recombineering is used. The MIC for several anti-mycobacterial antibiotics was observed and it was found to be similar in wild-type *Mycobacterium smegmatis* and lepA, indicating that deletion of lepA did not confer altered resistance, including rifampicin. However, when compared to the wild-type parent strain, the strain lacking lepA had significantly higher rifampicin survival, and this phenotype was complemented with wild-type lepA. There was no increased tolerance to isoniazid or streptomycin, indicating that lepA deletion was not the cause of non-specific antibiotic tolerance. A significant number of clinical isolates of *Mycobacterium tuberculosis* have mutations in the lepA gene. So, for this reason, a number of clinical isolate mutations that mapped to conserved residues in the protein's annotated GTP-binding domain should be used. The lepA strain was then supplemented with either the wild-type or mutated lepA genes. Surprisingly, all of the conserved mutations failed to fully complement lepA, but to varying degrees, implying that LepA function is lost in a proportion of circulating clinical *Mycobacterium tuberculosis* isolates.

CONCLUSION

Our transposon site insertion and deep sequencing (Tnseq) tools identify non-essential mycobacterial genes that cause rifampicin phenotypic resistance. It has been observed a number of genes previously linked to antibiotic tolerance in mycobacteria, as well as some new ones. MmpL11, Antigen85A, PstS, M SMEG5782c, and LytR are just a few of the proteins we found that are embedded in the cell wall/outer mycobacterial layer and/or are involved in cell-wall integrity. Finally, conserved mutations failed to complement lepA entirely, indicating the lost function of LepA among *Mycobacterium tuberculosis* isolates.

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