Antimicrobial resistance in Mycobacterium tuberculosis : mechanistic and evolutionary perspectives

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Antibiotic-resistant Mycobacterium tuberculosis strains are threatening progress in containing the global tuberculosis epidemic. Mycobacterium tuberculosis is intrinsically resistant to many antibiotics, limiting the number of compounds available for treatment. This intrinsic resistance is due to a number of mechanisms including a thick, waxy, hydrophobic cell envelope and the presence of drug degrading and modifying enzymes. Resistance to the drugs which are active against M. tuberculosis is, in the absence of horizontally transferred resistance determinants, conferred by chromosomal mutations. These chromosomal mutations may confer drug resistance via modification or overexpression of the drug target, as well as by prevention of prodrug activation. Drug resistance mutations may have pleiotropic effects leading to a reduction in the bacterium's fitness, quantifiable e.g. by a reduction in the in vitro growth rate. Secondary so-called compensatory mutations, not involved in conferring resistance, can ameliorate the fitness cost by interacting epistatically with the resistance mutation. Although the genetic diversity of M. tuberculosis is low compared to other pathogenic bacteria, the strain genetic background has been demonstrated to influence multiple aspects in the evolution of drug resistance. The rate of resistance evolution and the fitness costs of drug resistance mutations may vary as a function of the genetic background.
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