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Computer Based Identification of Possible Molecular Targets for Induction of Drug Resistance Reversion in Multidrug Resistant Mycobacterium Tuberculosis

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Abstract : Molecular docking approaches are widely used for design of new antibiotics and modeling of antibacterial activities of numerous ligands which bind specifically to active centers of indispensable enzymes and/or key signaling proteins of pathogens. Widespread drug resistance among pathogenic microorganisms calls for development of new antibiotics specifically targeting important metabolic and information pathways. A generally recognized problem is that almost all molecular targets have been identified already and it is getting more and more difficult to design innovative antibacterial compounds to combat the drug resistance. A promising way to overcome the drug resistance problem is an induction of reversion of drug resistance by supplementary medicines to improve the efficacy of the conventional antibiotics. In contrast to well established computer-based drug design, modeling of drug resistance reversion still is in its infancy. In this work, we proposed an approach to identification of compensatory genetic variants reducing the fitness cost associated with the acquisition of drug resistance by pathogenic bacteria. The approach was based on an analysis of the population genetic of Mycobacterium tuberculosis and on results of experimental modeling of the drug resistance reversion induced by a new anti-tuberculosis drug FS-1. The latter drug is an iodine-containing nanomolecular complex that passed clinical trials and was admitted as a new medicine against MDR-TB in Kazakhstan. Isolates of M. tuberculosis obtained on different stages of the clinical trials and also from laboratory animals infected with MDR-TB strain were characterized by antibiotic resistance, and their genomes were sequenced by the paired-end Illumina HiSeq 2000 technology. A steady increase in sensitivity to conventional anti-tuberculosis antibiotics in series of isolated treated with FS-1 was registered despite the fact that the canonical drug resistance mutations identified in the genomes of these isolates remained intact. It was hypothesized that the drug resistance phenotype in M. tuberculosis requires an adjustment of activities of many genes to compensate the fitness cost of the drug resistance mutations. FS-1 cased an aggravation of the fitness cost and removal of the drug-resistant variants of M. tuberculosis from the population. This process caused a significant increase in genetic heterogeneity of the Mtb population that was not observed in the positive and negative controls (infected laboratory animals left untreated and treated solely with the antibiotics). A large-scale search for linkage disequilibrium associations between the drug resistance mutations and genetic variants in other genomic loci allowed identification of target proteins, which could be influenced by supplementary drugs to increase the fitness cost of the drug resistance and deprive the drug-resistant bacterial variants of their competitiveness in the population. The approach will be used to improve the efficacy of FS-1 and also for computer-based design of new drugs to combat drug-resistant infections.

Keywords : complete genome sequencing, computational modeling, drug resistance reversion, Mycobacterium tuberculosis
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