[BIO06]

Interaction of isoniazid with *Mycobacterium tuberculosis* enoyl-acyl carrier protein reductase (INHA): from bioinformatics perspective

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The problem of tuberculosis drug resistance and the continuing rise in the disease incidence has prompted the research on new drug developments as well as on increasing the understanding of the mechanism of drug resistance. Molecular docking and molecular dynamics simulations were performed to study the binding of isoniazid (INH) onto the active site of InhA enzyme in an attempt to address the INH resistance of tuberculosis. The results support the theory that the activation of INH to INADH by KatG enzyme is highly desirable for the ultimate activity. It is shown that INADH has tremendously high binding affinity (nearly 3-fold) towards InhA forming more hydrogen bonds and better van der Waals, electrostatic, hydrophobic interactions and aromatic ring stacking interactions which have strengthen the binding of INADH compared to the parent drug (INH). S94A mutation caused INADH to deviate from its crystal structure probably due to the unfavorable contact between the hydrophobic Ala94 and the highly polar NADH moiety. However, the energetic differences revealed that S94A mutation is a low level resistance compared to the high level resistance due to mutation or absence of KatG enzyme. The simulation is able to address the resistance mechanism towards INH in InhA mutant strains of *M. tuberculosis*. The S94A substitution probably causes INH resistance through weak binding of INADH with InhA. We have also implicitly argued that the presence of KatG is highly necessary so as to convert the INH to INADH the ultimate inhibitor of InhA. In the wild type (WT) InhA, the INH derivatives have made not much influence towards InhA inhibitions as activated INH still the best inhibitor for InhA. In S94A MT InhA, INADH remains the best inhibitor. However, in the absent of activated INH, INH11 and INH16 remain a better inhibitor compare with un-hydrolyse INH and other INH derivatives. The study also suggests that designing of new anti-tuberculosis drug should not subject to KatG enzyme. By improving the INH structure similar to INADH structure might also be a viable approach to overcome INH resistant tuberculosis.