Truncated INH-NAD adduct, an active intermediate in the action of Isoniazid (INH) against InhA enzyme in tuberculosis

Tuberculosis (TB) remains as an important infectious disease, caused by *Mycobacterium tuberculosis* (MTB) which is responsible for around 1.5 million deaths and 9.6 million new cases annually. Isoniazid (INH), a bactericidal compound used as a first-line drug in the prevention and treatment of TB. The mechanism of INH action has been studied extensively. As INH is a prodrug, requiring activation by catalase-peroxidase (KatG) of MTB to generate an active INH intermediate which in the presence of NADH forms INH- nicotinamide adenine dinucleotide (NAD) adduct which inhibits InhA (2-trans-enoyl-acyl carrier protein reductase) affecting the synthesis of mycolic acid in tuberculosis. However, mutation in katG and/or ndh prevent adduct formation. Computational studies in our laboratory showed that a mutation in KatG (S315T/S315N) prevents free radical formation, thus in development of resistance to the drug. The truncated INH–NAD (oxidized) adduct, 4-isonicotinoylnicotinamide, isolated from urine samples of human TB patients treated with INH therapy is shown to have antimycobacterial activity. There are 17 metabolic enzymes of MTB which have been identified to bind INH–NAD(P) adducts coupled to Sepharose resin and out of those, six metabolic enzymes such as adenosylhomocysteinase (Rv3248c), universal stress protein (Rv2623), nicotinamide adenine dinucleotide (reduced)-dependent enoyl-acyl carrier protein reductase (Rv1484), oxidoreductase (Rv2971), dihydrofolate reductase (Rv2763c), pyrroline-5-carboxylate dehydrogenase (Rv1187) are having known three dimensional structure. These enzymes are reported to be involved in many important biochemical processes of MTB, including cysteine and methionine metabolism, mycobacterial growth regulation, mycolic acid biosynthesis, detoxification of toxic metabolites, folate biosynthesis, etc.

We have applied the computational approach to study the interaction between truncated INH–NAD adduct and INH-NAD(P)-binding proteins. In our docking study we have shown the mechanism of interaction of truncated INH-NAD adduct with six enzymes of MTB and found that INH–NAD adduct showed favorable binding interactions with docking energies ranging from -5.29 to -7.07 kcal/mol, thus possibly inhibiting different functional proteins and metabolic enzymes of MTB. Though, computational approach has been useful in elucidating mechanism of drug action, MTB culture studies extending this work will be useful in confirming the role of truncated INH-NAD adduct against different functional proteins of MTB in addition to InhA enzyme.

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Study of mechanism of interaction of truncated isoniazid-nicotinamide adenine dinucleotide adduct against multiple enzymes of Mycobacterium tuberculosis by a computational approach.
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