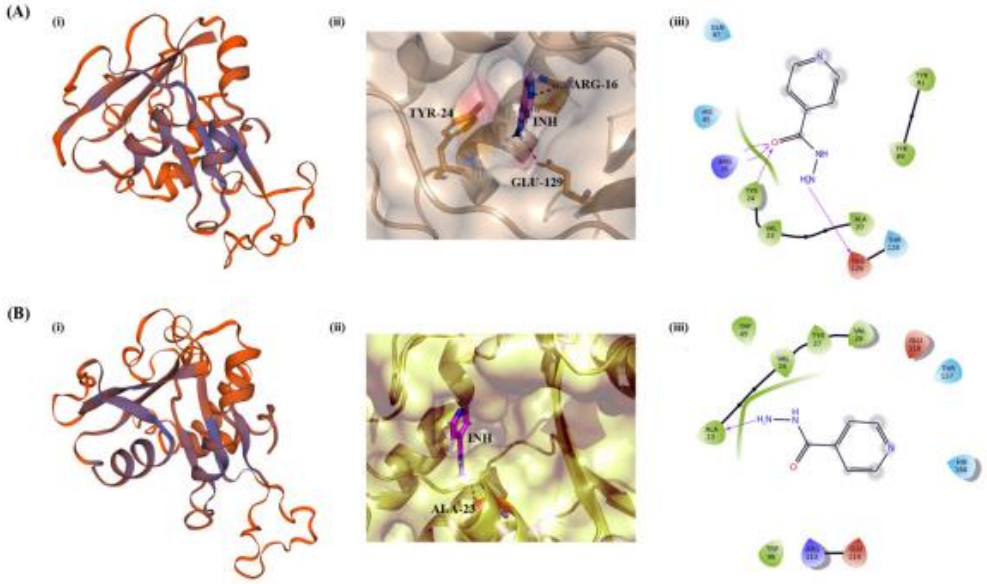
A novel mechanism of isoniazid resistance in *Mycobacterium tuberculosis*

Isoniazid (INH) is known to be acetylated in the liver and gastrointestinal tract of TB patients to form acetyl-INH, and the rate of this conversion can impact the outcome of treatment. Scientists at DBT's Rajiv Gandhi Centre for Biotechnology (RGCB), Thiruvananthapuram, hypothesized that *Mycobacterium tuberculosis* (MTB) might employ a similar mechanism to detoxify INH. To test this hypothesis, they cloned a few putative acetyltransferases in MTB and screened the purified enzymes for their acetyltransferase activity, and found that Rv2170 can catalyze transfer of the acetyl group of acetyl CoA to INH. Subsequently, acetyl-INH is broken down into two products, isonicotinic acid and acetylhydrazine. *M. smegmatis*, a fast growing, non-pathogenic mycobacterium which is normally susceptible to INH, is not inhibited by INH treated with Rv2170 *in vitro*. Mutant proteins of Rv2170 with amino acid substitutions in the INH binding pocket failed to modify INH. Recombinant *M. smegmatis* and avirulent *M. tuberculosis* H37Ra overexpressing Rv2170 acquired resistance to INH at minimum inhibitory concentrations that inhibited wild-type strains. Besides, intracellular *M. tuberculosis* H37Ra overexpressing Rv2170 survived better inside macrophages when treated with INH. The results strongly indicate that Rv2170 acetylates INH, and this could be one of the strategies adopted by at least some *M. tuberculosis* strains to overcome INH toxicity, although this needs to be validated in INH resistant clinical strains.



Tuberculosis (TB), caused by *M. tuberculosis*, has been one of the major reasons for death due to infections in humans. In spite of effective anti-TB drugs and the BCG vaccine, we still could not eradicate tuberculosis. *M. tuberculosis* is an incredibly successful pathogen with many cards up its sleeve to survive for decades within the human body. INH is one of the most potent first-line drugs used for the treatment of tuberculosis. INH actually is a pro-drug, and the bacterial KatG enzyme converts it into its active form which kills *M. tuberculosis* by hindering the biosynthesis of mycolic acid, a major component of the mycobacterial cell wall.

INH resistant clinical isolates usually have mutations in their *katG*, *inhA*, *ahpC*, *kasA*, and *ndh* genes. Interestingly, about 10% of INH resistant strains do not have mutations in any of these genes, suggesting that these strains may adopt some other mechanism to become resistant to INH. Acetylation is a well-known mechanism to modify drugs and drug targets to gain resistance.

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