Poster Presentation

MS45.P06

Structural insight into the function and anti-TB pro-drug activation by KatG

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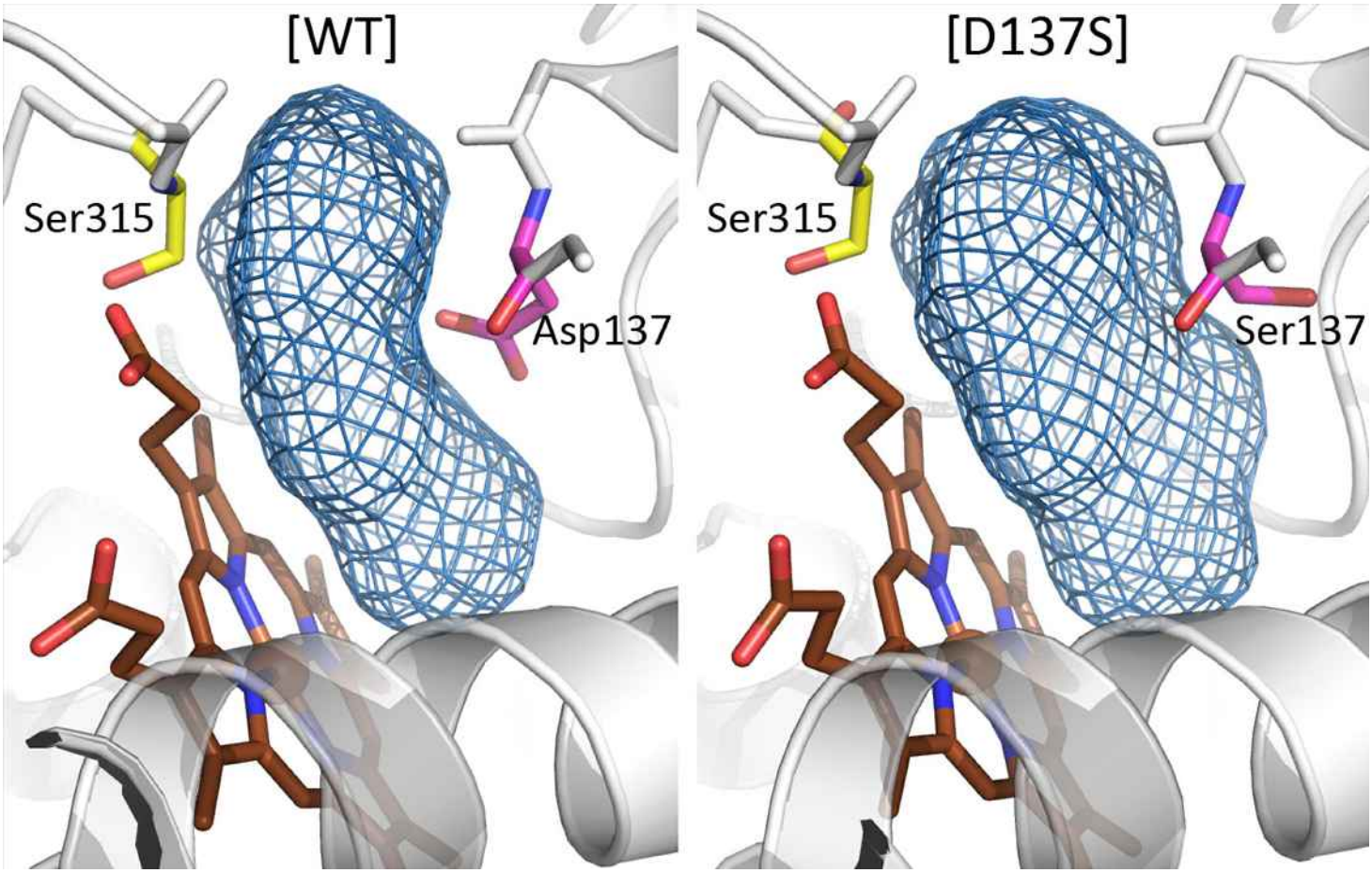
Catalase-peroxidase (KatG) is a dual functional enzyme with both catalase and peroxidase activity. KatGs protect aerobic microorganisms from oxidative damage through their high catalase activity, and in Mycobacterium tuberculosis (M.tb.) KatG's peroxidatic activity is central in converting the anti-tuberculosis (TB) pro-drug isoniazid (INH) into an active bactericidal molecule in vivo. There are several antibiotics currently in use to treat TB with INH being one of the first anti-TB agents. A central goal is to understand the catalytic function of M.tb. KatG in drug activation and how mutations in KatG found in INH-resistant strains interfere with this process. One of the most common INH-resistant M.tb. strains has the KatG[Ser315Thr] mutation, previously reported to cause narrowing of a substrate access channel. We have now solved the structure of another mutant [Asp137Ser], which shows enhanced INH-activation ascribed to an enlarged access channel. This study demonstrates that altering the dimensions of the bottleneck in the substrate access channel in KatG can impede or enhance INH peroxidation rates relative to the WT enzyme.

[1] *X. Zhao, H.-P. Hersleth, J. Zhu et al, Chem. Commun., 2013, 49, 11650-11652,* ***[2]*** *X. Zhao, H. Yu, S. Yu et al, Biochemistry, 2006, 45, 4131-4140,* ***[3]*** *X. Zhao, A. Khajo, S. Jarrett, J. Biol. Chem., 2012, 287, 37057-37065*



Keywords: catalase-peroxidase, Mycobacterium tuberculosis, protein crystallography