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Structural Biology 2020: Structural and functional characterization of mycolic acid methyl transferase A3 (MmaA3) enzyme of Mycobacterium tuberculosis - Bhawna Chaudhary - TERI School of Advanced Studies (SAS)

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Abstract:
Mycobacterium tuberculosis (Mtb) is the causative agent of tuberculosis (TB), which is a primary cause of mortality and morbidity worldwide. Mtb during course of time re-established themselves to evolve into Multi Drug Resistant Strains (MDR) and extensively Drug Resistant strains (XDR) Mtb have been concentrated on the unique chemical entities present in the cell envelope of this bacterium as it has been recognized as potential drug target. The cell wall of Mtb have a complex hydrophobic array of unique glycolipids and mycolic acids of which the mycolates are β-hydroxy fatty acids with a long α-alkyl side chain. The present study is mainly focusing on the cell wall of Mtb and more specifically the mycolate synthesis. Any structural alterations of mycolates impacts the virulence nature of Mtb. The mycolic acid biosynthesis pathway involves a series of enzymes and we are targeting the methyl transferase enzyme-MmaA3. During the synthesis of the cis-C59-methoxy- and trans- C60-methoxy-meroacids the MmaA3 enzyme introduces a methyl residue in the secondary alcohol compound which is crucial in mycolate synthesis. The mycolates thus generate virulent bacteria that are capable of evading host immune responses. This work aims to provide the structural information as how the enzyme MmaA3 functions to regulate the biosynthesis pathway of mycolic acid. This study will improve our understanding of the enzyme (MmaA3) mechanism of action and administer a rational approach to design an inhibitor against this bacterium and offer an in-depth perspective on how the Mtb in the host cells develop drug resistance.

Introduction: Tuberculosis (TB) is one of the world's deadliest sicknesses. The Centers for Disease Control and Prevention has revealed that every year, 8,000,000 individuals around the globe become debilitated with TB and there are more than 2,000,000 TB-related passings around the world. In addition, 33% of the total populace is tainted with TB. In this manner, Mycobacterium tuberculosis (the causative specialist of TB) is obviously the most prevalent worldwide human pathogen. Two decades back, it was believed that TB was leveled out and that it involved time before it would be annihilated. Today, this illness has restored itself because of a few variables. The absence of medication consistence, the presence of different medication safe strains, and the AIDS pestilence are a couple of elements that have prompted the resurgence in TB. Medication obstruction emerges following deficient consistence, and AIDS patients with debilitated invulnerable framework are entirely powerless to M. tuberculosis and the standard reason for death.

The cell envelope of M. tuberculosis is particular and is related with its pathogenicity. Highlights that are unmistakable in the phone envelope are the nearness of arabinogalactan-mycolate covalently connected to the phone divider peptidoglycan by means of a phosphodiester bond situated on the inward handout of the external layer and of a free glycolipid called trehalose dimycolate (TDM), which amasses in a rope like design on the outside of the phones . This gives a thick layer of lipid on the external piece of the cell and shields the tubercle bacillus from toxic synthetic compounds and the host's safe framework. Mycolic acids are the significant constituents of this defensive layer. They likewise assume other significant jobs as basic parts of the cell divider and envelope. All the more explicitly, the cyclopropane rings in mycolic acids of M. tuberculosis add to the auxiliary respectability of the cell divider complex and shield the bacillus from oxidative pressure (hydrogen peroxide).

Cancellation of the proximal cyclopropane ring of α-mycolic corrosive or of methoxy-and keto-mycolates in M. tuberculosis prompts a critical lessening in development of the two freaks in the mouse model of contamination (structures are demonstrated as follows). An erasure of the keto-mycolates prompts confined development of this freak in macrophages. Hence, the fine structure of mycolic acids is related with harmfulness of M. tuberculosis.

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