

Molecular basis for missense-mutation induced functional loss in Mtb PapA2

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Tuberculosis is caused by Mycobacterium tuberculosis complex (MTBC) members that have been classified into seven main phylogenetic lineages based on genetic diversity[1]. Though advent of whole genome sequencing has developed our understanding on association of these genetic variations and on infection outcome and inflammatory response[1], effect of genetic variations on protein structure-function is not well established.

Association of genome wide variations with structure-function of protein(s) involved in cell wall biogenesis expected to have mechanistic implication. The glycolipids of Mtb cell wall are potent host immune modulators[2]. Our genome wide variation analysis of Mtb strains from lineage-1 and lineage-3 of Indian subcontinent showed enrichment of missense mutations in lipid metabolic pathways. One of such missense mutation-A83P was found in papA2 gene of specific strains of lineage-1. PapA2 is an acyltransferase involved in the trans-esterification reaction in cell wall associated sulfoglycolipid biosynthesis. Further, these strains were found to be devoid of sulfoglycolipid and have been validated to result from reported missense mutation. Intrigued with this proline mutation induced loss of function, we sought to determine structure of PapA2.

PapA2 belongs to relatively structurally uncharacterized protein family named polyketide synthase associated protein of acyltransferase (PapA). This family comprises of 5 protein members (PapA1-5), each of them catalyze trans-esterification reaction in biosynthesis of glycolipids specific to pathogenic strains of mycobacteria[2] and have been well-established to have host immune modulatory function[2]. Even-though crystal structure of PapA5 has been solved at 2.75Å[3], considerably lower sequence identity (

[1] Krishnan N, et al. (2011). PLoS ONE 6(9):e23870.

[2] C. Passemar et al. (2014). Cellular Microbiology, 16(2), 195–213

[3] J. Buglino et al. (2004). J Biol Chem 279(29):30634-42

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