Poster Presentation

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Crystal structure of M. tuberculosis phosphopantetheinyl transferase PptT

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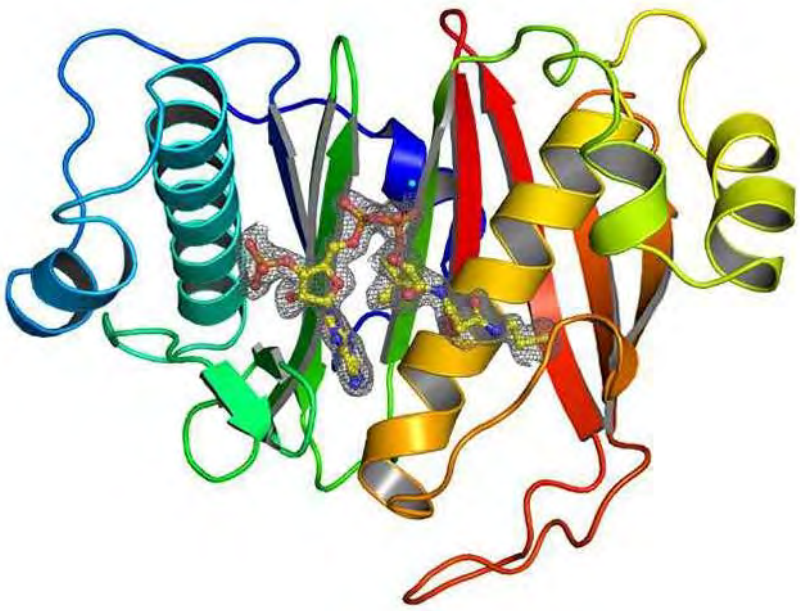
Phosphopantetheinyl transferases (PPTases) are essential enzymes that catalyze covalent attachment of the 4'-phosphopantetheine (4'-PP) moiety from coenzyme A (CoA) to a conserved serine residue on acyl (ACP) and peptidyl carrier proteins (PCP) [1]. This post-translational modification converts the inactive apo-carrier proteins to the functional form, shuttling the intermediates of biosynthetic reactions catalyzed by fatty acid synthases (FAS), polyketide synthases (PKS) and non-ribosomal peptide synthetases (NRPSs). In Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), two PPTases, AcpS (type-I) and PptT (type-II), are involved in the biosynthesis of essential lipids, virulence factors and siderophores, activating over 20 target proteins [2]. These two proteins have been shown to be independently essential, suggesting that PPTases could be targeted against tuberculosis [2, 3]. We have expressed the Mtb-PptT protein as a fusion protein with maltose binding protein (MBP). The use of the MBP-PptT fusion protein overcame stability and solubility problems and resulted in successful crystallization. The structure of Mtb-PptT in complex with CoA was determined from the crystal of the fusion protein, solved at 1.75 Å resolution. Excellent electron density is present for all parts of the CoA molecule, revealing a conserved CoA-binding mode. Conformational and charge distribution differences in the putative ACP binding cleft, however, suggest a different mode of ACP binding compared to other homologues. This is the first and only three-dimensional structure of a type-II PPTase from pathogenic bacteria, providing structural features that can be exploited in drug development when compared with its human counterpart.

[1] *Beld, J., et al., The phosphopantetheinyl transferases: Catalysis of a post-translational modification crucial for life. Natural Product Reports, 2014. 31(1): p. 61-108.,* ***[2]*** *Chalut, C., et al., The nonredundant roles of two 4'-phosphopantetheinyl transferases in vital processes of Mycobacteria. Proceedings of the National Academy of Sciences of the United States of America, 2006. 103(22): p. 8511-8516.,* ***[3]*** *Leblanc, C., et al., 4'-Phosphopantetheinyl Transferase PptT, a New Drug Target Required for Mycobacterium tuberculosis Growth and Persistence In Vivo. PLoS Pathogens, 2012. 8(12).*



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