Poster Presentation

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Bacterial flavin homeostasis: the role of an FAD pyrophosphatase/FMN transferase

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Treponema pallidum, an obligate parasite of humans and the causative agent of syphilis, has evolved the capacity to exploit host-derived metabolites for its survival. Flavin-containing compounds are essential cofactors that are required for metabolic processes in all living organisms, and riboflavin is a direct precursor of the cofactors FMN and FAD. Unlike many pathogenic bacteria, Treponema pallidum cannot synthesize riboflavin; we recently described a flavin-uptake mechanism composed of an ABC-type transporter [1]. However, there is a paucity of information about flavin utilization in bacterial periplasms. We have identified the TP0796 lipoprotein as a previously uncharacterized Mg2+-dependent FAD pyrophosphatase/FMN transferase within the ApbE superfamily [2,3]. Biochemical and structural investigations revealed that the enzyme has a unique bimetal Mg2+ catalytic center. Furthermore, the pyrophosphatase activity is product-inhibited by AMP, indicating a possible role for this molecule in modulating FMN and FAD levels in the treponemal periplasm. The ApbE superfamily was previously thought to be involved in thiamine biosynthesis, but our characterization of TP0796 prompts a renaming of this superfamily as a periplasmic flavin-trafficking protein (Ftp). Treponemal Ftp (Ftp_Tp) is the first structurally and biochemically characterized metal-dependent FAD pyrophosphatase/FMN transferase in bacteria. We have shown in vitro and in vivo that Ftps from several types of pathogenic bacteria are capable of flavinylating proteins through covalent attachment of FMN via a phosphoester bond to threonine residues of an appropriate sequence signature. Progress on the structural characterization of a product of this post-translational modification will be presented. This new paradigm for a bacterial flavin utilization pathway may prove to be useful for future inhibitor design.

[1] *R. Deka, C. Brautigam, B. Biddy, et al., mBio, 2013, 4, e00615-e00612,* ***[2]*** *R. Deka, C. Brautigam, W. Liu, et al., Journal of Biological Chemistry, 2013, 288, 11106-11121,* ***[3]*** *Y. Bertsova, M. Fadeeva, V. Kostyrko, et al., Journal of Biological Chemistry, 2013, 288, 14276-14286*

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