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cAMP mediated cell signaling in mycobacteria
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Abstract:

Mycobacteria contain an abundance of proteins involved in cyclic AMP (cAMP) metabolism. Genome analysis followed by biochemical studies have revealed that a number of enzymes are capable of synthesizing and regulating cAMP levels in these bacteria, under different environmental conditions. Interestingly, only a single cAMP phosphodiesterase has been characterized so far, but the ability of mycobacteria to secrete large amounts of cAMP suggests that secretion, rather than hydrolysis of cAMP, may be a more efficient means of regulating intracellular cAMP. The importance of secreted cAMP in modulating macrophage response to *Mycobacterium tuberculosis,* the causative agent for tuberculosis, has been described, and elevated levels of cAMP of bacterial origin are observed in macrophages following infection by mycobacteria. The high levels of cAMP found in both pathogenic and non-pathogenic mycobacteria however suggest that basic cellular processes are regulated by cAMP in these bacteria. Thus, it is pertinent to study various aspects of bacterial intra- and extra-cellular cyclic nucleotide signaling so that the potential of a bacterium to interfere with host cyclic nucleotide cascades can be determined. In *M. tuberculosis*, high levels of cAMP are synthesized by 16 adenylyl cyclases, and the gene Rv0805 codes for the only known cAMP phosphodiesterase (PDE), which hydrolyses it and thus shuts down the cAMP-mediated signaling. Interestingly, orthologs of Rv0805 are found only in pathogenic mycobacteria.
cAMP in mycobacterial cells binds to several cAMP-binding proteins and thereby allosterically activates them. In *M. tuberculosis* there are 11 proteins with cAMP-binding domain and 3 proteins with a GAF (common to cGMP phosphodiesterases, Anabaena adenylyl cyclase and *E. coli* FhlA transcription factor) domains, fused to other diverse domains. These proteins carry out different activities upon cAMP binding, acting as transcription factors, ion channels or enzymes.
In my talk I will summarize our recent work on the only known cAMP PDE from *M. tuberculosis*, Rv0805 protein, and its mammalian ortholog, MPPED2. Furthermore, I will also present our recent data on a unique mycobacterial cAMP-regulated acetyltransferase.