STRUCTURAL AND FUNCTIONAL STUDIES OF MYC OBACTERIAL SER/THR PROTEIN KINASES AND PHOSPHATASES

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M. tuberculosis pathogenicity relies on the peculiar ability of this microorganism to survive and replicate inside human macrophages, establishing persistent infection. To understand the pathogen response to the host's environment, we are studying molecular mechanisms involved in mycobacterial signal transduction using a combined approach of X-ray crystallography, biochemistry and physico-chemistry in solution.

The essential Ser/Thr kinase PknB and its cognate phosphatase PstP are encoded in a conserved operon thought to be involved in the control of cell shape and division. Structural and biochemical studies of both proteins have revealed a striking similarity in protein fold and catalytic mechanism when compared to their eukaryotic counterparts, suggesting similar implications in reversible phosphorylation signalling networks.

Here we report studies of kinase-substrate and kinase-inhibitor interactions that provide hints to identify putative signal transduction pathways in mycobacteria and to develop novel compounds with potential therapeutic applications. Furthermore we report the atomic resolution structures of different phosphatase-ligand complexes that give new insights into the mechanism of a large class of eukaryotic and prokaryotic Ser/Thr protein phosphatases.

Keywords: mycobacteria, signal transduction, atomic resolution, catalytic mechanism