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Investigating the role of arginine phosphorylation in the regulation of Clp protease-mediated degradation of cellular proteins in *Mycobacterium tuberculosis*

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Mycobacterium tuberculosis remains a leading cause of mortality worldwide. Increasing antibiotic resistance associated with the bacterium makes it critical to study potential targets for development of novel therapeutics. The Clp protease system which comprises of a peptidase barrel (ClpP) and an unfoldase (ClpC1 or ClpX) has been studied extensively in a host of other bacteria and is essential for protein homeostasis and viability in mycobacteria. This work proposes to describe the relationship between arginine phosphorylation tagging (as carried out by a specific arginine kinase McsB which is well characterized in *Bacillus subtilis*) and the biochemical activity of the Clp protease system in *Mycobacterium tuberculosis*. To study the arginine phosphorylation mechanics further, *in vitro* reconstruction of the McsB-ClpC1P1P2 system was done to test the direct correlation between arginine phosphorylation tag and substrate recognition by ClpC1 and its eventual degradation by the ClpP1P2 peptidase. Epitope-tagged active-site mutants of ClpP1 and ClpP2 would be utilized in an *in vivo* substrate-trapping analysis to reveal arginine phosphorylated ClpC1P1P2 substrates within the degradome to be generated upon appropriate affinity-based pull-down and quantitative mass spectrometry. More specifically, an arginine phosphatase trap (YwlE C7A mutant) has been constructed and would be used for identification of arginine-phosphorylated substrate proteins and interaction partners in lysate from *Mycobacterium tuberculosis* or its non-pathogenic close relative *M. smegmatis*. In totality, the proposal hypothesizes that arginine phosphorylation plays a key role in marking protein substrates for Clp-mediated proteolysis in *Mycobacterium tuberculosis*.

Biography

Emmanuel Ogbonna is a PhD student at the University of Delaware. He works in the Schmitz Lab in the Department of Biological Sciences, which is a protein biochemistry and structural biology laboratory that studies the caseinolytic proteases (Clp proteases) in Mycobacterium tuberculosis(Mtb), with the aim of understanding how the component proteins work, and how they interact with specific substrates. He had previously worked on identifying substrates for the ClpXP1P2 system in Mtb, but now studies how some of these substrates might be specifically tagged on arginine residues prior to degradation by the Clp proteasome-like machinery.

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