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A study of the interaction mechanism of GTP with CodY of *Bacillus anthracis*

Shikha Joon[31a], Monisha Gopalani[1a], Amit Rahi[1a], Parul Kulshreshtha[2b], Himanshu Gogoi[1b], Sonika Bhatnagar [3*] and **Rakesh Bhatnagar[1**]**
Jawaharlal Nehru University, India

Bacillus anthracis, a prioritized bioterrorism agent, is a gram-positive, sporulating, non-motile, aerobic bacterium which causes the fatal zoonotic disease, anthrax, with humans as contingent victims. CodY, a global transcriptional regulator, controls diverse cellular activities such as metabolism, amino acid biosynthesis and transport systems, nitrogen uptake, motility, sporulation, pellicle, and biofilm formation, and most importantly virulence in almost all low G+C gram-positive bacteria. In *B. anthracis*, about 500 genes are perceived to be the targets of CodY, including the master regulator AtxA, which is pivotal to the manifestation of toxic constituents; namely a lethal factor, edema factor and protective antigen. GTP and Branched Chain Amino Acids are the metabolic effectors of CodY, which affects its DNA-binding ability. In order to gain an insight into the interaction mechanism of CodY and GTP, of which scarce is known presently, we carried out an *in vitro* GTP binding assay. We have demonstrated that CodY of *B. anthracis* binds to GTP. Homology modeling and sequence/structure analysis of CodY of *B. anthracis* revealed conserved GTP binding residues. Interestingly, we found that the CodY of *B. anthracis* could undergo autophosphorylation with GTP as a phosphoryl group donor. Furthermore, the phosphorylation site mutant (Ser^{215} to Ala^{215}) of CodY failed to retain this autophosphorylation activity and hence is the critical residue involved in autophosphorylation. Since the Ser^{215} lies in the Helix-turn-Helix DNA binding motif of CodY and is conserved amongst its homologs, autophosphorylation may be speculated as a self-regulatory mechanism of CodY activity in the cell. Inquisitively, we proceeded to test the GTPase activity of CodY by thin-layer chromatography and found that the recombinant protein could withal hydrolyze GTP, albeit weakly, as quantified spectrophotometrically. Predicated on these findings, we conclude that in contrast to its homologs in other organisms, CodY of *B. anthracis* exhibits unique biochemical attributes such as GTP hydrolysis and autophosphorylation, which might be further exploited as a novel drug target.

shikhasriv86@gmail.com