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Structural Insights into Mechanism of Antibiotic Regulation in Streptomyces

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Streptomyces species are well-known for their wide variety of biologically active secondary metabolites and contribute to two-third of naturally occurring antibiotics. Production of antibiotics and resistance pathways in these species are dictated by interplay of transcriptional regulatory proteins that trigger downstream responses to either small diffusible molecules (autoinducers) or by binding to the antibiotic intermediates. These regulators have a ligand binding site and a DNA binding site and they carry out their transcription regulation via conformational changes induced upon ligand or DNA binding. To decipher the structural mechanism of action here we present the crystal structure of CprB in complex with its consensus DNA element to a resolution of 3.2 Å. The structure revealed that CprB belongs to the tetracycline family of antibiotic resistance efflux pumps regulators. CprB binds to the DNA as a tetramer via the helix-turn-helix (HTH) motif with the mode of DNA binding is most analogous to that observed for the broad spectrum multidrug resistance regulator QacR from Staphylococcus aureus. The binding of the DNA induces the restructuring of the CprB dimeric interface, thereby inducing a pendulum like motion of the HTH motif that inserts into the major grove of the DNA. A genome wide search for the cognate DNA element revealed that CprB serves as an autoregulatory protein and binds to its own promoter sequence. Our studies suggest that CprB is a part of a network of proteins that regulate the antibiotic production and resistance pathways in Streptomyces. Fluorescence anisotropy lifetime studies performed with both consensus and CprB promoter helped in concluding that both the sequence have an analogous mode of binding with the CprB DNA exhibiting a stronger binding profile as supported by ITC studies. A sequential binding mode, similar to a clamp and click model of binding was proposed.

Keywords: streptomyces, antibiotic, CprB