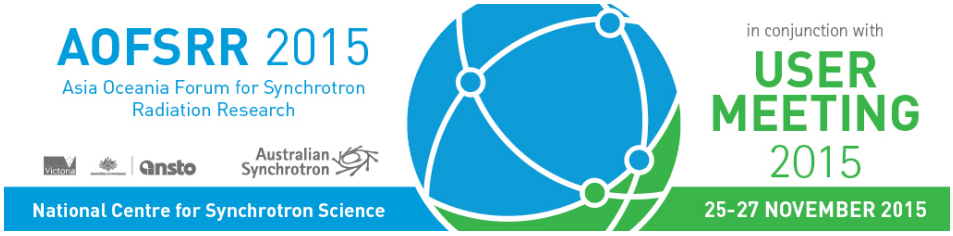

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Structural and functional investigation of CprB, a member of the TetR-family of proteins from Streptomyces coelicolor A3(2)

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Metabolic pathways activated by small chemical signaling molecules in the soil-dwelling, filamentous Gram-positive bacterial genus *Streptomyces* regulate antibiotics production, morphogenesis and resistance mechanisms. These species produce a wide spectrum of biologically active secondary metabolites contributing to > 70% of the known naturally occurring antibiotics. Small diffusible molecules, γ-butyrolactones (GBLs) are signaling molecules in *Streptomyces* and interact with transcriptional regulatory proteins that trigger downstream responses. Their identity and mode of action in *Streptomyces coelicolor* is hitherto unknown. In this investigation, purified CprB, a GBL receptor, was used as an affinity matrix to enrich and identify the target molecule(s) from an extracellular extract of *S. coelicolor*. Results from LC-ESI-MS/MS studies of compounds bound to CprB suggest that there is more than one signaling molecule that controls its DNA binding activity. Furthermore, in order to decipher the structural basis and associated conformational changes during CprB-DNA interaction, we here present a CprB-DNA complex crystal structure at 3.25 Å resolution. CprB binds to the DNA as dimer of dimers via the helix-turn-helix (HTH) motif with the mode of DNA binding analogous to the broad spectrum multidrug resistance regulator QacR from *Staphylococcus aureus*. Binding of the DNA induces restructuring of the CprB dimeric interface, thereby triggering a pendulum-like motion of the HTH motif. Our studies suggest that CprB serves as an autoregulator and is a part of a regulatory network for antibiotic production and resistance pathways responding to signalling molecules in *S. coelicolor*.

Keywords

Antibiotic production, Resistance, Streptomyces coelicolor, CprB-DNA complex, Signaling molecules,

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