Poster Presentation

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Structural basis of DNA sequence recognition by the response regulator PhoP

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The PhoP-PhoR two-component system plays a key role in regulating virulence of Mycobacterium tuberculosis. The response regulator PhoP is a transcription regulator, and it regulates expression of more than 100 genes. PhoP belongs to the OmpR/PhoB subfamily of response regulators. Despite extensive research in recent years, the molecular mechanism of DNA sequence recognition by this large subfamily of response regulators is not fully understood, especially the role of the N-terminal regulatory domain on DNA binding of the effector domain. Here we present a crystal structure of the full-length PhoP in complex with a direct-repeat DNA sequence. PhoP binds to DNA as a dimer. The two effector domains bind in tandem, each interacting with a half site of the direct repeat DNA. The DNA recognition helix inserts into the major groove, reading the sequence of a 7-bp motif. The wing residues interact with the downstream sequence, with a conserved arginine side chain inserting into the minor groove. Surprisingly, the regulatory domain also forms a tandem arrangement, instead of the anticipated symmetric dimer. The regulatory domain of the upstream protomer interacts with both domains of the downstream protomer. The structural elements of the alpha4-beta5-alpha5 face, which often found to be involved in dimer interface of the regulatory domain, play important roles in the interactions between the protomers. The crystal structure explains why PhoP recognizes direct repeats of two 7-bp motifs with a strict spacing of 4 bp and the highly cooperative binding of the two monomers. Detailed analysis of the structure along with analysis of the DNA sequence requirements and ITC measurements of protein-DNA binding interactions will be presented.

Keywords: protein-DNA complex, response regulator, transcription regulation