Poster Presentation

MS93.P03

Understanding disease mutations from the crystal structure of SOX9 with DNA

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SRY(Sex determining Region Y)-box or SOX transcription factors are important in early development and maintenance of different cell pools after birth. Of the ~20 SOX proteins (SRY, SOX1-SOX15, SOX17, SOX18, SOX21 and SOX30), SOX2, SOX9 and SOX10 mutations are primarily disease-associated: SOX2 with Combined Pituitary Hormone Deficiency, Microphthalmia, Septo-optic dysplasia and anophthalmic syndrome; SOX9 with Campomelic Dysplasia (affects development of the reproductive and skeletal system); and SOX10 (~94% sequence identity to SOX9) with Waardenburg Syndrome (affects audition and pigmentation in hair, eyes and skin; and specifically with WS types 2 and 4). As part of our Protein Structure Initiative (PSI)-Biology partnership, we performed structural and mutational analyses including x-ray crystallography and surface plasmon resonance assays, on the DNA-binding HMG domain of SOX9 with duplex DNA. Crystals were obtained in C222 space group and the structure was determined by molecular replacement to 2.77 Å resolution with final Rcryst/Rfree of 24.8/27.8%. The overall structure of the SOX9-DNA complex is similar to other SOX/SRY protein complexes. The SOX9-DNA protein-DNA interactions suggested a panel of mutations to assay for biochemical activity, which allowed us to understand the molecular basis of five mutations identified in Campomelic Dysplasia. These mutated residues have direct contact with DNA as well as indirect contacts, i.e., these mutations lead to allosteric secondary structure changes in the protein, which affect residues in direct contact with DNA. Due to the very high sequence identity between SOX9 and SOX10, our crystal structure also helps to rationalize the effect of SOX10 mutations in Waardenburg Syndrome. This work is supported by NIH grants U54 GM094586 and U01 GM094614. SSRL operations are funded by DOE BES, and the SSRL SMB program by DOE BER, NIH NCRR BTP and NIH NIGMS.

Keywords: PSI-Biology, Transcription factor, Stem Cell Biology