BBB seminar (BMED380)

SCAN ME

Thursday, April 13, 14:30 at the BBB, Auditorium 4

Structural insights into SMAD function

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SMAD proteins are highly conserved transcription factors that act as downstream effectors of Transforming Growth Factor Beta (TGFβ) signaling. This cascade plays key roles in embryonic development, tissue regeneration, immune system maintenance and neuroprotection. R-SMADs and SMAD4 are modular proteins of around 50 kDa that share a common architecture; two globular domains connected via a flexible and partially structured linker. In healthy conditions, external TGFβ stimuli induce the pathway's receptors to phosphorylate two serine residues at the C-terminus of R-SMADs. Thus, these proteins are activated and form heterotrimers with SMAD4. These complexes constitute the transcriptionally active units that translocate into the nucleus and, together with other cofactors, drive gene expression. Defects in the TGFβ cascade are linked to diseases. Mutations in SMAD2 and SMAD4 inactivate the pathway's tumor suppressor function in cancer and de novo single point mutations cause developmental pathologies, including cardiovascular disorders and Myhre Syndrome.

Our laboratory has been working on SMADs for the last ten years. We have determined several complexes of the MH1 domains bound to DNA, and of the linkers bound to activators and ubiquitin ligases. Very recently, we developed a multidisciplinary approach that combines X-ray structures, NMR information, MD simulations and SAXS data, has resulted in the integrative description of the conformational landscape and stoichiometry of isolated SMAD2 and SMAD4 full-length proteins in solution. I will present our recent advances in the structures of SMADs and FoxH1, one of its cofactors, and whose DNA-interacting domain structure we have recently unveiled. Combined with programs of screening and chemical biology these novel insights are aiding in the development of potential novel therapies for cancer and Myhre Syndrome.

Chair: Aurora Martinez <aurora.martinez@uib.no>, Dept. of Biomedicine