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Combining low (SAXS) and high (crystallography) resolution structural analysis to resolve the activation mechanism of Vascular Endothelial Growth Factor Receptors

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Understanding the structure of a protein gives insights into its cellular functions, but obtaining high resolution structural information on large, flexible protein complexes or membrane proteins is very challenging. Therefore, we have combined crystallography with solution small-angle X-ray scattering (SAXS) experiments for studying Vascular Endothelial Growth Factors. VEGFs regulate blood and lymph vessel formation by activating receptors VEGFR-1, -2 and -3. We solved structures of VEGFs in complex with the ligand binding domain D23 of VEGFR-2 by crystallography [1] and generated a model of the full length extracellular domain using SAXS data [2]. Combined with thermodynamic characterization, this data allowed us to (i) visualize the details of the ligand binding with insights into receptor specificity, (ii) pin-point the domains which undergo major conformational re-orientation upon ligand binding and (iii) postulate a proofreading mechanism which ensures that spontaneous receptor activation in the absence of ligand is efficiently suppressed.

[1] Brozzo et al., submitted
[2] Kisko et al., FASEB J 2011

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