Crystal Structure of the HGF β-chain in Complex with the Sema Domain of the Met Receptor

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The Met tyrosine kinase receptor and its ligand, hepatocyte growth factor (HGF), play a key role during development as an important switch that stimulates proliferation, branching and motility. Inappropriate activation of Met signalling promotes invasive growth of many tumor types, which makes Met and its ligand attractive targets for therapeutics. HGF undergoes a maturation cleavage to form a heterodimeric α/β form, which is required for Met activation; however the precise mechanism of Met activation by HGF is still poorly understood. We have solved the crystal structure of the N-terminal 560 residues of the Met receptor in complex with the β-chain of HGF. This fragment of the Met receptor comprises a SEMA domain, a structural motif that is also found in integrins and semaphorins, and a small cysteine rich PSI domain. SEMA domains are 7-bladed β-propellers; the structure shows how HGF-β binds to of the 'bottom' face of this propeller, and identifies residues on Met and HGF that play key roles in this interaction. The structural epitope on HGF-β identified in this crystal structure is in excellent agreement with biochemical and biological studies with HGF and HGF-β mutants.

[1] Stamos J., Lazarus R.A., Yao X., Kirchhofer D., Wiesmann C., *EMBO J.*, 2004, **23**, 2325-2335.

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