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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.

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Keywords: HGF, met-receptor, sema-domain

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Crystal Structure of Human C-type Lectin-like Oxidized LDL Receptor 1(LOX-1)
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C-type lectin-like oxidized low-density lipoprotein (LDL) receptor 1, LOX-1, is the major receptor for oxidized LDL (OxLDL) in endothelial cells. LOX-1 plays a critical role in endothelial dysfunction that leads to atherosclerosis. Lox-1 is also expressed in macrophages and smooth muscle cells; these cells progress atherogenesis in sub-endothelial space through interaction with OxLDL in the intima. Thus, LOX-1 is recognized as a therapeutically important target receptor for the pathogenesis of vascular disorder, especially atherosclerosis. To gain the insight into the binding surface structure of LOX-1 to OxLDL, we have determined the crystal structure of the ligand-binding CTLD domain of LOX-1, with a short stalk region connecting the domain to the membrane-spanning region, as a homodimer linked by an inter-chain disulfide bond. . In vivo assays using LOX-1 mutants revealed that the "basic spine", consisting of linearly aligned arginine residues spanning over the dimer surface, is responsible for ligand binding. Single amino acid substitution in the dimer interface caused the severe reduction of LOX-1 binding activity, suggesting that the correct dimmer arrangement is crucial for the binding to OxLDL. Based on the LDL model structure, the possible binding modes of LOX-1 to OxLDL are proposed.
Keywords: atherosclerosis, membrane receptors, three-dimensional protein structure

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The 'Active-like' Structure of the Unphosphorylated Response Regulator StyR
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The crystal structure of unphosphorylated StyR has been solved at 2.2 Å resolution. StyR belongs to the FixJ family of signal transduction response regulators; it controls transcription of the *styABCD* operon coding for styrene catabolism in *Pseudomonas fluorescens* ST [1]. StyR is composed of an N-terminal regulatory domain (StyR-N), and a C-terminal DNA binding domain (StyR-C). The two domains are separated by an elongated linker α-helix (34 residues), a new feature in response regulator known structures. StyR-C is structured similarly to the DNA binding domain of the response regulator NarL [2]. StyR-N shows structural reorganization of the phosphate receiving region involved in activation/homodimerization: specific residues adopt 'active-like' conformations, and the α4-helix, involved in dimerization of the homologous FixJ response regulator [3], is trimmed to just one helical turn. Overall, structural considerations suggest that phosphorylation may act as an allosteric switch, shifting a pre-existing StyR equilibrium towards the active, dimeric, DNA-binding form.

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Keywords: two-component signal transduction, response regulator, phosphorylation

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Insecticide Selectivity: Structure of a Hemipteran Ecdysone Receptor LBD
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We report here the X-ray structure of the ecdysone receptor ligand-binding domain (LBD) of the hemipteran *Bemisia tabaci* (silverleaf whitefly) in complex with the ecdysone analogue ponasterone A and compare it with the corresponding known structure from the lepidopteran *Heliothis virescens* ecdysone receptor [1]. Our structure reveals the overall mode of ponasterone A binding is very similar in the two cases, but that the *B. tabaci* ecdysteroid-binding pocket is structured differently to that of *H. virescens* in those parts that are not in contact with ponasterone A. We propose that these differences in the ligand-binding pocket provide a molecular basis for the taxonomic order-selectivity of bisacylhydrazine insecticides [2,3].

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Keywords: insecticides, nuclear receptors, ecdysone

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Structural Basis for Autoinhibition and Activation of eIF2α Protein Kinase GCN2
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The GCN2 protein kinase (PK) couples the rate of protein synthesis to amino acid stores by phosphorylating eukaryotic