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Structure and Function of the GDNF Coreceptor alpha1. Adrian Goldman, Veli-Matti Leppänen, Maxim M. Bespalov, Pia Runeberg-Roos, Ülo Purand, Andres Merits, Mart Saarma, Inst. of Biotechnology, Univ. of Helsinki, Viikinkaari 1, Helsinki, FIN-00014 FINLAND.

GDNF (glial-derived neurotrophic factor) has two receptors which work together: the GDNF family co-receptor alpha 1 (GFR α 1), which provides GDNF specificity, and a receptor tyrosine kinase, RET. GFR α 1 appears to be made of three homologous cysteine-rich domains, where domains 2 and 3 together bind GDNF. We report here the 1.8 Å crystal structure of GFR α 1 domain 3 solved by Se-Met MAD, with a final R-factor of 19.3 %. GFR α 1 domain 3 has an entirely novel protein fold: it is an all-alpha five-helix bundle stabilized by five disulfide bridges. We have used the structure to model the homologous domain 2, the other half of the GDNF-binding fragment, and to construct the first structural model of the GDNF-GFR α 1 interaction. Site-directed mutagenesis identified that Phe213, Arg224, Arg225 and Ile229 form the GDNF binding surface. Mutating each one of them had slightly different effects on GDNF binding and RET phosphorylation. In addition, the R217E mutant bound GDNF equally well in the presence and absence of RET and so Arg217 may be involved in the allosteric properties of GFR α 1.

We have used our GDNF-GFR α 1 model to construct related homology models for the other GDNF-family ligands with their cognate co-receptors and can thus begin to explain the structural basis of receptor specificity and cross-talk.