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How ligand binds to the insulin-like growth factor receptor

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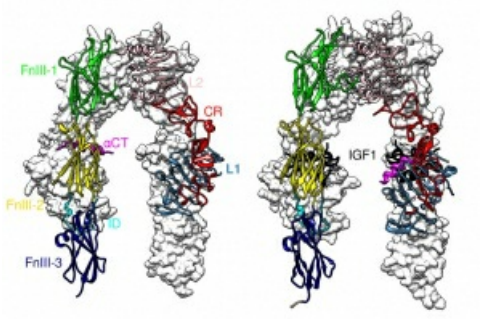
The human insulin and type 1 insulin-like growth factor receptor are homologous receptor tyrosine kinases. They are formed as disulphide-linked homodimers and share 58% sequence identity. The type 1 insulin-like growth factor receptor (IGF-1R) is involved in normal human growth and development. Aberrant IGF-1R signalling is implicated in cancer proliferation and metastasis and the receptor hence has undergone extensive investigation as a potential anti-cancer target. Insulin-like growth factor binding is understood to relax conformational restraints within the homodimer, initiating trans-phosphorylation of the receptor tyrosine kinase domains.

Our earlier crystallographic studies have focused on the insulin receptor [1]. However, there are no three-dimensional structural data for the intact IGF-1R ectodomain that might inform atomic-level understanding of how insulin-like growth factors (i.e., IGF-1 and IGF-2) bind to this recptor. To resolve these issues, we present the first and landmark crystal structures of the intact IGF-1R ectodomain —in both apo- and IGF-1 bound form, refined using data to 3.2 and 3.4 Å resolution, respectively (see images below).

In addition to providing a wealth of atomic detail, these structures lead us to suggest that the way in which ligand binds is fundamentally different to the paradigm that has been in place for a number of decades.

[1]Menting J et al. (2013) Nature 493, 241-245.



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