Structural studies of the thrombopoietin-thrombopoietin receptor signalling complex


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The hormone thrombopoietin (TPO) is the primary regulator of megakaryocyte and platelet development. Binding of TPO to the TPO receptor on the surface of these cells and their precursors leads to receptor dimerisation and activation of the JAK/STAT signalling pathway. Loss of function mutations affecting TPO signalling result in congenital amegakaryocytic thrombocytopenia, while activating mutations are associated with a collection of rare blood cancers known as the myeloproliferative neoplasms.

The TPO receptor is a member of the homodimeric type 1 cytokine receptor family along with growth hormone receptor, erythropoietin receptor, prolactin receptor and granulocyte colony stimulating factor receptor. The extracellular domains of these receptors contain a cytokine receptor homology module (CRH) through which they bind their respective ligand. Based on homology to related cytokines, TPO is expected to bridge two receptor chains, meaning that there are two receptor binding sites on TPO termed site I and site II, which have been characterised by mutagenesis [1-4]. The TPO receptor is unique amongst type I cytokine receptors due to the presence of a 2nd non-binding CRH module in its extracellular domain, the role of which is unknown. Currently there is no structural data on the TPO Receptor.

We have used cryo EM single particle analysis to solve the structure of the full murine TPO:TPO receptor extracellular domain complex to a resolution of ~4Å. This is the first ever structure of any part of the TPO Receptor. We were able to identify the residues involved in site I and site II interactions between TPO and its receptor, which are consistent with previous mutational analyses of TPO. We have also performed biochemical analysis of the interaction using surface plasmon resonance.

Figure 1. Surface representation of TPO (orange) bound to TPOR (purple)