

First insights into the structure of the insulin receptor ectodomain homodimer

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The insulin receptor (IR) is a phylogenetically ancient tyrosine kinase receptor found in organisms as primitive as cnidarians and insects. The key role of the insulin receptor (IR) is in glucose uptake and metabolism by muscle and fat. Dysfunctional IR signaling has been implicated in diseases including type I and type II diabetes, dementia and cancer. The IR exists as two splice variant isoforms IR-A and IR-B. The IR-B isoform is responsible for signaling metabolic responses. In contrast, IR-A signals predominantly mitogenic responses, is the preferentially expressed isoform in several cancers and is capable of binding insulin-like growth factor receptor (IGF-II) with high affinity. Here we present the crystal structure of the IR-A ectodomain dimer. The structure reveals, for the first time, the domain arrangement in the disulphide-linked ectodomain dimer and shows that it adopts a folded-over conformation that places the ligand-binding regions in juxtaposition.