IGF2-TRAP: High affinity receptors to sequester growth factors linked to cancer

Researchers at the University of Oxford have identified key mutations that increase the affinity of Insulin-like Growth Factor 2 Receptor (IGFR2) for its ligand, reducing hypoglycaemia and tumour volume.

Insulin-like growth factors (IGF) are overexpressed in cancer cells and reductions in their expression are associated with tumour reduction. Previous efforts to inhibit IGF signalling by focussing on the IGF1 receptor have so far been unsuccessful.

Researchers at the University of Oxford have investigated the IGF2 receptor (IGF2R) and have identified mutations in domain 11 of IGF2R that increase the affinity of IGF2 to its receptor. These mutated receptors have been shown to treat hypoglycaemia and reduce tumour volume.

Insulin-like Growth Factor 2 (IGF2) encodes a member of the insulin family of polypeptide growth factors, which are involved in development and growth. Overexpression of this growth factor gene has been reported in a wide range of cancers and is associated with an increased risk of developing early childhood tumours.

IGF2 activates MAPK and PI3K pathways by binding to the ubiquitously expressed IGF1 receptor (IGF1R) and isoform A of the Insulin Receptor (IR-A). Unlike IGF1R, which is responsible for active signalling, IGF2R acts as an IGF2 sink to prevent excess IGF2 signalling.

Ligand bioavailability in cancer is often increased due to increased IGF2 expression, proteolytic cleavage of inhibitory proteins and loss of function of the sink receptor IGF2R. IGF2 is thought to be a major driver of resistance to several therapies, including anti-HER2, anti-EGFR and anti-Androgen in breast, colorectal, prostate and lung cancers.

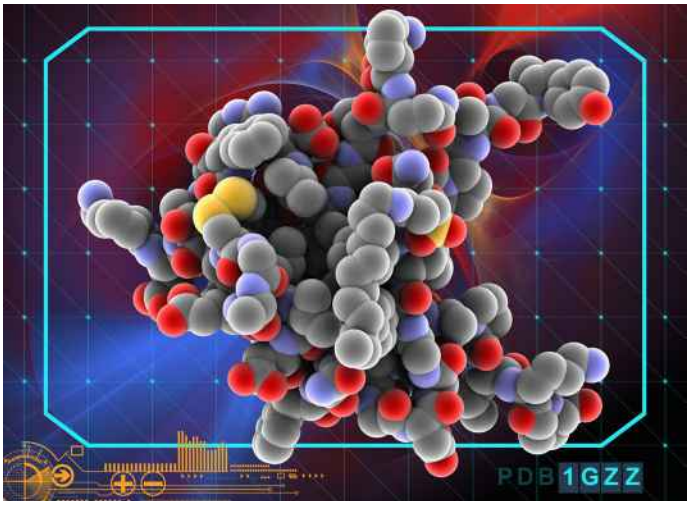
Inhibition of IGF signalling has been an area of major focus by pharma, with many failures due to either receptor redundancy (between IGF1R and IR-A) or the IGF1 feedback loop. This causes the pituitary gland to produce more growth hormone, instructing the liver to produce more IGF1, generating a potential dose limiting toxicity of hyperglycaemia.

Tumours that cause hypoglycaemia overexpress IGF2 and secrete excessive amounts of partially processed precursors of IGF2, named big-IGF2. This causes the rare condition of non-islet cell tumour hypoglycaemia (NICTH).

Researchers at the University of Oxford, along with their collaborators, have identified a number of key mutations in the IGF2R that increase affinity with IGF2. These mutated receptors act as traps for IGF2 (IGF2-TRAP), thus sequestering this overexpressed ligand. The mutated IGF2R have been tested *in vivo* – IGF2-induced hypoglycaemia in mice was abolished in the presence of the IGF2-TRAP, and a reduction in tumour volume was observed in Ewing sarcoma cells xenograft models treated with IGF2-TRAP.

The Oxford researchers have gone on to identify two PI3 kinase inhibitors that act synergistically with the IGF2-TRAP to reduce the dose requirements of these inhibitors and improve the long-term tumour-killing efficacy of IFG2-TRAP.

The IGF2R mutations are protected by a patent now granted in Europe and the USA, and another international patent application.



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