## Phylogeny

The insulin-like growth factor 1 receptor (IGF1R) is a receptor tyrosine kinase of the Tyrosine Kinase group, Insulin Receptor family (Fan et al., 2012; Li et al., 2009; Shahid et al., 2024). It shares high sequence similarity with the insulin receptor, including ~72 % identity in the kinase domain and complete identity in the ATP-binding segment (Ekyalongo & Yee, 2017; Li et al., 2009). Orthologues are conserved throughout vertebrates, consistent with its fundamental role in growth and metabolism (Baxter, 2023; Li et al., 2009).

## Reaction Catalyzed

ATP + protein-L-tyrosine → ADP + phosphoprotein-L-tyrosine (Fan et al., 2012; Li et al., 2009; Tao et al., 2007).

## Cofactor Requirements

Kinase activity requires a divalent cation, typically Mg²⁺ (preferred) or Mn²⁺ (Li et al., 2009; Sehat et al., 2007; Tao et al., 2007; Baserga, 2000).

## Substrate Specificity

IGF1R preferentially phosphorylates tyrosine residues within a consensus sequence that favours an acidic residue (Asp/Glu) at the +1 position and a bulky hydrophobic residue at +3 (Fan et al., 2012; Li et al., 2009; Sehat et al., 2007; Shahid et al., 2024).

## Structure

The mature receptor is an α₂β₂ heterotetramer generated from a single precursor that is proteolytically cleaved (Li et al., 2009; Shahid et al., 2024).  
• α-subunits: entirely extracellular, form the ligand-binding domain.  
• β-subunits: span the membrane and harbour the intracellular tyrosine kinase domain containing the activation loop, C-helix and catalytic loop (Li et al., 2009; Sehat et al., 2007).  
Autophosphorylation sites Y1131, Y1135 and Y1136 within the activation loop are essential for full activity (Baxter, 2023; Fan et al., 2012; Shahid et al., 2024). Crystal structures of the isolated kinase domain have been deposited in the Protein Data Bank (Baxter, 2023; Li et al., 2009).

## Regulation

Activation: Binding of IGF-1 or IGF-2 triggers conformational rearrangement and autophosphorylation on Y1131/Y1135/Y1136, enhancing catalytic activity (Baxter, 2023; Li et al., 2009; Tao et al., 2007).  
Negative regulation:  
• Protein tyrosine phosphatases PTP1B and PP2A dephosphorylate the receptor (Fan et al., 2012; Baxter, 2023; Li et al., 2009).  
• Ubiquitination by E3 ligases such as c-Cbl promotes internalisation and lysosomal/proteasomal degradation (Fan et al., 2012; Li et al., 2009; Sehat et al., 2007).

## Function

IGF1R is broadly expressed and supports neuronal survival, cardiac function and glucose homeostasis (Li et al., 2009). Upon activation it phosphorylates adaptor proteins IRS1/2 and Shc1, initiating PI3K/AKT/mTOR signalling for survival/protein synthesis and Ras/MAPK signalling for proliferation (Baxter, 2023; Tao et al., 2007; Iams & Lovly, 2015). IGF1R can heterodimerise with the insulin receptor, altering downstream outputs (Ekyalongo & Yee, 2017; Li et al., 2009).

## Inhibitors

Therapeutic antagonists include:  
• Monoclonal antibodies blocking ligand binding: cixutumumab (IMC-A12), figitumumab (CP-751,871) (Baxter, 2023).  
• ATP-competitive tyrosine kinase inhibitors: linsitinib, NVP-AEW541, BMS-536924 (Iams & Lovly, 2015; Fan et al., 2012).  
• Other agents: nordihydroguaiaretic acid, picropodophyllin, HSP90 inhibitor 17-AAG (Li et al., 2009; Xue et al., 2012).

## Other Comments

IGF1R is frequently overexpressed or hyperactivated in breast, lung, colon and prostate cancers, contributing to tumour progression, metastasis and resistance to EGFR/HER2-targeted therapies (Baxter, 2023; Li et al., 2009; Tao et al., 2007). The IGF1R gene maps to chromosome 15q26.3 (Ekyalongo & Yee, 2017; Shahid et al., 2024). Rare mutations can impair function; for example, substitution of the ATP-binding lysine 1003 abolishes kinase activity (Baxter, 2023; Baserga, 2000).

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