## Phylogeny

Fibroblast Growth Factor Receptor 4 (FGFR4) belongs to the Tyrosine Kinase (TK) group and, within that group, to the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases (Manning et al., 2002; Farrell & Breeze, 2018; Roskoski, 2020). FGFR4 is conserved throughout vertebrates and is one of four paralogous FGFR proteins, displaying the lowest sequence homology among them (Farrell & Breeze, 2018; Lang & Teng, 2019; Levine et al., 2020).

## Reaction Catalyzed

ATP + [a protein]-L-tyrosine ⇌ ADP + [a protein]-L-tyrosine phosphate (Hagel et al., 2015).

## Cofactor Requirements

Mg²⁺ is required for catalysis (Dai et al., 2019).

## Substrate Specificity

An intrinsic substrate-profiling study defined the preferred motif from P-3 to P + 3 as:  
P-3 (F ≫ other hydrophobics) – P-2/P-1 (E/D) – P0 (Y) – P + 1 (G) – P + 2 (A) – P + 3 (S/T) (Yaron-Barir et al., 2024). Thus, FGFR4 favors a phenylalanine three residues N-terminal to the target Tyr, acidic residues at P-2 and P-1, a small glycine or alanine immediately C-terminal, and a polar Ser/Thr at P + 3.

## Structure

FGFR4 (UniProt P22455, 802 aa, 95–110 kDa) displays the canonical receptor tyrosine kinase topology:  
• Extracellular region (aa 1–369) containing a signal peptide, an acid box, and three Ig-like domains (D1–D3). D2/D3 form the high-affinity ligand-binding pocket, whereas D1 plus the acid box exert autoinhibition (Lang & Teng, 2019; Farrell & Breeze, 2018). Unlike FGFR1-3, FGFR4 expresses only the IIIc Ig-like isoform (Levine et al., 2020).  
• Single-pass transmembrane helix (aa 370–390).  
• Intracellular bilobed kinase domain (aa 454–767) with a flexible αC-helix in the N-lobe and a C-lobe containing the activation loop with the conserved DFG motif (Dai et al., 2019). Assembly of regulatory and catalytic spines and re-orientation of the αC-helix switch the enzyme from an inactive “DFG-out” to an active “DFG-in” conformation (Roskoski, 2020).  
• A unique cysteine (Cys552) in the hinge region confers a covalent inhibitor binding site (Levine et al., 2020; Marseglia et al., 2019).

## Regulation

• Autoinhibition: the extracellular D1/acid-box module and an intracellular “molecular brake” (E562–K638) keep the receptor inactive (Farrell & Breeze, 2018; Roskoski, 2020).  
• Activation: ligand binding (e.g., FGF19 ± β-klotho) drives receptor dimerisation, αC-helix rotation and activation-loop phosphorylation (Dai et al., 2019).  
• Post-translational control: trans-autophosphorylation of Y642/Y643 in the activation loop is required for full activity; additional sites include Y754, Y764 and S573 (Dai et al., 2019; Wu et al., 2016; Levine et al., 2020).

## Function

FGFR4 regulates embryogenesis, tissue repair and adult metabolic processes such as bile-acid synthesis and glucose homeostasis. It is highly expressed in liver and present in muscle and lung (Farrell & Breeze, 2018; Lang & Teng, 2019; Lu et al., 2018).  
• Ligands/co-receptors: endocrine FGF19 (β-klotho-dependent) and canonical FGFs (FGF1/2/4/8) with heparan sulfate proteoglycans (Lang & Teng, 2019; Dai et al., 2019).  
• Downstream signalling: phosphorylated FGFR4 recruits FRS2 and PLCG1, initiating Ras–MAPK and PI3K–Akt cascades and a PLCγ/PKC branch; additional outputs include Src and GSK3β/β-catenin pathways (Lang & Teng, 2019; Lu et al., 2018).

## Inhibitors

• Covalent, Cys552-targeted inhibitors: BLU-554 (fisogatinib), H3B-6527, FGF401 (roblitinib), INCB062079 (Hagel et al., 2015; Lu et al., 2018; Levine et al., 2020).  
• Reversible ATP-competitive inhibitors (often pan-FGFR): LY2874455, erdafitinib, dovitinib, ponatinib (Dai et al., 2019; Wu et al., 2016; Lesca et al., 2014).

## Other Comments

Genetic or ligand-driven hyperactivation of the FGF19–FGFR4 axis contributes to hepatocellular carcinoma and other solid tumours (Dai et al., 2019; Hagel et al., 2015). Clinically relevant activating mutations include V550L/E (gatekeeper), G388R (germline SNP) and Y367C, which can promote oncogenesis and influence inhibitor sensitivity (Lu et al., 2018; Tang et al., 2018; Schwarz et al., 2024).

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