## Phylogeny

• Orthologs include mouse Fgfr3 and chicken Cek-2, grouping tightly with human FGFR1 and FGFR2 within the FGFR branch of receptor tyrosine kinases (keegan1991isolationofan pages 3-4).  
• The kinase domain preserves the HRD catalytic loop and DFG activation-loop motifs seen across the protein tyrosine kinase group (mohammadi1996structureofthe pages 2-3).

## Reaction Catalyzed

• ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (mohammadi1996structureofthe pages 6-8).

## Cofactor Requirements

• Activity is supported by ATP or the non-hydrolysable analog AMP-PCP; additional divalent metal cofactors were not reported in the in-vitro assays described (mohammadi1996structureofthe pages 6-8).

## Substrate Specificity

• Autophosphorylation of activation-loop tyrosines Y647 and Y648 markedly enhances catalytic activity (farrell2018structureactivationand pages 2-4).  
• Phosphorylation of Y724 in the C-terminal lobe creates a high-affinity site for downstream effectors (farrell2018structureactivationand pages 2-4).  
• Phosphorylated juxtacatalytic tyrosines Y760, Y762, Y770 and Y779 function as SH2-domain docking platforms (farrell2018structureactivationand pages 2-4).  
• Y724 phosphorylation promotes cellular transformation, whereas Y770 phosphorylation suppresses it (lhote2005cellresponsesto pages 11-12).  
• The kinase phosphorylates adaptor proteins FRS2 and PLCG1 on tyrosine motifs that initiate MAPK and PLCγ signaling, respectively (lhote2005cellresponsesto pages 2-3).

## Structure

• The 806-residue receptor contains a signal peptide, three extracellular Ig-like domains separated by an acidic box, a 25-residue transmembrane helix, a juxtamembrane region, a split intracellular kinase domain with an internal insert, and a C-terminal tail (keegan1991isolationofan pages 3-4).  
• Crystal structure of the kinase domain (PDB 4K33) shows a bilobal fold with a Gly-rich GXGXXG loop, an HRD catalytic motif, and a DFG motif controlling activation-loop positioning (farrell2018structureactivationand pages 6-8).  
• Unphosphorylated kinase adopts an autoinhibitory activation-loop conformation that blocks substrate binding, as exemplified by the FGFR1 structure (mohammadi1996structureofthe pages 2-3).  
• Active state is stabilized by the Lys508–Glu525 salt bridge within the αC helix and by an aligned hydrophobic spine (farrell2018structureactivationand pages 6-8).  
• Disease-associated K650E mutation in the activation loop mimics phosphorylation and locks the loop in an extended active conformation (farrell2018structureactivationand pages 6-8).  
• Additional structural templates include kinase domain PDB 3GQI and extracellular Ig-domain model based on FGFR1 PDB 1RY7 (farrell2018structureactivationand pages 6-8).

## Regulation

• Ligand-induced dimerization triggers ordered phosphorylation of seven cytoplasmic tyrosines, sequentially activating the kinase and exposing adaptor docking sites (narayana2015fgfr3biologyand pages 3-6).  
• The E3 ubiquitin ligase CBL polyubiquitinates activated FGFR3, targeting it for lysosomal degradation (lhote2005cellresponsesto pages 2-3).  
• Gain-of-function mutations reduce CBL-mediated ubiquitination, prolonging receptor signaling (narayana2015fgfr3biologyand pages 6-7).  
• Seven predicted N-linked glycosylation sites in the extracellular region are required for correct folding and surface transport (keegan1991isolationofan pages 3-4).  
• Hsp90–Cdc37 chaperoning stabilizes FGFR3; Hsp90 inhibition recruits CHIP and drives proteasomal degradation (narayana2015fgfr3biologyand pages 6-7).  
• Regulated intramembrane proteolysis yields a soluble intracellular fragment that translocates to the nucleus (narayana2015fgfr3biologyand pages 7-10).  
• Sprouty proteins and Sef provide negative feedback by dampening MAPK signaling downstream of FGFR3 (bogale2024therolesof pages 3-5).

## Function

• IIIc splice isoform dominates in growth-plate chondrocytes; IIIb isoform is enriched in epithelial tissues (lhote2005cellresponsesto pages 1-2).  
• Expression is documented in brain, skeleton, gut and skin (narayana2015fgfr3biologyand pages 1-3).  
• FGF1 and FGF9 activate both isoforms, with FGF9 showing preference for IIIc; heparan-sulfate proteoglycans are obligatory co-factors (lhote2005cellresponsesto pages 1-2).  
• Phosphorylated FRS2 recruits GRB2, GAB1, PIK3R1 and SOS1 to stimulate RAS–MAPK and PI3K–AKT pathways (lhote2005cellresponsesto pages 2-3).  
• PLCG1 phosphorylation links the receptor to diacylglycerol and IP₃ production, activating PKC signaling (lhote2005cellresponsesto pages 2-3).  
• STAT1 activation in chondrocytes enforces growth arrest, whereas STAT3/5 activation in other contexts promotes proliferation (lhote2005cellresponsesto pages 11-12).  
• FGFR3 limits chondrocyte proliferation and differentiation, thereby restraining bone elongation (narayana2015fgfr3biologyand pages 1-3).  
• Constitutive activation via point mutations or FGFR3-TACC3 fusion sustains MAPK and AKT signaling that drives oncogenic growth (karkera2017oncogeniccharacterizationand pages 15-19).

## Inhibitors

• Erdafitinib is a type I½A inhibitor that binds the DFG-Din inactive state and inhibits FGFR3 with an IC₅₀ of 4 nM (roskoski2020theroleof pages 27-31).  
• AZD4547 is a reversible type I inhibitor forming hinge hydrogen bonds and stabilizing a DFG-Din conformation (roskoski2020theroleof pages 35-39).  
• BGJ398 (infigratinib) selectively targets FGFR1-3 and is under clinical investigation for solid tumors (roskoski2020theroleof pages 82-85).  
• Futibatinib is a covalent type VI inhibitor that locks the kinase in an autoinhibited state (roskoski2020theroleof pages 35-39).  
• Ponatinib binds the DFG-Dout configuration and shows pan-FGFR activity (roskoski2020theroleof pages 27-31).  
• FGFR3-TACC3-positive tumor models display heightened sensitivity to erdafitinib (karkera2017oncogeniccharacterizationand pages 15-19).

## Other Comments

• Germline mutations G380R (transmembrane) and K650M/E/N/Q (activation loop) cause achondroplasia and thanatophoric dysplasia, with increasing kinase activation correlating to clinical severity (lhote2005cellresponsesto pages 13-13).  
• Somatic extracellular cysteine substitutions such as S249C and R248C promote ligand-independent dimerization in bladder carcinoma (lhote2005cellresponsesto pages 13-13).  
• K650E mutation stabilizes the active kinase conformation and drives constitutive signaling (farrell2018structureactivationand pages 6-8).

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