## Phylogeny

FGFR1 is a member of the receptor tyrosine kinase (RTK) family, forming a distinct branch of the FGFR subfamily that diverges near the PDGFR and VEGFR lineages of the human kinome (Rebscher et al., 2009). Orthologues characterised in mouse and rat retain the three-Ig extracellular module and split kinase core seen in the human enzyme (D’Aniello et al., 2008). Zebrafish fgfr1 supports comparable developmental roles, underscoring conservation across vertebrates (Trokovic et al., 2003). More distant homologues in Drosophila (breathless) and Caenorhabditis elegans (egl-15) indicate that the lineage predates the protostome–deuterostome split (Rebscher et al., 2009). Comparative activation-segment analyses highlight signature residues flanking Tyr653/Tyr654 that differentiate FGFRs from neighbouring RTK families (McSkimming et al., 2016).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (FGFR1-Dependency Prediction…, 2014).

## Cofactor Requirements

Catalysis requires a divalent metal ion—Mg²⁺ or Mn²⁺—to coordinate ATP in the active site (Tucker et al., 2014).

## Substrate Specificity

Kinase-wide peptide profiling defined a preference for tyrosines in a pY-[E/D]-x-[V/L/I] motif (Roskoski, 2020). Autophosphorylation proceeds in an ordered fashion: Tyr653 is modified first, followed by Tyr654, raising catalytic efficiency ~1000-fold (Furdui et al., 2006). Cellular proximity-labelling studies identified PLCG1, FRS2, RPS6KA3/RSK2, SRC and SHB as principal substrates, which typically reside in flexible, proline-poor regions that interact with SH2-domain effectors (Kostas et al., 2018).

## Structure

FGFR1 consists of a signal peptide, three Ig-like extracellular domains (D1–D3) separated by an acidic box, a single-pass transmembrane helix, a juxtamembrane segment, a bilobal split kinase domain containing a kinase-insert loop, and a C-terminal tail (Rand et al., 2005). Crystal structures of FGF1-bound ectodomains show ligand contacts centred on D3 and heparan-sulfate-stabilised 2:2 receptor dimers (Plotnikov et al., 2000). Kinase-domain structures capture both active DFG-in and inhibitor-bound DFG-out states; the latter are exemplified by complexes with AZD4547 and ponatinib (Tucker et al., 2014). NMR and cross-linking reveal a symmetric head-to-tail dimer mediated by α-helix G that positions the activation loop for trans-autophosphorylation (Kobashigawa et al., 2015). Key regulatory elements include the activation loop (Tyr653/Tyr654), the mobile αC-helix and a hydrophobic spine that aligns during activation (Kobashigawa et al., 2015).

## Regulation

Signal initiation requires heparan-sulfate-dependent assembly of a 2:2:2 FGF–FGFR1–heparin complex, which drives receptor dimerisation and ordered autophosphorylation (Heparan Sulfate Regulation…, 2003). Sequential phosphorylation of Tyr653/Tyr654 activates the kinase, while additional sites (Tyr463, Tyr583/Tyr585, Tyr766) create docking platforms for downstream proteins (Kobashigawa et al., 2015). The phosphatase PTPRG dephosphorylates Tyr653/Tyr654, dampening ERK and PLCγ pathways (Kostas et al., 2018). Activated receptors are ubiquitinated by the CBL E3 ligase, targeting them for endocytic degradation (Identification and Validation…, 2014). Feedback inhibitors SPRY and SEF restrain MAPK output (Roskoski, 2020). Mutations that disrupt the α-helix G interface impair dimerisation and reduce autophosphorylation, highlighting an allosteric control point (Kobashigawa et al., 2015).

## Function

Alternative splicing yields FGFR1b (epithelial) and FGFR1c (mesenchymal). High expression is reported in embryonic mesoderm, CNS, osteoblasts and haematopoietic progenitors (Givol & Yayon, 1992). Paracrine FGFs (FGF1/2/4/7/8/9) bind the receptor with isoform-specific affinities to govern limb development, neurogenesis and angiogenesis (FGFR1-Dependency Prediction…, 2014). Ligand engagement phosphorylates FRS2, PLCG1, SHC1 and SRC, activating MAPK/ERK, PI3K-AKT, PLCγ–Ca²⁺/PKC and mTOR pathways that promote proliferation, migration and survival (Kostas et al., 2018). In osteosarcoma cells, internalised FGFR1 sustains ERK signalling from early endosomes (Kostas et al., 2018).

## Inhibitors

• AZD4547: reversible type-I inhibitor, IC₅₀ ≈ 0.2 nM; reduced PTPRG levels necessitate higher doses (Dai et al., 2019; Kostas et al., 2018).  
• BGJ398/INCB054828: type-I inhibitor, IC₅₀ ≈ 0.9 nM, selective over FGFR4 (Dai et al., 2019).  
• PD173074: nanomolar ATP-competitive probe binding the DFG-in state (Roskoski, 2020).  
• SU5402: low-micromolar inhibitor widely used in developmental studies (Roskoski, 2020).  
• FIIN-1: covalent inhibitor targeting Cys486 with sub-nanomolar potency and high FGFR selectivity (Liu et al., 2020).  
• Ponatinib: binds a DFG-out conformation, acting as a pan-FGFR scaffold (Tucker et al., 2014).

## Other Comments

FGFR1 amplification or over-expression drives oncogenesis in squamous lung, breast, bladder and ovarian cancers and can confer therapy resistance (Liu et al., 2020). Co-amplification with PTPRG deletion correlates with reduced inhibitor sensitivity (Kostas et al., 2018). Somatic activating mutations cluster around the activation loop (e.g., K656E, R646, D652) and recur in tumours (McSkimming et al., 2016). Germline gain-of-function mutations such as P252R cause Pfeiffer and Kallmann syndromes (Dai et al., 2019). Oncogenic fusions (FGFR1-BCR, FGFR1-OPN, FGFR1-ZMYM2) underlie 8p11 myeloproliferative syndrome (Roskoski, 2020).

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