## Phylogeny

PDGFRβ belongs to the type III receptor tyrosine kinase subfamily together with PDGFRα, KIT, FLT3 and CSF1R; all share a split-kinase catalytic core and a five-Ig extracellular module (Chen et al., 2013). Verified orthologues exist in mouse, rat, zebrafish, Drosophila (PvR) and Caenorhabditis elegans (ver-1), indicating conservation from vertebrates to invertebrates (Bredrup et al., 2019).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (Claesson-Welsh, 1994; Al-Obeidi et al., 1998).

## Cofactor Requirements

Catalysis requires two Mg²⁺ ions that coordinate the β- and γ-phosphates of ATP (Al-Obeidi et al., 1998; Johnson, 2009).

## Substrate Specificity

Peptide-array profiling places PDGFRβ in a basophilic specificity group that favours basic residues at positions −2/−1 and +1 relative to the phospho-Tyr, and tolerates an acidic or bulky hydrophobic residue at +3. A consensus sequence is D/E-x-Y-[R/K/E]-Φ, where Φ denotes a hydrophobic residue (Yaron-Barir et al., 2024). The receptor autophosphorylates 11 tyrosines (e.g., Y740, Y751, Y857, Y1021) that subsequently recruit PI3K, Src-family kinases, PLCγ, SHP2, Grb2 and STATs (Heldin & Lennartsson, 2013).

## Structure

The mature receptor comprises (i) an extracellular region with five Ig-like domains, where D2–D3 bind PDGF dimers and D4–D5 mediate receptor–receptor contacts; (ii) a single 23-residue transmembrane helix; (iii) a juxtamembrane segment that folds over the N-lobe to autoinhibit the kinase; and (iv) a split kinase domain with a 100-aa insert and an acidic C-terminal tail (Chen et al., 2013).  
Crystal and EM data show:  
• PDGF-B–PDGFRβ D1–D3 complex (PDB 2VVL) buries ~2,900 Å², with Tyr205, Tyr207, Phe136 and Phe138 dictating ligand selectivity (Shim et al., 2010).  
• Negative-stain EM of the full-length dimer reveals a V-shaped extracellular assembly and an asymmetric intracellular kinase dimer poised for trans-phosphorylation (Chen, Unger, & He, 2015).  
• Activation-loop phosphorylation of Y857 locks the kinase in the αC-in/DFG-in active conformation and completes the hydrophobic spine (Nemaysh & Luthra, 2017).

## Regulation

Post-translational control includes (i) autophosphorylation on 11 tyrosines to create SH2/PTB docking sites (Claesson-Welsh, 1994); (ii) dephosphorylation by SHP2 and TC-PTP (Šrámek et al., 2018); (iii) ubiquitination by c-Cbl (via Alix) and SOCS3, directing lysosomal degradation (Šrámek et al., 2018; Bredrup et al., 2019); (iv) extensive N-linked glycosylation of D1–D3, which supports folding and surface stability (Chen et al., 2013); and (v) accelerated proteasomal turnover of the pathogenic p.R987W variant (Sanchez-Contreras et al., 2014). Ligand-induced ββ or αβ dimerisation displaces the juxtamembrane brake and permits activation-loop phosphorylation, whereas active Ras down-regulates PDGFRB transcription, providing negative feedback (Heldin & Lennartsson, 2013; Raica & Cîmpean, 2010).

## Function

PDGFRβ is highly expressed in vascular smooth-muscle cells, pericytes and other mesenchymal derivatives (Carrasco-Garcia et al., 2014; Andrae et al., 2008). Cognate ligands PDGF-BB, PDGF-DD and PDGF-AB bind the D2/D3 clamp—often aided by heparan-sulfate proteoglycans—to trigger receptor dimerisation (Chen et al., 2013). Activated receptors launch PI3K–Akt, Ras–Raf–ERK, PLCγ/Ca²⁺ and Src/Myc pathways that drive proliferation, survival, chemotaxis and cytoskeletal remodelling (Heldin & Lennartsson, 2013; Šrámek et al., 2018). Signal localisation is refined by scaffolding with integrins, FAK and the PDZ-domain adaptor NHERF (Andrae et al., 2008).

## Inhibitors

Type II ATP-competitive inhibitor imatinib blocks oncogenic fusions and germline Asn666Ser variants (Hassan et al., 2019; Bredrup et al., 2019). The multi-target type I inhibitor sunitinib is compromised by K634 and T681 mutations (Šrámek et al., 2018; Nemaysh & Luthra, 2017). Additional clinically used inhibitors with PDGFRβ activity include sorafenib, dasatinib, ponatinib, crenolanib and nilotinib (Hassan et al., 2019; Lierman & Cools, 2007).

## Other Comments

Oncogenic fusions ETV6-PDGFRB, TEL-PDGFRB and CEP110-PDGFRB drive myeloproliferative neoplasms that are exquisitely imatinib-sensitive (Lierman & Cools, 2007; Hassan et al., 2019). Germline gain-of-function p.Asn666Ser causes Penttinen progeroid syndrome, whereas p.Asn666His or p.Asp850Val underlie infantile myofibromatosis; loss-of-function alleles p.L658P, p.R695C and p.R987W cause idiopathic basal-ganglia calcification (Bredrup et al., 2019; Sanchez-Contreras et al., 2014). PDGF-BB/PDGFRβ over-expression correlates with glioblastoma aggressiveness and poor prognosis (Carrasco-Garcia et al., 2014).

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