Protein: Platelet-derived growth factor receptor β (PDGFRβ) ‑ gene PDGFRB, UniProt P09619

| Phylogeny PDGFRβ is a member of the type III receptor tyrosine kinase (RTK) subfamily that also includes PDGFRα, KIT, FLT3 and CSF1R, all of which share the split-kinase topology and five-Ig extracellular architecture (chen2013plateletderivedgrowthfactors pages 3-4). Verified orthologs are present in Mus musculus (Pdgfrb), Rattus norvegicus (Pdgfrb), Danio rerio (pdgfrb), Drosophila melanogaster (PvR) and Caenorhabditis elegans (ver-1), underscoring conservation from vertebrates to invertebrates (bredrup2019atyrosinekinaseactivating pages 8-8). |
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| Reaction Catalyzed ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine phosphate (claessonwelsh1994plateletderivedgrowthfactor pages 1-1, alobeidi1998proteintyrosinekinases pages 3-5). |

Cofactor Requirements  
Catalytic turnover requires two Mg²⁺ ions that coordinate the β- and γ-phosphates of ATP and orient the catalytic Lys and Asp residues (alobeidi1998proteintyrosinekinases pages 3-5, johnson2009proteinkinaseinhibitors pages 5-7).

| Substrate Specificity Positional-scanning peptide arrays position PDGFRβ in a basophilic specificity cluster that prefers basic residues at −2/−1 and +1 around the target Tyr and tolerates an acidic or bulky hydrophobic residue at +3; a consensus motif derived from the highest-scoring peptides is D/E-x-Y-[R/K/E]-Φ, where Φ is hydrophobic (yaronbarir2024theintrinsicsubstrate pages 5-5, yaronbarir2024theintrinsicsubstrate pages 16-17, yaronbarir2024theintrinsicsubstrate pages 17-19). Intrinsic autophosphorylation occurs on 11 tyrosines, including Y740, Y751, Y771, Y857, Y1009 and Y1021, which subsequently recruit PI3K, Src-family kinases, PLCγ, Shp2, Grb2 and STATs (heldin2013structuralandfunctional pages 1-3, heldin2013structuralandfunctional pages 3-4). |
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| Structure Domain organisation • Extracellular region: five Ig-like domains (D1–D5). D1 is heavily N-glycosylated; D2-D3 clamp PDGF dimers; D4-D5 mediate homotypic receptor contacts (chen2013plateletderivedgrowthfactors pages 4-5, shim2010structuresofa pages 2-4). • Single 23-residue transmembrane helix couples extracellular rearrangements to the cytoplasm (chen2013plateletderivedgrowthfactors pages 4-5). • Juxtamembrane segment folds over the N-lobe to autoinhibit the kinase (heldin2013structuralandfunctional pages 3-4). • Split kinase domain: N-lobe + αC helix (PDB 3MJG), 100-aa insert, and C-lobe that ends in an acidic Ser/Thr-rich tail (alobeidi1998proteintyrosinekinases pages 3-5, chen2013plateletderivedgrowthfactors pages 4-5). |
| 3-D organisation The PDGF-B–PDGFRβ D1–D3 complex (PDB 2VVL) shows ~2,900 Å² buried surface with key aromatic receptor residues Tyr205, Tyr207, Phe136 and Phe138 dictating ligand selectivity (shim2010structuresofa pages 4-5). Full-length negative-stain EM reveals a V-shaped extracellular dimer, membrane-proximal D4-D5 contacts and an asymmetric intracellular kinase dimer poised for trans-phosphorylation (chen2015structureoffulllength pages 4-6, chen2015structureoffulllength pages 8-10). Catalytic features: the activation loop spans DFG 850 to APE and contains Y857; phosphorylation locks the αC-in/DFG-in active conformation and completes the hydrophobic spine (nemaysh2017computationalanalysisrevealing pages 1-2). |

Regulation  
Post-translational modifications  
• Autophosphorylation on 11 tyrosines activates the kinase and forms SH2/PTB docking sites (claessonwelsh1994plateletderivedgrowthfactor pages 1-1).  
• Dephosphorylation by SHP2 and TC-PTP attenuates signalling and promotes receptor recycling (sramek2018effectsofsunitinib pages 6-8).  
• Ubiquitination by c-Cbl (via adaptor Alix) and by SOCS3 directs lysosomal degradation (sramek2018effectsofsunitinib pages 6-8, bredrup2019atyrosinekinaseactivating pages 8-8).  
• Extensive N-linked glycosylation on D1–D3 enhances folding and surface stability (chen2013plateletderivedgrowthfactors pages 4-5).  
• The pathogenic p.R987W variant increases proteasomal turnover, reversible with MG-132 (sanchezcontreras2014geneticscreeningand pages 11-15).

Conformational/allosteric regulation  
Ligand-induced ββ or αβ dimerisation brings two kinase domains together, displaces the juxtamembrane brake and enables activation-loop phosphorylation (heldin2013structuralandfunctional pages 3-4). Active Ras down-regulates PDGFRβ transcription, providing negative feedback (raica2010plateletderivedgrowthfactor pages 1-3).

| Function Expression is highest in vascular smooth-muscle cells, pericytes and other mesenchymal derivatives (carrascogarcia2014roleofreceptor pages 8-11, andrae2008roleofplateletderived pages 5-6). Cognate ligands PDGF-BB, PDGF-DD and PDGF-AB bind D2/D3 and, often anchored by heparan-sulfate proteoglycans, trigger receptor dimerisation (chen2013plateletderivedgrowthfactors pages 6-7, andrae2008roleofplateletderived pages 5-6). Activated PDGFRβ initiates PI3K–Akt, Ras–Raf–ERK, PLCγ/Ca²⁺ and Src/Myc axes that drive proliferation, survival, chemotaxis and actin remodelling (heldin2013structuralandfunctional pages 3-4, sramek2018effectsofsunitinib pages 6-8, carrascogarcia2014roleofreceptor pages 8-11). Scaffolding with integrins, FAK and PDZ-domain adaptor NHERF spatially restricts signalling to focal adhesions and primary cilia (andrae2008roleofplateletderived pages 5-6). |
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| Inhibitors Type II ATP-competitive inhibitor imatinib blocks oncogenic fusions and germline Asn666Ser receptors (hassan2019novelpdgfrbrearrangement pages 15-15, bredrup2019atyrosinekinaseactivating pages 8-8). Multi-target type I inhibitor sunitinib is compromised by K634 or T681 mutations (sramek2018effectsofsunitinib pages 6-8, nemaysh2017computationalanalysisrevealing pages 1-2). Additional clinical inhibitors with PDGFRβ activity include sorafenib, dasatinib, ponatinib, crenolanib and nilotinib (hassan2019novelpdgfrbrearrangement pages 14-15, lierman2007etv6andpdgfrb pages 3-3). |

Other Comments  
Oncogenic fusion genes ETV6-PDGFRB, TEL-PDGFRB and CEP110-PDGFRB drive myeloproliferative neoplasms that are highly imatinib-sensitive (lierman2007etv6andpdgfrb pages 3-3, hassan2019novelpdgfrbrearrangement pages 14-15).  
Germline gain-of-function p.Asn666Ser causes Penttinen progeroid syndrome, whereas somatic p.Asp850Val and germline/somatic p.Asn666His underlie infantile myofibromatosis (bredrup2019atyrosinekinaseactivating pages 8-8).  
Loss-of-function alleles p.L658P, p.R695C and p.R987W cause idiopathic basal-ganglia calcification by impairing receptor processing or signalling (sanchezcontreras2014geneticscreeningand pages 11-15).  
Paracrine over-expression of PDGF-BB and PDGFRβ contributes to glioblastoma aggressiveness and adverse prognosis (carrascogarcia2014roleofreceptor pages 8-11).

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