## Phylogeny

Human platelet-derived growth factor receptor α (PDGFRA) belongs to the tyrosine kinase (TK) group, class III receptor tyrosine-kinase family that also includes KIT, FLT3 and CSF1R (Ip et al., 2018; Liang et al., 2016). Orthologous receptors are described in Mus musculus (Guérit et al., 2021), Danio rerio and Xenopus laevis (Unknown Authors, 2018).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + phospho-protein-L-tyrosine (Guérit et al., 2021).

## Cofactor Requirements

Catalytic activity requires a divalent cation; Mg²⁺ is used in in-vitro kinase assays (Guérit et al., 2021; Liang et al., 2016).

## Substrate Specificity

Intrinsic autophosphorylation occurs on Tyr572/Tyr574 (SRC recruitment), Tyr720, Tyr742, Tyr754, and C-terminal Tyr762, Tyr1009 and Tyr1021 (Guérit et al., 2021; Paugh et al., 2013). No global linear consensus motif has been reported in available specificity atlases.

## Structure

Signal peptide → five Ig-like extracellular domains (D1–D5) → single transmembrane helix → juxtamembrane (JM) regulatory segment → bilobal kinase domain → C-terminal tail (Guérit et al., 2021).  
Crystal structure 5K5X (2.17 Å) captures an auto-inhibited kinase in which Val561 in the JM hydrophobic pocket and a Lys627–Glu644 salt bridge stabilize the inactive conformation; the activation loop contains the DFG motif (Asp842) and a unique αJ helix in the C-lobe (Liang et al., 2016). Cryo-EM reveals an asymmetric active dimer where activation-loop phosphorylation releases JM autoinhibition (Guérit et al., 2021).

## Regulation

• Autophosphorylation of JM Tyr572/Tyr574 relieves autoinhibition, and phosphorylation of activation-loop Tyr849/Tyr857 locks the active state (Guérit et al., 2021).  
• Additional phosphorylations (Tyr762, Tyr1009, Tyr1021) create PLCγ docking sites (Guérit et al., 2021).  
• CBL family E3 ligases bind phospho-receptor to promote ubiquitin-dependent internalisation and degradation (Ip et al., 2018).  
• Ligand-induced dimerisation triggers trans-phosphorylation; JM (e.g., V561D) or activation-loop (e.g., D842V) mutations bypass this control (Liang et al., 2016).

## Function

PDGFRA is predominantly expressed in mesenchymal progenitors, neural-crest derivatives, intestinal mesenchyme and the oligodendrocyte lineage; knockout mice exhibit craniofacial, skeletal and gastrointestinal defects and die embryonically (Guérit et al., 2021). Ligands PDGF-AA, ‑AB, ‑BB and ‑CC induce receptor dimerisation (Guérit et al., 2021). Phospho-Tyr572/574 recruits SRC family kinases; phospho-Tyr742 binds PI3K-p85; phospho-Tyr720/Tyr754 engage SHP2 and GRB2; C-terminal sites dock PLCγ, collectively activating PI3K-AKT, RAS-MAPK, SRC-RAC and STAT pathways to control proliferation, migration, extracellular-matrix synthesis and platelet activation (Guérit et al., 2021; Paugh et al., 2013; Ozawa et al., 2010).

## Inhibitors

• Type II (DFG-out) inhibitors: imatinib and sunitinib block wild-type and JM mutant receptors but not D842V (Liang et al., 2016; Guérit et al., 2021).  
• Type I (DFG-in) inhibitors: crenolanib and avapritinib inhibit activation-loop mutants, including D842V; avapritinib occupies a Gα sub-pocket revealed by co-crystal structures (Liang et al., 2016; Teuber et al., 2024).  
• Broad-spectrum TKIs dasatinib and PTK787 reduce signalling from extracellular mutants and fusion oncogenes (Ip et al., 2018; Ozawa et al., 2010).

## Other Comments

Oncogenic gain-of-function mutations cluster in the JM (V561D), N-lobe (N659K) and activation loop (D842V and exon 18 insertions), driving gastrointestinal stromal tumours and inflammatory fibroid polyps (Guérit et al., 2021). Diverse extracellular, transmembrane and kinase-domain mutations cause ligand-independent signalling in paediatric high-grade gliomas (Paugh et al., 2013). Neomorphic extracellular Y288C and myxoid glioneuronal tumour-specific K385I/L mutations promote constitutive dimerisation with altered subcellular localisation and differential TKI sensitivity (Ip et al., 2018; Villenfagne et al., 2024). Activation-loop D842V markedly increases ATP affinity (Km ≈ 5 µM), explaining resistance to type II inhibitors (Liang et al., 2016).

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