Phylogeny  
Human PDGFRA is a member of the Tyrosine Kinase (TK) group, class III receptor tyrosine-kinase family that also contains KIT, FLT3 and CSF1R (ip2018neomorphicpdgfraextracellular pages 13-14, liang2016structuralandbiochemical pages 12-17). Orthologs are reported in Mus musculus (guerit2021pdgfreceptormutations pages 1-2), Danio rerio and Xenopus laevis (unknownauthors2018daniorerioand pages 15-19).

Reaction Catalyzed  
ATP + protein-L-tyrosine → ADP + phospho-protein-L-tyrosine (guerit2021pdgfreceptormutations pages 2-5).

Cofactor Requirements  
Catalytic activity requires a divalent cation; Mg²⁺ is used in in-vitro kinase assays of PDGFRA (guerit2021pdgfreceptormutations pages 1-2, liang2016structuralandbiochemical pages 12-17).

Substrate Specificity  
Intrinsic autophosphorylation occurs on Tyr572/Tyr574 (SRC recruitment), Tyr720 and Tyr754 (SHP2/GRB2 binding) and Tyr742 (PI3K-p85 binding) (paugh2013noveloncogenicpdgfra pages 4-5). No global linear consensus motif has been reported in the 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 (guerit2021pdgfreceptormutations pages 1-2).  
Crystal structure 5K5X (2.17 Å) depicts an auto-inhibited kinase with N-lobe β-sheet, αC helix, activation loop containing the DFG motif (Asp842) and a unique αJ helix in the C-lobe; Val561 in the JM hydrophobic pocket and the Lys627-Glu644 salt bridge stabilize the inactive conformation (liang2016structuralandbiochemical pages 6-9, liang2016structuralandbiochemical pages 12-17). Cryo-EM shows an asymmetric active dimer in which activation-loop phosphorylation releases JM autoinhibition (guerit2021pdgfreceptormutations pages 2-5).

Regulation  
Autophosphorylation of JM Tyr572/Tyr574 relieves autoinhibition; phosphorylation of activation-loop Tyr849/Tyr857 locks the active state (guerit2021pdgfreceptormutations pages 2-5, paugh2013noveloncogenicpdgfra pages 4-5). Additional sites Tyr762, Tyr1009 and Tyr1021 support PLCγ docking (guerit2021pdgfreceptormutations pages 1-2). CBL family E3 ligases bind phospho-receptor and mediate ubiquitin-dependent internalisation and degradation (ip2018neomorphicpdgfraextracellular pages 13-14). Ligand-induced dimerisation triggers trans-phosphorylation; JM mutations (e.g., V561D) or activation-loop mutations (e.g., D842V) bypass this control (liang2016structuralandbiochemical pages 6-9).

Function  
Expression is predominant in mesenchymal progenitors, neural-crest derivatives, intestinal mesenchyme and oligodendrocyte lineage; knockout mice display craniofacial, skeletal and gastrointestinal defects with embryonic lethality (guerit2021pdgfreceptormutations pages 1-2, guerit2021pdgfreceptormutations pages 10-11). Ligands PDGF-AA, PDGF-AB, PDGF-BB and PDGF-CC induce receptor dimerisation (guerit2021pdgfreceptormutations pages 1-2). 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 that control proliferation, migration, extracellular-matrix synthesis and platelet activation (guerit2021pdgfreceptormutations pages 2-5, paugh2013noveloncogenicpdgfra pages 4-5, ozawa2010pdgfragenerearrangements pages 8-9).

Inhibitors  
Type II (DFG-out) inhibitors: imatinib, sunitinib block wild-type and JM mutant receptors but not D842V (liang2016structuralandbiochemical pages 6-9, guerit2021pdgfreceptormutations pages 8-9).  
Type I (DFG-in) inhibitors: crenolanib and avapritinib suppress activation-loop mutants including D842V; avapritinib occupies a Gα sub-pocket revealed by co-crystal structures (liang2016structuralandbiochemical pages 6-9, teuber2024avapritinibbasedsarstudies pages 1-2, teuber2024avapritinibbasedsarstudies pages 2-2).  
Broad-spectrum TKIs dasatinib and PTK787 reduce signalling from extracellular mutants and fusion oncogenes (ip2018neomorphicpdgfraextracellular pages 11-11, ozawa2010pdgfragenerearrangements pages 8-9).

Other Comments  
Oncogenic gain-of-function mutations cluster in the JM (V561D), N-lobe (N659K) and activation loop (D842V and related exon 18 insertions) driving gastrointestinal stromal tumours and inflammatory fibroid polyps (guerit2021pdgfreceptormutations pages 2-5). Diverse extracellular, transmembrane and kinase-domain mutations confer ligand-independent signalling in paediatric high-grade gliomas (paugh2013noveloncogenicpdgfra pages 1-2, paugh2013noveloncogenicpdgfra pages 8-9). Neomorphic extracellular Y288C and MGNT-specific K385I/L mutations promote constitutive dimerisation with distinct subcellular localisation and differential TKI sensitivity (ip2018neomorphicpdgfraextracellular pages 11-11, villenfagne2024pdgfrak385mutants pages 1-2, villenfagne2024pdgfrak385mutants pages 8-9). Activation-loop D842V markedly increases ATP affinity (Km ≈ 5 µM) explaining resistance to type II inhibitors (liang2016structuralandbiochemical pages 12-17).

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