## Phylogeny

VEGFR1/FLT1 is a member of the tyrosine kinase (TK) group, receptor tyrosine kinase (RTK) class, belonging to the PDGFR/VEGFR family that is highly conserved across vertebrates (Manning et al., 2002). Orthologues include mouse Flt1, rat Flt1/Vegfr1 and the C. elegans kinase VER-3 (Yaron-Barir et al., 2024). Mapping of VEGFR genes to paralogous HOX clusters points to origin by ancient genome and local duplications (Manning et al., 2002).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine-phosphate (Yaron-Barir et al., 2024; Koizumi et al., 2022).

## Cofactor Requirements

ATP is the phosphate donor; catalysis requires divalent Mg²⁺ or Mn²⁺ ions (Yaron-Barir et al., 2024).

## Substrate Specificity

Intrinsic specificity is dictated by residues flanking the target Tyr (0). One motif shows preference for Pro at –2 and +3, Ala at –3, and hydrophobic residues (Leu at +1/+2, Phe at +1) (Yaron-Barir et al., 2024). An alternative description notes acidic residues (Glu/Asp) at –5 to –1 and hydrophobic residues (Phe/Leu/Val) at +1 to +4 (Yaron-Barir et al., 2024).

## Structure

Single-pass transmembrane receptor comprising (i) an extracellular region with seven Ig-like domains that bind VEGF-A, VEGF-B and PGF, chiefly via domains 2–3 (Wang et al., 2011); (ii) a single α-helical transmembrane segment; and (iii) an intracellular tyrosine kinase domain interrupted by a kinase-insert sequence (Cai et al., 2011). Crystal structures of the human kinase domain (PDB 3HNG, 4D2N) reveal a canonical bilobal fold, with an N-lobe β-sheet, C-helix, catalytic loop and phosphorylation-regulated activation loop in the C-lobe (Asthana, 2019).

## Regulation

• Ligand binding promotes dimerisation and trans-autophosphorylation on Tyr-1169, Tyr-1213, Tyr-1242 and Tyr-1333, activating the kinase (Wang et al., 2011; Yaron-Barir et al., 2024).  
• VE-PTP, recruited by presenilin-1, dephosphorylates VEGFR1; PEDF also suppresses phosphorylation (Cai et al., 2011).  
• γ-Secretase cleaves the receptor within the transmembrane segment (Val767), releasing an intracellular fragment (Cai et al., 2011).  
• Membrane FLT1 is ubiquitinated and degraded via the proteasome; TNFSF15 promotes this process by inhibiting Akt (Qi et al., 2013).  
• TNFSF15 shifts splicing towards the soluble sFlt1 isoform through PKC, Src and Erk1/2 activation and Jmjd6 down-regulation (Qi et al., 2013).  
• In colorectal cancer cells, intracrine signalling renders VEGFR1 function independent of kinase activity (Unknown authors, 2016).

## Function

Expressed in endothelial cells, endothelial progenitor cells, macrophages and trophoblasts (Wang et al., 2011; Qi et al., 2013; Wu et al., 2017).  
• Signalling: principally drives cell migration via PI3K/Akt and Rac1; can also activate PLCγ-MAPK, p38 MAPK and modulate nitric-oxide production (Wang et al., 2011; Blanot et al., 2024).  
• Interactors: RACK1 scaffolds PI3K/Akt activation; pTyr-1169 recruits PLCγ; SHC1 and GRB2 participate downstream (Wang et al., 2011; Qi et al., 2013).  
• Angiogenesis: high-affinity but low-activity receptor acts as a VEGF-A “decoy,” restraining embryonic angiogenesis via sFlt1, yet can promote endothelial proliferation, survival and migration in adult tissues (Cai et al., 2011; Qi et al., 2013; Blanot et al., 2024).

## Inhibitors

• Direct kinase: ZM-306416 blocks PGF/FLT1 signalling (Wu et al., 2017).  
• Pathway: PI3K inhibitors (wortmannin, LY294002), Src inhibitor (PP2) and Erk1/2 inhibitors attenuate downstream signalling (Wang et al., 2011; Qi et al., 2013).  
• Process: γ-secretase inhibitor DAPT prevents intramembrane cleavage; MG132 (proteasome) and PYR-41 (ubiquitin-activating enzyme) block mFlt1 degradation (Cai et al., 2011; Qi et al., 2013).  
• Neutralising antibodies against FLT1 inhibit ligand binding (Wang et al., 2011).

## Other Comments

Elevated sFlt1 contributes to pre-eclampsia (Blanot et al., 2024; Qi et al., 2013). VEGFR1 supports tumour angiogenesis, invasion and metastasis in several cancers (Koizumi et al., 2022; Unknown authors, 2017). It is implicated in pathological ocular angiogenesis, fetal growth restriction, and Alzheimer’s disease-associated vascular pathology (Blanot et al., 2024; Wu et al., 2017; Wu et al., 2025). Mutation V767A abolishes γ-secretase cleavage of the receptor (Cai et al., 2011).

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