## Phylogeny

VEGFR1/FLT1 is classified within the Tyrosine Kinase (TK) group and is a member of the Receptor Tyrosine Kinase (RTK) class (manning2002theproteinkinase pages 2-3, manning2002theproteinkinase pages 3-3). Specifically, it belongs to the PDGFR/VEGFR family of RTKs, which are highly conserved across vertebrates (manning2002theproteinkinase pages 3-4). Orthologs have been identified in mouse (Flt1), rat (Flt1 or Vegfr1), and *Caenorhabditis elegans* (VER-3) (yaronbarir2024theintrinsicsubstrate pages 16-16, yaronbarir2024theintrinsicsubstrate pages 5-6). The mapping of VEGFR family members to paralogous HOX clusters suggests an origin via ancient genome and local gene duplications (manning2002theproteinkinase pages 2-3).

## Reaction Catalyzed

VEGFR1 is a tyrosine-protein kinase that catalyzes the transfer of a phosphate group from ATP to a tyrosine residue on a protein substrate (yaronbarir2024theintrinsicsubstrate pages 1-2, yaronbarir2024theintrinsicsubstrate pages 16-16). The reaction is: ATP + a [protein]-L-tyrosine = ADP + a [protein]-L-tyrosine phosphate (yaronbarir2024theintrinsicsubstrate pages 1-2, koizumi2022vegfapromotesthe pages 10-12).

## Cofactor Requirements

The catalytic kinase activity requires ATP as a phosphate donor cofactor (yaronbarir2024theintrinsicsubstrate pages 1-2, yaronbarir2024theintrinsicsubstrate pages 16-16, yaronbarir2024theintrinsicsubstrate pages 19-22). The reaction may also require divalent metal ions like Mg²⁺ or Mn²⁺ (yaronbarir2024theintrinsicsubstrate pages 4-5).

## Substrate Specificity

The intrinsic substrate specificity of VEGFR1 is determined by the amino acid sequence surrounding the target tyrosine residue (yaronbarir2024theintrinsicsubstrate pages 1-2, yaronbarir2024theintrinsicsubstrate pages 16-16). The preferred phosphorylation motif shows specific amino acid preferences at positions flanking the tyrosine (position 0). One characterization indicates preferences for Proline (P) at positions -2 and +3, Alanine (A) at -3, and hydrophobic residues such as Leucine (L) at +1 or +2 and Phenylalanine (F) at +1 (yaronbarir2024theintrinsicsubstrate pages 4-5). An alternative description of the motif shows preferences for acidic residues (Glutamate, Aspartate) at positions -5 to -1 and hydrophobic residues (Phenylalanine, Leucine, Valine) at positions +1 to +4 (yaronbarir2024theintrinsicsubstrate pages 16-16).

## Structure

VEGFR1 is a single-pass transmembrane receptor composed of an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain (cai2011γsecretaseandpresenilin pages 1-2, wang2011rack1regulatesvegfflt1mediated pages 1-2). \* **Extracellular Domain**: Contains seven immunoglobulin (Ig)-like domains responsible for binding ligands such as VEGF-A, VEGF-B, and PGF (cai2011γsecretaseandpresenilin pages 1-2, blanot2024afliberceptofftargeteffects pages 19-20). VEGF binding specifically occurs via the second and third Ig-like domains (wang2011rack1regulatesvegfflt1mediated pages 1-2). \* **Transmembrane Domain**: A single alpha-helix that anchors the receptor to the plasma membrane (cai2011γsecretaseandpresenilin pages 1-2). \* **Intracellular Domain**: Contains a tyrosine kinase domain that is split by a kinase-insert sequence (cai2011γsecretaseandpresenilin pages 1-2). The human VEGFR1 kinase domain has been structurally characterized by crystal structures, including PDB IDs 3HNG and 4D2N (asthana2019structuralandfunctional pages 5-13, asthana2019structuralandfunctional pages 86-91). These structures show a canonical bilobal fold with an N-terminal lobe composed of beta sheets and a larger, primarily helical C-terminal lobe (asthana2019structuralandfunctional pages 86-91). Key regulatory elements include the C-helix, located in the N-lobe, which aligns catalytic residues; the catalytic loop in the C-lobe, which facilitates phosphoryl transfer; and the activation loop, also in the C-lobe, which controls substrate access and kinase activity through phosphorylation-dependent conformational changes (asthana2019structuralandfunctional pages 5-13, asthana2019structuralandfunctional pages 86-91).

## Regulation

Regulation of VEGFR1 is multifaceted, involving ligand-induced activation, post-translational modifications, and proteolytic processing. \* **Phosphorylation**: Ligand binding induces dimerization and trans-autophosphorylation on specific tyrosine residues within the intracellular domain, which activates the kinase (wang2011rack1regulatesvegfflt1mediated pages 1-2, qi2013tnfsf15inhibitsvasculogenesis pages 6-6). Key autophosphorylation sites include Tyr-1169, Tyr-1213, Tyr-1242, and Tyr-1333 (wang2011rack1regulatesvegfflt1mediated pages 1-2, yaronbarir2024theintrinsicsubstrate pages 4-5). Dephosphorylation is mediated by vascular endothelial protein-tyrosine phosphatase (VE-PTP), a process facilitated by full-length presenilin 1 (Fl.PS1) acting as an adaptor (cai2011γsecretaseandpresenilin pages 1-2). Pigment epithelium-derived factor (PEDF) also inhibits VEGFR1 phosphorylation (cai2011γsecretaseandpresenilin pages 1-2). However, in the context of intracrine signaling in colorectal cancer cells, VEGFR1 function is independent of its kinase activity and autophosphorylation (unknownauthors2016intracrinevegfsignaling pages 6-8). \* **Proteolytic Cleavage**: VEGFR1 undergoes regulated intramembrane proteolysis by the γ-secretase complex at valine 767 in the transmembrane domain, which releases an intracellular fragment (cai2011γsecretaseandpresenilin pages 1-2). \* **Ubiquitination**: The membrane-bound form (mFlt1) is targeted for degradation by the ubiquitin-proteasome pathway, a process induced by TNFSF15 via deactivation of Akt (qi2013tnfsf15inhibitsvasculogenesis pages 2-4, qi2013tnfsf15inhibitsvasculogenesis pages 4-5). \* **Isoform Expression**: The balance between the membrane-bound (mFlt1) and soluble (sFlt1) isoforms is regulated. TNFSF15 enhances sFlt1 production by activating PKC, Src, and Erk1/2 signaling and by down-regulating the splicing factor Jmjd6 (qi2013tnfsf15inhibitsvasculogenesis pages 4-5, qi2013tnfsf15inhibitsvasculogenesis pages 5-6).

## Function

VEGFR1 is expressed on endothelial cells, endothelial progenitor cells (EPCs), macrophages, and trophoblasts, and it plays a complex role in vascular biology (wang2011rack1regulatesvegfflt1mediated pages 1-2, qi2013tnfsf15inhibitsvasculogenesis pages 4-5, wu2017decreasedpgfmay pages 7-8). \* **Signaling Pathways**: Activation of VEGFR1 predominantly stimulates cell migration through the PI3K/Akt and Rac1 signaling pathways (wang2011rack1regulatesvegfflt1mediated pages 1-2, wang2011rack1regulatesvegfflt1mediated pages 8-10). It can also activate other pathways, including PLCγ-MAPK and p38 MAPK, and modulate nitric oxide synthesis (wang2011rack1regulatesvegfflt1mediated pages 1-2, blanot2024afliberceptofftargeteffects pages 19-20). \* **Interacting Partners**: The scaffolding protein RACK1 directly interacts with Flt1 to mediate PI3K/Akt activation and cell migration (wang2011rack1regulatesvegfflt1mediated pages 8-10). Phosphorylated Tyr-1169 serves as a docking site for phospholipase C gamma (PLCγ) (wang2011rack1regulatesvegfflt1mediated pages 1-2). Other downstream interacting partners include SHC1 and GRB2 (qi2013tnfsf15inhibitsvasculogenesis pages 6-6, wang2011rack1regulatesvegfflt1mediated pages 1-2). \* **Role in Angiogenesis**: VEGFR1 has a dual role. It acts as a negative regulator of embryonic angiogenesis by sequestering VEGF-A, functioning as a “decoy receptor” due to its high ligand affinity but weak kinase activity (cai2011γsecretaseandpresenilin pages 1-2, wang2011rack1regulatesvegfflt1mediated pages 1-2). The soluble sFlt1 isoform is a primary mediator of this inhibitory effect (qi2013tnfsf15inhibitsvasculogenesis pages 6-6). In adults, it can act as a positive regulator, promoting endothelial cell proliferation, survival, and migration (blanot2024afliberceptofftargeteffects pages 19-20, koizumi2022vegfapromotesthe pages 13-13).

## Inhibitors

Experimental inhibitors that target VEGFR1 or its signaling pathways include: \* **Direct Kinase Inhibitors**: ZM-306416 is a specific inhibitor of PGF/FLT1 signaling (wu2017decreasedpgfmay pages 7-8). \* **Pathway Inhibitors**: PI3K inhibitors (wortmannin, LY294002), a Src inhibitor (PP2), and Erk1/2 inhibitors suppress VEGFR1-mediated signaling or regulation (wang2011rack1regulatesvegfflt1mediated pages 8-10, qi2013tnfsf15inhibitsvasculogenesis pages 2-4). \* **Process Inhibitors**: γ-secretase inhibitors (e.g., DAPT) block proteolytic cleavage, while proteasome (MG132) and ubiquitin (PYR-41) inhibitors prevent mFlt1 degradation (cai2011γsecretaseandpresenilin pages 1-2, qi2013tnfsf15inhibitsvasculogenesis pages 4-5). \* **Neutralizing Antibodies**: Antibodies against Flt1 can suppress its function by blocking ligand binding (wang2011rack1regulatesvegfflt1mediated pages 8-10).

## Other Comments

Dysregulation of VEGFR1 signaling is associated with several human diseases. \* **Pre-eclampsia**: Elevated circulating levels of the soluble sFlt1 isoform are a key pathogenic factor, causing endothelial dysfunction by sequestering VEGF and PGF (blanot2024afliberceptofftargeteffects pages 19-20, qi2013tnfsf15inhibitsvasculogenesis pages 6-6). \* **Cancer**: VEGFR1 promotes tumor angiogenesis, invasion, and metastasis, and its expression is elevated in several cancers, including glioblastoma, melanoma, and colorectal cancer (koizumi2022vegfapromotesthe pages 13-13, unknownauthors2017fmsrelatedtyrosine pages 1-2). \* **Ocular Diseases**: The receptor is implicated in pathological angiogenesis and vascular leakage in conditions such as diabetic retinopathy and cancer-associated retinopathy (blanot2024afliberceptofftargeteffects pages 19-20). \* **Fetal Growth Restriction (FGR)**: Reduced PGF/FLT1 signaling is linked to trophoblast dysfunction, compromised placental angiogenesis, and FGR (wu2017decreasedpgfmay pages 7-8). \* **Alzheimer’s Disease**: Increased FLT1 expression in brain endothelial cells and microglia correlates with cognitive decline and Aβ pathology (wu2025associationoften pages 4-5). \* **Disease Mutations**: A mutation of the γ-secretase cleavage site from valine to alanine (V767A) prevents the generation of the receptor’s intracellular fragment (cai2011γsecretaseandpresenilin pages 1-2).

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