## Phylogeny

• Kinome position: TK group → RTK family → VEGF receptor (type V) subfamily (stuttfeld2009structureandfunction pages 1-2).  
• Orthologs reported in Homo sapiens, Mus musculus, Rattus norvegicus, Gallus gallus, Xenopus laevis, Danio rerio; a single ancestral VEGFR-like receptor (D-VEGFR/PVR) occurs in Drosophila, indicating duplication/triplication events early in vertebrate evolution (shibuya2006signaltransductionby pages 1-2, stuttfeld2009structureandfunction pages 1-2, gordon2013flt4vegfr3andmilroy pages 25-30).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (roskoski2008vegfreceptorprotein–tyrosine pages 1-2).

## Cofactor Requirements

Catalytic activity requires Mg²⁺ to coordinate ATP phosphates (roskoski2008vegfreceptorprotein–tyrosine pages 1-2).

## Substrate Specificity

• Autophosphorylation sites in homodimers: Y1230, Y1231, Y1265, Y1337, Y1363 (lee2025vascularendothelialgrowth pages 7-8).  
• In VEGFR3–VEGFR2 heterodimers only Y1230, Y1231, Y1265 are phosphorylated, indicating context-dependent site usage (lee2025vascularendothelialgrowth pages 7-8).  
• Y1337 forms an SH2 docking motif recruiting SHC and GRB2 (asthana2019structuralandfunctional pages 33-36).  
• No consensus exogenous substrate motif has been defined in the available literature (roskoski2008vegfreceptorprotein–tyrosine pages 3-4).

## Structure

• Extracellular region: seven Ig-like domains; proteolytic cleavage within domain 5 leaves two fragments linked by a disulfide bond, modulating ligand access (shibuya2006signaltransductionby pages 2-4).  
• Transmembrane helix: residues 776–797 (roskoski2008vegfreceptorprotein–tyrosine pages 1-2).  
• Juxtamembrane segment: residues 798–844 (roskoski2008vegfreceptorprotein–tyrosine pages 1-2).  
• Cytoplasmic region: split kinase domain with canonical bilobed fold; key residues include Lys868 (β3) for ATP anchoring, Glu885 (αC) for catalytic salt-bridge, Asp1028 (HRD) as catalytic base, and Asp1046 (DFG) for Mg²⁺ coordination (roskoski2008vegfreceptorprotein–tyrosine pages 3-4).  
• Activation segment phosphorylation stabilizes the active conformation; hydrophobic spine and αC positioning are inferred to mirror VEGFR2 due to high sequence identity (roskoski2008vegfreceptorprotein–tyrosine pages 3-4).  
• No experimentally solved FLT4 crystal structure is presently cited; structural expectations derive from homologous VEGFR2 data (roskoski2008vegfreceptorprotein–tyrosine pages 4-5).

## Regulation

Post-translational modifications  
– Ligand-triggered autophosphorylation at Y1230/Y1231/Y1265/Y1337/Y1363 activates signaling (lee2025vascularendothelialgrowth pages 7-8).  
– Heterodimerization with VEGFR2 suppresses phosphorylation of Y1337 and Y1363, altering downstream signaling specificity (roskoski2008vegfreceptorprotein–tyrosine pages 3-4).  
– Integrin engagement activates c-Src, which phosphorylates VEGFR3 independent of ligand binding (asthana2019structuralandfunctional pages 139-142).

Proteolytic processing  
– Extracellular cleavage within Ig-domain 5 modulates ligand specificity and receptor activation (shibuya2006signaltransductionby pages 2-4, lee2025vascularendothelialgrowth pages 28-29).

Alternative splicing  
– Two C-terminal isoforms are produced; isoform 2 lacks several autophosphorylation sites and shows reduced signaling capacity (roskoski2008vegfreceptorprotein–tyrosine pages 2-3).

## Function

Expression  
– Broad endothelial expression during embryogenesis; post-natally restricted to lymphatic endothelium, fenestrated capillaries and selected veins (shibuya2006signaltransductionby pages 2-4, taipale1999vascularendothelialgrowth pages 4-6).

Upstream activators  
– VEGF-C and VEGF-D homodimers bind Ig-domains 1-2, driving receptor dimerization (shibuya2006signaltransductionby pages 2-4, taipale1999vascularendothelialgrowth pages 4-6).

Downstream signaling  
– Y1337-mediated SHC/GRB2 recruitment → RAS-MAPK cascade supporting proliferation (asthana2019structuralandfunctional pages 33-36).  
– PI3K-AKT pathway promotes survival (asthana2019structuralandfunctional pages 33-36, unknownauthors2022vegfavegfrssystemin pages 33-37).  
– PKC contributes to ERK activation (unknownauthors2022vegfavegfrssystemin pages 33-37).

Physiological roles  
– Essential for embryonic vascular remodeling; Vegfr3 knockout mice die by E9.5-E11 from blood-vessel defects (roskoski2008vegfreceptorprotein–tyrosine pages 3-4, taipale1999vascularendothelialgrowth pages 4-6).  
– Governs lymphangiogenesis, endothelial migration and sprouting in adult tissues (shibuya2001structureandfunction pages 1-4, unknownauthors2022vegfavegfrssystemin pages 29-33).  
– Forms heterodimers with VEGFR2, modulating KDR signaling output (lee2025vascularendothelialgrowth pages 28-29).

## Inhibitors

• Small-molecule tyrosine-kinase inhibitors active on VEGFR3: MAZ51, tivozanib, axitinib, vandetanib, sorafenib (asthana2019structuralandfunctional pages 139-142).  
• Multi-targeted agents approved for oncology, such as sunitinib and sorafenib, block VEGFR3 alongside VEGFR1/2 and PDGFRs (roskoski2008vegfreceptorprotein–tyrosine pages 4-5, roskoski2008vegfreceptorprotein–tyrosine pages 5-5).  
• Soluble receptor “ligand traps” sequester VEGF-C/D, functioning as decoy inhibitors (lee2025vascularendothelialgrowth pages 28-29).

## Other Comments

Disease associations  
– Germline loss-of-function mutations in FLT4 cause congenital lymphoedema 1 (Milroy disease) (gordon2013flt4vegfr3andmilroy pages 1-6).  
– Over 58 pathogenic variants catalogued; most are missense changes within the kinase domains that impair autophosphorylation and surface expression (gordon2013flt4vegfr3andmilroy pages 1-6, gordon2013flt4vegfr3andmilroy pages 10-15).  
– p.Ile1053Phe in the Chy mouse replicates human phenotype, confirming pathway relevance (gordon2013flt4vegfr3andmilroy pages 1-6).  
– A recessive p.Ser1235Cys variant causes mild hereditary lymphoedema via diminished kinase activity (melikhanrevzin2015anovelmissense pages 4-5).

References

1. (lee2025vascularendothelialgrowth pages 28-29): Chunsik Lee, Myung-Jin Kim, Anil Kumar, Han-Woong Lee, Yunlong Yang, and Yonghwan Kim. Vascular endothelial growth factor signaling in health and disease: from molecular mechanisms to therapeutic perspectives. Signal Transduction and Targeted Therapy, May 2025. URL: https://doi.org/10.1038/s41392-025-02249-0, doi:10.1038/s41392-025-02249-0. This article has 3 citations and is from a peer-reviewed journal.
2. (asthana2019structuralandfunctional pages 139-142): Mayanka Asthana. Structural and functional characterization of extracellular domains of vascular endothelial growth factor receptor 1 and 2. Unknown journal, 2019. URL: https://doi.org/10.5451/unibas-007168930, doi:10.5451/unibas-007168930. This article has 0 citations.
3. (asthana2019structuralandfunctional pages 33-36): Mayanka Asthana. Structural and functional characterization of extracellular domains of vascular endothelial growth factor receptor 1 and 2. Unknown journal, 2019. URL: https://doi.org/10.5451/unibas-007168930, doi:10.5451/unibas-007168930. This article has 0 citations.
4. (roskoski2008vegfreceptorprotein–tyrosine pages 1-2): Robert Roskoski. Vegf receptor protein–tyrosine kinases: structure and regulation. Biochemical and Biophysical Research Communications, 375:287-291, Oct 2008. URL: https://doi.org/10.1016/j.bbrc.2008.07.121, doi:10.1016/j.bbrc.2008.07.121. This article has 354 citations and is from a peer-reviewed journal.
5. (roskoski2008vegfreceptorprotein–tyrosine pages 2-3): Robert Roskoski. Vegf receptor protein–tyrosine kinases: structure and regulation. Biochemical and Biophysical Research Communications, 375:287-291, Oct 2008. URL: https://doi.org/10.1016/j.bbrc.2008.07.121, doi:10.1016/j.bbrc.2008.07.121. This article has 354 citations and is from a peer-reviewed journal.
6. (roskoski2008vegfreceptorprotein–tyrosine pages 3-4): Robert Roskoski. Vegf receptor protein–tyrosine kinases: structure and regulation. Biochemical and Biophysical Research Communications, 375:287-291, Oct 2008. URL: https://doi.org/10.1016/j.bbrc.2008.07.121, doi:10.1016/j.bbrc.2008.07.121. This article has 354 citations and is from a peer-reviewed journal.
7. (shibuya2001structureandfunction pages 1-4): M. Shibuya. Structure and function of vegf/vegf-receptor system involved in angiogenesis. Cell structure and function, 26 1:25-35, Feb 2001. URL: https://doi.org/10.1247/csf.26.25, doi:10.1247/csf.26.25. This article has 775 citations and is from a peer-reviewed journal.
8. (shibuya2006signaltransductionby pages 1-2): M. Shibuya and L. Claesson-Welsh. Signal transduction by vegf receptors in regulation of angiogenesis and lymphangiogenesis. Experimental cell research, 312 5:549-60, Mar 2006. URL: https://doi.org/10.1016/j.yexcr.2005.11.012, doi:10.1016/j.yexcr.2005.11.012. This article has 1436 citations and is from a peer-reviewed journal.
9. (shibuya2006signaltransductionby pages 2-4): M. Shibuya and L. Claesson-Welsh. Signal transduction by vegf receptors in regulation of angiogenesis and lymphangiogenesis. Experimental cell research, 312 5:549-60, Mar 2006. URL: https://doi.org/10.1016/j.yexcr.2005.11.012, doi:10.1016/j.yexcr.2005.11.012. This article has 1436 citations and is from a peer-reviewed journal.
10. (taipale1999vascularendothelialgrowth pages 4-6): J. Taipale, T. Makinen, E. Arighi, E. Kukk, M. Karkkainen, and K. Alitalo. Vascular endothelial growth factor receptor-3. Current Topics in Microbiology and Immunology, 237:85-96, Jan 1999. URL: https://doi.org/10.1007/978-3-642-59953-8\_5, doi:10.1007/978-3-642-59953-8\_5. This article has 145 citations and is from a peer-reviewed journal.
11. (gordon2013flt4vegfr3andmilroy pages 1-6): K. Gordon, S. Spiden, F. Connell, G. Brice, S. Cottrell, J. Short, Rohan Taylor, S. Jeffery, P. Mortimer, S. Mansour, and P. Ostergaard. Flt4/vegfr3 and milroy disease: novel mutations, a review of published variants and database update. Human Mutation, Jan 2013. URL: https://doi.org/10.1002/humu.22223, doi:10.1002/humu.22223. This article has 101 citations and is from a domain leading peer-reviewed journal.
12. (gordon2013flt4vegfr3andmilroy pages 10-15): K. Gordon, S. Spiden, F. Connell, G. Brice, S. Cottrell, J. Short, Rohan Taylor, S. Jeffery, P. Mortimer, S. Mansour, and P. Ostergaard. Flt4/vegfr3 and milroy disease: novel mutations, a review of published variants and database update. Human Mutation, Jan 2013. URL: https://doi.org/10.1002/humu.22223, doi:10.1002/humu.22223. This article has 101 citations and is from a domain leading peer-reviewed journal.
13. (gordon2013flt4vegfr3andmilroy pages 25-30): K. Gordon, S. Spiden, F. Connell, G. Brice, S. Cottrell, J. Short, Rohan Taylor, S. Jeffery, P. Mortimer, S. Mansour, and P. Ostergaard. Flt4/vegfr3 and milroy disease: novel mutations, a review of published variants and database update. Human Mutation, Jan 2013. URL: https://doi.org/10.1002/humu.22223, doi:10.1002/humu.22223. This article has 101 citations and is from a domain leading peer-reviewed journal.
14. (lee2025vascularendothelialgrowth pages 7-8): Chunsik Lee, Myung-Jin Kim, Anil Kumar, Han-Woong Lee, Yunlong Yang, and Yonghwan Kim. Vascular endothelial growth factor signaling in health and disease: from molecular mechanisms to therapeutic perspectives. Signal Transduction and Targeted Therapy, May 2025. URL: https://doi.org/10.1038/s41392-025-02249-0, doi:10.1038/s41392-025-02249-0. This article has 3 citations and is from a peer-reviewed journal.
15. (melikhanrevzin2015anovelmissense pages 4-5): Svetlana Melikhan-Revzin, Alina Kurolap, E. Dagan, A. Mory, and R. Gershoni-baruch. A novel missense mutation in flt4 causes autosomal recessive hereditary lymphedema. Lymphatic research and biology, 13 2:107-11, Jun 2015. URL: https://doi.org/10.1089/lrb.2014.0044, doi:10.1089/lrb.2014.0044. This article has 10 citations and is from a peer-reviewed journal.
16. (roskoski2008vegfreceptorprotein–tyrosine pages 4-5): Robert Roskoski. Vegf receptor protein–tyrosine kinases: structure and regulation. Biochemical and Biophysical Research Communications, 375:287-291, Oct 2008. URL: https://doi.org/10.1016/j.bbrc.2008.07.121, doi:10.1016/j.bbrc.2008.07.121. This article has 354 citations and is from a peer-reviewed journal.
17. (roskoski2008vegfreceptorprotein–tyrosine pages 5-5): Robert Roskoski. Vegf receptor protein–tyrosine kinases: structure and regulation. Biochemical and Biophysical Research Communications, 375:287-291, Oct 2008. URL: https://doi.org/10.1016/j.bbrc.2008.07.121, doi:10.1016/j.bbrc.2008.07.121. This article has 354 citations and is from a peer-reviewed journal.
18. (stuttfeld2009structureandfunction pages 1-2): Edward Stuttfeld and Kurt Ballmer‐Hofer. Structure and function of vegf receptors. IUBMB Life, Sep 2009. URL: https://doi.org/10.1002/iub.234, doi:10.1002/iub.234. This article has 352 citations and is from a peer-reviewed journal.
19. (unknownauthors2022vegfavegfrssystemin pages 29-33): VEGF-A/VEGFRs system in neuropathies: a crossroad between pain and neuroprotection
20. (unknownauthors2022vegfavegfrssystemin pages 33-37): VEGF-A/VEGFRs system in neuropathies: a crossroad between pain and neuroprotection