1. Phylogeny  
   Vascular endothelial growth factor receptor 3 (VEGFR3), encoded by the FLT4 gene and also known as Fms‐like tyrosine kinase 4, is a member of the receptor tyrosine kinase family that specifically belongs to the VEGF receptor subfamily responsible for vascular and lymphatic development (brunet2016wholegenomeduplications pages 4-4, brunet2016wholegenomeduplications pages 7-7). Orthologs of VEGFR3 are conserved across all mammalian species and its evolutionary origins can be traced back to the whole genome duplications that occurred in jawed vertebrates, a process that expanded the receptor tyrosine kinase repertoire and gave rise to distinct VEGFR paralogues (brunet2016wholegenomeduplications pages 4-4, brunet2016wholegenomeduplications pages 7-7). In addition, its phylogenetic relationship with other members of the VEGF receptor family—such as VEGFR1 and VEGFR2—places VEGFR3 within an evolutionarily conserved signaling module pivotal to both angiogenesis and lymphangiogenesis (clark2022pullingbackthe pages 23-24).
2. Reaction Catalyzed  
   VEGFR3 functions as a receptor tyrosine kinase that catalyzes an ATP-dependent phosphorylation reaction; it transfers the γ-phosphate group from ATP to tyrosine residues on substrate proteins, including autophosphorylation sites on its own intracellular domain (shibuya2010tyrosinekinasereceptor pages 1-2, haddad2012theimmunopharmacologicpotential pages 5-6). This reaction can be summarized as: ATP + [protein]-L-tyrosine → ADP + [protein]-phosphotyrosine + H⁺ (shibuya2010tyrosinekinasereceptor pages 1-2, haddad2012theimmunopharmacologicpotential pages 5-6).
3. Cofactor Requirements  
   The kinase activity of VEGFR3 is dependent on divalent metal ions, primarily Mg²⁺, which are required to coordinate ATP within its active site and facilitate the efficient transfer of the phosphate group during catalysis (haddad2012theimmunopharmacologicpotential pages 5-6, gao2013abroadactivity pages 6-8).
4. Substrate Specificity  
   VEGFR3 phosphorylates specific tyrosine residues on its cytoplasmic tail via autophosphorylation, thereby creating docking sites for downstream adaptor proteins containing SH2 domains; these interactions are crucial for the propagation of intracellular signaling cascades involved in lymphangiogenesis and vascular remodeling (shibuya2010tyrosinekinasereceptor pages 2-3, haddad2012theimmunopharmacologicpotential pages 5-6). Although a defined consensus substrate motif for VEGFR3 has not been explicitly detailed in the literature provided, its substrate specificity is inferred from its role in phosphorylation of signaling effectors that mediate endothelial cell responses.
5. Structure  
   VEGFR3 is organized into three major regions. The extracellular domain is composed of approximately seven immunoglobulin-like (Ig-like) loops that provide the structural framework for high-affinity binding to its ligands, VEGF-C and VEGF-D; notably, the fifth Ig-like domain undergoes proteolytic cleavage, and the resultant fragments remain linked by a disulfide bond, conferring stability and specificity to ligand binding (zecchin2014reversibleacetylationregulates pages 55-60, zecchin2014reversibleacetylationregulates pages 75-80). This is followed by a single transmembrane helix that anchors the receptor in the plasma membrane. The intracellular portion contains a split tyrosine kinase domain responsible for catalyzing the phosphorylation reaction; this catalytic module includes essential features such as the activation loop, the hydrophobic spine, and the C-helix, all of which are critical for the conformational changes required for full enzymatic activity (zecchin2014reversibleacetylationregulates pages 50-55). Isoform diversity further refines its function: isoform 1 and isoform 2 are membrane-anchored, with isoform 2 possessing a truncated C-terminus that lacks several phosphotyrosine docking sites, rendering it less efficient in downstream signal transduction, while a secreted isoform (isoform 3) may function as a decoy receptor to attenuate VEGF-C/VEGF-D signaling (kunnapuu2021proteolyticcleavagesin pages 1-2).
6. Regulation  
   The activation of VEGFR3 is initiated by ligand binding; VEGF-C and VEGF-D, which are synthesized as inactive precursor proteins, must undergo regulated proteolytic cleavages to become fully active and capable of binding VEGFR3 (kunnapuu2021proteolyticcleavagesin pages 13-14). Ligand binding triggers receptor dimerization and subsequent autophosphorylation on key tyrosine residues within its intracellular domain, thereby generating docking sites for downstream signaling molecules (shibuya2010tyrosinekinasereceptor pages 1-2). This receptor-mediated signaling is further modulated through heterodimerization with VEGFR2 (KDR), which alters the overall signaling output and influences angiogenic sprouting (haddad2012theimmunopharmacologicpotential pages 3-5). In addition, activated VEGFR3 engages in a positive feedback mechanism by promoting the enhanced production of VEGF-C (and, to a lesser extent, VEGF-A), thereby further amplifying its own signal (kunnapuu2021proteolyticcleavagesin pages 19-20). Post-translational modifications—primarily phosphorylation, and in related receptors reversible acetylation as observed for VEGFR2—play an essential role in tuning the kinase activity and downstream signaling pathways (zecchin2014reversibleacetylationregulates pages 172-176).
7. Function  
   VEGFR3 is primarily expressed on lymphatic endothelial cells and is essential for the process of lymphangiogenesis, both during embryonic development of the vascular network and in the maintenance of the adult lymphatic system (kunnapuu2021proteolyticcleavagesin pages 1-2, hong2004developmentofthe pages 4-5). Upon activation by its ligands, active VEGFR3 promotes proliferation, survival, and migration of endothelial cells, thus playing a pivotal role in the formation of new lymphatic vessels and the regulation of angiogenic sprouting (shibuya2010tyrosinekinasereceptor pages 1-2). Furthermore, VEGFR3 modulates blood vascular development by forming heterodimers with VEGFR2, contributing to fine-tuning the balance between angiogenesis and lymphangiogenesis (haddad2012theimmunopharmacologicpotential pages 3-5). The positive feedback loop established by VEGFR3 signaling—namely, the receptor’s ability to enhance local production of VEGF-C and, to a lesser degree, VEGF-A—further underscores its critical role in maintaining vascular homeostasis (kunnapuu2021proteolyticcleavagesin pages 19-20).
8. Other Comments  
   Isoform diversity of VEGFR3 contributes to its complex regulatory roles; for instance, the secreted isoform 3 functions as a decoy receptor to sequester VEGF-C and VEGF-D, thereby acting as a negative regulator of lymphangiogenesis and angiogenesis (kunnapuu2021proteolyticcleavagesin pages 1-2). Furthermore, genetic studies have identified mutations in FLT4 that are linked to hereditary lymphedema, such as Milroy disease, with specific point mutations in the kinase domain (e.g., I1053F) resulting in impaired receptor signaling (clark2022pullingbackthe pages 23-24). Pharmacological targeting of VEGFR3 has been investigated using small-molecule tyrosine kinase inhibitors—for example, compounds initially developed for anti-angiogenic therapy, including SU-5416, have demonstrated inhibitory effects on VEGFR signaling, offering potential therapeutic benefits for conditions such as tumor lymphangiogenesis and metastasis (haddad2012theimmunopharmacologicpotential pages 19-20, gao2013abroadactivity pages 6-8). Additionally, proper proteolytic processing of VEGF-C and VEGF-D is critical for effective VEGFR3 activation, and dysregulation of these proteolytic events can lead to pathological states associated with lymphatic vascular disorders (kunnapuu2021proteolyticcleavagesin pages 19-20).
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