1. Phylogeny  
   Vascular endothelial growth factor receptor 2 (VEGFR2), also known as KDR or FLK1, belongs to the receptor tyrosine kinase family and is a member of the VEGF receptor subgroup, which also includes VEGFR1 and VEGFR3. Its domain organization, characterized by extracellular immunoglobulin‐like repeats and an intracellular kinase domain, is highly conserved across vertebrate species, with orthologs found in mouse (Flk-1) and human (KDR) that have maintained similar functional roles in vascular development and angiogenesis (shaik2020structuralbasisfor pages 1-4, nascimento2021diagnosticvalueof pages 1-2).
2. Reaction Catalyzed  
   VEGFR2 catalyzes the transfer of a phosphate group from ATP to specific tyrosine residues on substrate proteins. The overall chemical reaction can be expressed as: ATP + protein – tyrosine → ADP + protein – phosphotyrosine + H⁺, which is typical for receptor tyrosine kinases acting on their substrates during autophosphorylation and downstream signal propagation (zhang2009preparationofextracellular pages 1-2, nascimento2021diagnosticvalueof pages 1-2).
3. Cofactor Requirements  
   The kinase activity of VEGFR2 is dependent on the coordination of ATP and requires divalent metal ions, specifically Mg²⁺, to stabilize the phosphates of ATP during the phosphorylation reaction. This cofactor requirement is essential for the catalytic function of VEGFR2 and for efficient transfer of phosphate groups to tyrosine residues (nascimento2021diagnosticvalueof pages 1-2, shaik2020structuralbasisfor pages 10-12).
4. Substrate Specificity  
   VEGFR2 displays substrate specificity characteristic of receptor tyrosine kinases by preferentially phosphorylating tyrosine residues on its own cytoplasmic domain and on downstream signaling proteins. Key autophosphorylation sites, such as Y801, Y951, Y1059, and Y1175, serve as docking sites for adaptor proteins and enzymes that propagate downstream signaling signals, thereby regulating endothelial cell migration, proliferation, and survival (shaik2020structuralbasisfor pages 12-14).
5. Structure  
   VEGFR2 is organized into a modular structure comprising an extracellular region, a single transmembrane helix, and an intracellular portion. The extracellular domain contains seven immunoglobulin-like (Ig-like) domains, which mediate high-affinity binding to VEGF ligands and participate in ligand-induced dimerization; domains not only promote ligand recognition but also contribute to homotypic interactions essential for receptor activation (zhang2009preparationofextracellular pages 1-2, shaik2020structuralbasisfor pages 1-4). The transmembrane segment is a hydrophobic α-helical domain that anchors the receptor in the plasma membrane and participates in non-covalent receptor oligomerization. The intracellular region comprises a juxtamembrane domain, a split tyrosine kinase (TK) domain that is structurally organized into N-terminal and C-terminal lobes forming an ATP-binding cleft, and a flexible C-terminal tail. Key catalytic features of the kinase domain include a glycine-rich loop, a conserved hinge region, an activation loop (A-loop) containing the DFG motif essential for Mg²⁺ coordination, and a catalytic HRD motif, all of which are critical for kinase activity and inhibitor binding (shaik2020structuralbasisfor pages 4-6, hilberg2008bibf1120triple pages 3-4).
6. Regulation  
   VEGFR2 is regulated primarily through ligand-induced dimerization and subsequent autophosphorylation on multiple intracellular tyrosine residues. Binding of VEGF-A, VEGF-C, or VEGF-D to the extracellular Ig-like domains induces receptor dimerization, which facilitates trans-autophosphorylation at key sites such as Y801, Y951, Y1059, and Y1175; these phosphorylated residues then act as recruitment sites for downstream signaling proteins (shaik2020structuralbasisfor pages 12-14, hilberg2008bibf1120triple pages 1-2). In addition to phosphorylation, allosteric conformational changes in the kinase domain—including rearrangements of the activation loop and the C-helix—further regulate enzymatic activity. These post-translational modifications control the assembly of signaling complexes and modulate receptor internalization, recycling, and degradation, thereby fine-tuning VEGFR2-mediated signal transduction (hilberg2008bibf1120triple pages 1-2, shaik2020structuralbasisfor pages 23-24).
7. Function  
   VEGFR2 functions as the primary signal transducer for vascular endothelial growth factors, playing an essential role in angiogenesis, vascular permeability, and vascular development. Upon ligand binding, activated VEGFR2 promotes autophosphorylation and triggers multiple downstream signaling cascades, including the phospholipase C-γ (PLCγ), MAP kinase, and PI3K/AKT pathways. These cascades mediate critical biological processes such as endothelial cell proliferation, migration, survival, and reorganization of the actin cytoskeleton. In addition, VEGFR2 is involved in embryonic hematopoiesis and modulates lymphangiogenesis by forming heterodimers with FLT4, thereby influencing FLT4 signaling through isoforms that act as decoy receptors (nascimento2021diagnosticvalueof pages 1-2, koo2021therapeuticefficacyof pages 22-23).
8. Other Comments  
   Several inhibitors have been developed that specifically target VEGFR2, including both monoclonal antibodies (e.g., ramucirumab) and small-molecule tyrosine kinase inhibitors (e.g., BIBF 1120, sunitinib, sorafenib, and lenvatinib). These agents are used clinically to treat cancers and neovascular ocular diseases by suppressing pathological angiogenesis driven by VEGFR2 signaling. In addition to its canonical signaling functions, alternative isoforms of VEGFR2 lacking the transmembrane domain may function as decoy receptors to attenuate VEGF-A, VEGF-C, and VEGF-D activity, thereby modulating the intensity of angiogenic responses. Although specific disease-related mutations in VEGFR2 are not extensively detailed in the provided sources, alterations in receptor structure and function have been implicated in drug resistance and aberrant vascular growth in pathological conditions (hilberg2008bibf1120triple pages 8-9, stahl2002naturalproductderived pages 3-4, koo2021therapeuticefficacyof pages 22-23).
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