## Phylogeny

Vascular endothelial growth factor receptor 2 (VEGFR-2; human KDR, murine Flk-1) belongs to the receptor tyrosine kinase (RTK) family, tyrosine kinase group, and specifically to the PDGFR/VEGFR subfamily. It shares sequence homology with VEGFR-1, VEGFR-3, PDGFRα/β, c-Kit and CSF-1R (McTigue et al., 1999; Modi & Kulkarni, 2019). The mouse ortholog Flk-1 is ~85 % identical to the human protein (Boyer, 2002).

## Reaction Catalyzed

ATP + protein-L-tyrosyl → ADP + H⁺ + O-phospho-protein-L-tyrosyl (McTigue et al., 1999; Modi & Kulkarni, 2019). The reaction proceeds strongly in the forward (phosphorylation) direction.

## Cofactor Requirements

Catalysis requires divalent cations, optimally Mg²⁺ or Mn²⁺; Kₘ for MgATP ≈ 150 µM (Huang et al., 2012; Modi & Kulkarni, 2019; Park et al., 2018; Shah et al., 2025; McTigue et al., 1999).

## Substrate Specificity

Consensus motifs derived from peptide screens show preferred acidic residues (E/D) at −3 and −2, basic residues (R/K) at −1, small/polar residues (S/T/G) at +1, and hydrophobic/aliphatic residues at +2/+3 (Yaron-Barir et al., 2024). An alternative dataset reports enrichment for basic residues (R/K) at −3 and small residues (S) at −1, indicating context-dependent variability (Yaron-Barir et al., 2024).

## Structure

The 1 356-residue glycoprotein comprises: signal peptide (1–19), extracellular region with seven Ig-like domains (20–764), transmembrane helix (765–789), juxtamembrane segment (790–833), bilobal cytoplasmic kinase domain containing a 68-residue insert (ATP-binding N-lobe, catalytic C-lobe) and a C-terminal tail (Shah et al., 2025; McTigue et al., 1999). Key regulatory elements are the αC-helix, hydrophobic spine (e.g., Phe918, Phe1047) and activation loop (1045–1075) (McTigue et al., 1999; Shah et al., 2025; Toledo et al., 2017). Representative crystal structures include the phosphorylated apo-kinase (PDB 1VR2) and an axitinib complex (PDB 4AG8) (McTigue et al., 1999; Toledo et al., 2017).

## Regulation

Ligand binding (VEGF-A/C/D) drives receptor dimerization and trans-autophosphorylation on ∼15 intracellular tyrosines (Huang et al., 2012; Park et al., 2018). Major sites include Y951 (TSAd recruitment), Y1054/Y1059 (activation loop), Y1175 (PLCγ binding) and Y1214 (actin remodelling) (Modi & Kulkarni, 2019; McTigue et al., 1999). N-linked glycosylation (18 sites) supports maturation; ubiquitination can promote degradation (Modi & Kulkarni, 2019; Shah et al., 2025). Small-molecule inhibitors may stabilize inactive “DFG-out” conformations (Huang et al., 2012).

## Function

VEGFR-2 is highly expressed in vascular endothelial cells and hematopoietic stem cells (Huang et al., 2012). Upon activation it recruits SHB, SCK, PLCγ and others, initiating PLCγ, PI3K/Akt and MAPK cascades that drive angiogenesis, vasculogenesis, endothelial proliferation, survival, migration and vascular permeability (Huang et al., 2012; McTigue et al., 1999; Shah et al., 2025).

## Inhibitors

ATP-competitive TKIs include sunitinib, axitinib, sorafenib, lenvatinib, pazopanib, regorafenib, cabozantinib and vatalanib; binding modes are classified as type I–III (Huang et al., 2012; Modi & Kulkarni, 2019). Biologics comprise ramucirumab (receptor-directed) and bevacizumab (ligand-directed) (Park et al., 2018).

## Other Comments

Hyperactive VEGFR-2 signalling underlies pathological angiogenesis in cancers (breast, cervical, NSCLC, HCC, renal) and eye disease (macular degeneration) (Huang et al., 2012; Modi & Kulkarni, 2019; McTigue et al., 1999). Somatic KDR mutations occur in 1–3 % of tumours: L840F in the ATP pocket reduces activity and confers TKI resistance, R1032Q sensitises to cabozantinib, and K868M is kinase-dead (Toledo et al., 2017).

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