## Phylogeny

Orthologs are conserved throughout vertebrates, including mouse Tie2, rat Tie2, zebrafish tek, and chicken Tek, underscoring an essential vascular role (duran2021targetingtie2in pages 1-2, sato1998characterizationoftek pages 6-8).  
Within the human kinome TEK/TIE2 belongs to the receptor tyrosine kinase (RTK) group, Tie sub-family, which comprises Tie1 and Tie2 and is evolutionarily closest to the FGFR branch based on sequence/structural homology (barton2014tie2andeph pages 1-2, shewchuk2000structureofthe pages 2-3).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (shewchuk2000structureofthe pages 2-3).

## Cofactor Requirements

Catalysis requires a divalent cation; crystal structures show Mg²⁺ coordinated by the activation-loop Asp and ATP phosphates (shewchuk2000structureofthe pages 3-4).

## Substrate Specificity

The 2024 human tyrosine-kinome atlas includes TEK/TIE2 in its specificity clustering, indicating that an intrinsic positional weight matrix has been determined; however, the explicit consensus motif is not provided in the excerpt (yaronbarir2024theintrinsicsubstrate pages 16-16).

## Structure

Domain organization  
• Extracellular ectodomain: Ig1–Ig3 → EGF1–EGF3 → FNIII1–FNIII3 (barton2014tie2andeph pages 4-5).  
• Single-pass transmembrane helix.  
• Cytoplasmic region: split kinase domain (residues 808-1124) followed by an extended C-terminal tail harbouring three regulatory tyrosines (barton2014tie2andeph pages 5-6).

Three-dimensional features  
• Ectodomain forms an arrowhead; Ig2 is the ligand-binding tip that engages angiopoietin fibrinogen-like domains with minimal induced fit (barton2014tie2andeph pages 4-5).  
• FNIII3 mediates constitutive homodimerization via an intermolecular β-sheet placing the two C-termini ~25 Å apart; this geometry is essential for activation and is further stabilized by agonistic antibody hTAAB (leppanen2017structuralbasisof pages 5-6, jo2021structuralinsightsinto pages 1-2).  
• Kinase domain crystal structure (PDB 1FVR, 2.2 Å) displays the canonical bilobal RTK fold with distinctive autoinhibitory elements:  
– Gly-rich nucleotide-binding loop (832-836) folds into the ATP site, blocking ligand binding (shewchuk2000structureofthe pages 4-6).  
– Activation loop (982-1008) is in an “active-like” conformation yet unphosphorylated; contains single Tyr992 (shewchuk2000structureofthe pages 3-4).  
– αC helix is displaced 2.5-5.5 Å relative to FGFR1, disrupting the Lys855-Glu872 salt bridge and suppressing catalysis (shewchuk2000structureofthe pages 2-3).  
– Hydrophobic regulatory spine is present but misaligned in the inhibited state (shewchuk2000structureofthe pages 8-9).  
– C-terminal tail (1100-1124) packs under the catalytic cleft as a substrate mimetic (barton2014tie2andeph pages 5-6, shewchuk2000structureofthe pages 4-6).

## Regulation

Post-translational modifications  
• Autophosphorylation sites: Tyr1101 (recruits Grb2/p85-PI3K), Tyr1107 (binds Dok-R), Tyr1112 (binds SH-PTP2), and Tyr992 in the activation loop (barton2014tie2andeph pages 5-6, shewchuk2000structureofthe pages 3-4).  
• VE-PTP (PTPRB) directly dephosphorylates TEK, restraining signalling; pharmacologic or genetic VE-PTP inhibition increases TEK phosphorylation (fonodi2024roleofprotein pages 18-20).  
• VEGF-triggered PI3K/Akt activation stimulates ADAM protease–mediated ectodomain shedding, generating soluble TIE2 and dampening signalling (findley2007vegfinducestie2 pages 11-15, findley2007vegfinducestie2 pages 7-7).  
• Shear stress enhances phosphorylation; ubiquitination or acetylation have not been reported in the cited literature (du2017reviewofthe pages 8-9).

Conformational and allosteric control  
• Autoinhibition is enforced by the nucleotide-binding loop, activation loop and C-tail; deletion of the last 15 residues markedly increases activity (barton2014tie2andeph pages 5-6).  
• Tie1 forms ligand-independent heterodimers that reduce TEK phosphorylation; Ang1 disrupts whereas Ang2 stabilises these complexes (barton2014tie2andeph pages 5-6).  
• Receptor clustering via FNIII3 domain or multimeric agonists overrides autoinhibition and is obligatory for kinase activation (leppanen2017structuralbasisof pages 5-6, jo2021structuralinsightsinto pages 1-2).  
• Activating missense mutations such as R849W or Y897S destabilise the inhibitory nucleotide-binding loop and cause ligand-independent signalling (shewchuk2000structureofthe pages 4-6).

## Function

Expression pattern  
Highly expressed in vascular and lymphatic endothelial cells, endothelial progenitors, subsets of CD34⁺ hematopoietic stem cells, and ~20 % of CD19⁺ B lymphocytes; up-regulated in tumour vasculature (duran2021targetingtie2in pages 1-2, sato1998characterizationoftek pages 5-6).

Upstream ligands  
Angiopoietin-1 (full agonist), Angiopoietin-2 (context-dependent partial agonist/antagonist), and Angiopoietin-4 (agonist) bind Ig2 (thurston2003roleofangiopoietins pages 2-3, sato1998characterizationoftek pages 3-5).

Downstream signalling  
Phospho-Tyr1101 recruits p85-PI3K and Grb2, activating Akt and MAPK; phospho-Tyr1107 engages Dok-R to drive motility; phospho-Tyr1112 binds SH-PTP2 to provide negative feedback (barton2014tie2andeph pages 5-6, natynki2015commonandspecific pages 5-6).

Biological roles  
Controls vascular sprouting, maturation, barrier integrity, anti-inflammatory quiescence, and adhesion/quiescence of hematopoietic stem cells (duran2021targetingtie2in pages 1-2, sato1998characterizationoftek pages 6-8).

## Inhibitors

• Rebastinib: multi-target kinase inhibitor with high affinity for TEK; suppresses tumour growth and metastasis in breast-cancer models (unknownauthors2020characterizationofthe pages 31-34).  
• Regorafenib: clinically approved multi-kinase inhibitor that includes TEK among its targets (khan2021ang2inhibitorsand pages 6-7).  
• AKB-9778: selective VE-PTP inhibitor that indirectly enhances TEK phosphorylation and vascular stabilisation (khan2021ang2inhibitorsand pages 9-10, saharinen2017therapeutictargetingof pages 16-17).

## Other Comments

Heterozygous activating TEK mutations (e.g., R849W, Y897S, Y897F-R915L) cause autosomal-dominant venous malformations with ectatic, pericyte-poor vessels (thurston2003roleofangiopoietins pages 2-3, natynki2015commonandspecific pages 5-6).  
Tek-null mice die by embryonic day 10.5 from defective vascular remodelling and hematopoietic failure, demonstrating its non-redundant developmental function (thurston2003roleofangiopoietins pages 2-3).

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