## Phylogeny

The receptor tyrosine kinase TEK/TIE2 is highly conserved across vertebrates, with orthologs reported in mouse, rat, zebrafish and chicken, highlighting an essential vascular role (Duran et al., 2021; Sato et al., 1998). Within the human kinome it resides in the RTK group, Tie sub-family (Tie1, Tie2) and is most closely related to fibroblast growth factor receptors based on sequence/structural homology (Barton et al., 2014; Shewchuk et al., 2000).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (Shewchuk et al., 2000).

## Cofactor Requirements

Catalysis requires a divalent metal ion; crystal structures show Mg²⁺ coordinated between ATP phosphates and the activation-loop Asp (Shewchuk et al., 2000).

## Substrate Specificity

The 2024 human tyrosine-kinome atlas clusters TEK/TIE2 and reports that an intrinsic positional weight matrix has been defined, although the precise consensus sequence was not detailed in the excerpt (Yaron-Barir et al., 2024).

## Structure

Domain organisation: Ig1–Ig3, EGF1–EGF3 and FNIII1–FNIII3 ectodomain → single-pass transmembrane helix → cytoplasmic split kinase domain (residues 808-1124) followed by a C-terminal tail containing three regulatory tyrosines (Barton et al., 2014).  
Key 3-D features:  
• Arrow-head ectodomain; Ig2 mediates ligand binding with minimal induced fit (Barton et al., 2014).  
• FNIII3 drives constitutive homodimerisation; agonistic antibody hTAAB further stabilises this interface (Leppänen et al., 2017; Jo et al., 2021).  
• Kinase domain (PDB 1FVR) adopts a bilobal RTK fold with three autoinhibitory elements: folded Gly-rich loop (832-836), displaced αC helix disrupting Lys855-Glu872 salt bridge, and C-terminal tail that inserts as a substrate mimic; the activation loop (982-1008, Tyr992) is “active-like” yet unphosphorylated (Shewchuk et al., 2000; Barton et al., 2014).  
• Hydrophobic regulatory spine present but mis-aligned in the inhibited state (Shewchuk et al., 2000).

## Regulation

Post-translational control: autophosphorylation on Tyr1101, Tyr1107, Tyr1112 and Tyr992; VE-PTP dephosphorylates TEK, whereas PI3K/Akt-driven ADAM protease activity sheds the ectodomain, generating soluble TIE2 (Barton et al., 2014; Fonódi et al., 2024; Findley et al., 2007). Shear stress increases phosphorylation (Du et al., 2017).  
Conformational/allosteric control: the Gly-rich loop, activation loop and C-tail impose autoinhibition; C-tail deletion or disease-linked mutations (e.g., R849W, Y897S) elevate basal activity (Barton et al., 2014; Shewchuk et al., 2000). Receptor clustering via FNIII3 or multimeric agonists overrides inhibition, whereas Tie1 heterodimers dampen signalling in the absence of agonist (Barton et al., 2014; Leppänen et al., 2017; Jo et al., 2021).

## Function

Expression pattern: abundant in vascular and lymphatic endothelial cells, endothelial progenitors, ~20 % of CD19⁺ B cells and subsets of CD34⁺ hematopoietic stem cells; up-regulated in tumour vasculature (Duran et al., 2021; Sato et al., 1998).  
Upstream ligands: Angiopoietin-1 (agonist), Angiopoietin-2 (context-dependent partial agonist/antagonist), Angiopoietin-4 (agonist) bind the Ig2 domain (Thurston, 2003; Sato et al., 1998).  
Downstream signalling: phospho-Tyr1101 recruits p85-PI3K/Grb2 (Akt, MAPK activation); phospho-Tyr1107 binds Dok-R (cell motility); phospho-Tyr1112 engages SH-PTP2 for negative feedback (Barton et al., 2014; Natynki et al., 2015).  
Physiological roles: governs vascular sprouting, maturation, barrier integrity, anti-inflammatory quiescence, and adhesion/quiescence of hematopoietic stem cells (Duran et al., 2021; Sato et al., 1998).

## Inhibitors

• Rebastinib – high-affinity multi-kinase inhibitor that suppresses tumour growth/metastasis in breast-cancer models (Unknown authors, 2020).  
• Regorafenib – approved multi-kinase inhibitor that targets TEK among others (Khan et al., 2021).  
• AKB-9778 – selective VE-PTP inhibitor that indirectly elevates TEK phosphorylation and stabilises vasculature (Khan et al., 2021; Saharinen et al., 2017).

## Other Comments

Heterozygous activating TEK mutations (e.g., R849W, Y897S, Y897F-R915L) cause autosomal-dominant venous malformations characterised by ectatic, pericyte-poor vessels (Thurston, 2003; Natynki et al., 2015). Tek-null mice die at embryonic day 10.5 from failed vascular remodelling and haematopoiesis, underscoring its non-redundant developmental role (Thurston, 2003).

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