## Phylogeny

Orthologous genes are present in mouse, rat, cow, and zebrafish; the Ser/Thr-rich juxtamembrane segment containing Thr794 is conserved from human to zebrafish (Reinardy et al., 2015, pp. 82–89; “Tied Together,” 2010, pp. 22–28). Tie-1 belongs to the receptor tyrosine kinase (RTK) group, Tie subfamily, and is the closest paralogue of Tie-2/TEK, sharing ~75 % identity within the kinase domain (Reinardy et al., 2015, pp. 36–42, 82–89). Tie receptors are chordate-specific; no invertebrate homologues have been described (Saharinen et al., 2015, pp. 13–17).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine phosphate (“Regulation and Physiological Role,” 2004, pp. 69–75).

## Cofactor Requirements

No metal-ion cofactor requirement has been reported for Tie-1 (Reinardy et al., 2015, pp. 54–59).

## Substrate Specificity

No clear peptide consensus is defined. Tie-1 shows weak autophosphorylation and is often trans-phosphorylated by Tie-2 (Reinardy et al., 2015, pp. 54–59; “Regulation and Physiological Role,” 2004, pp. 69–75). Thr794 resides in a unique PAK1 recognition motif absent from Tie-2 (Reinardy et al., 2015, pp. 129–137).

## Structure

Domain organisation: N-terminal signal peptide; extracellular segment with two Ig-like domains, three EGF-like repeats, and three FNIII repeats; single transmembrane helix; Ser/Thr-rich juxtamembrane region (Thr794); split bilobal tyrosine kinase domain; short C-terminal tail (“Regulation and Physiological Role,” 2004, pp. 69–75; Reinardy et al., 2015, pp. 82–89).  
3-D information: homology models and AlphaFold (AF-P35590-F1) show a canonical RTK kinase fold with conserved HRD and DFG motifs, an activation loop centred on Tyr1008, and a regulatory C-helix analogous to Tie-2 (Reinardy et al., 2015, pp. 36–42; “The Role of Angiopoietin-2,” 2010, pp. 51–56).  
Unique features: positively charged extracellular surface favouring heterodimerisation with Tie-2 and nuclear localisation of the full-length receptor in endothelial cells (Reinardy et al., 2015, pp. 65–71, 97–108).

## Regulation

Phosphorylation  
– Thr794 is phosphorylated by PAK1 downstream of Rac1; required for Rac1 docking and angiogenic signalling (Reinardy et al., 2015, pp. 129–137).  
– Akt can also phosphorylate Thr794 in vitro and in endothelial cells (Reinardy et al., 2015, pp. 89–97).  
– Thr792 becomes phosphorylated when Thr794 is absent; Thr811 and Tyr1023 follow in a phosphorylation cascade (Reinardy et al., 2015, pp. 97–108).  
– Weak Ang1-induced tyrosine phosphorylation occurs via Tie-2 (Reinardy et al., 2015, pp. 97–108).  
– VE-PTP associates with Tie receptors and attenuates tyrosine phosphorylation (Saharinen et al., 2015, pp. 32–33; Reinardy et al., 2015, pp. 36–42).

Proteolytic processing  
– ADAM17/TACE mediates ectodomain shedding; the remaining 45 kDa fragment undergoes γ-secretase cleavage and proteasomal degradation (Marron et al., 2007, pp. 1–2).  
– Shedding is enhanced by phorbol esters, VEGF, and disturbed shear stress (Marron et al., 2007, pp. 1–2; Singh et al., 2012, p. 9).  
– Loss of the ectodomain heightens Tie-2 ligand responsiveness (Marron et al., 2007, pp. 1–2).

Receptor interactions  
– Tie-1 and Tie-2 form constitutive heteromultimers; Ang1 promotes dissociation, whereas Ang2 shows minimal activation when Tie-1 is present (Reinardy et al., 2015, pp. 65–71).

Functional consequences  
– Phosphorylation at Thr794 is required for endothelial migration and sprouting; both T794A and T794E mutants impair angiogenesis (Reinardy et al., 2015, pp. 97–108, 137–142).

## Function

Expression  
– Endothelium-specific, highest during embryonic vasculogenesis and angiogenesis in lung, kidney, heart, and capillaries (Reinardy et al., 2015, pp. 54–59).  
– Enriched at vascular bifurcations and sites of disturbed flow, e.g., atherosclerotic plaques and aneurysms (Reinardy et al., 2015, pp. 59–65).  
– A 110 kDa splice variant appears on activated platelets (Reinardy et al., 2015, pp. 49–54).

Interacting partners and signalling components  
– Forms heteromeric complexes with Tie-2 (Marron et al., 2007, pp. 1–2).  
– Rac1 binds phospho-Thr794; PAK1 is the upstream kinase (Reinardy et al., 2015, pp. 129–137).  
– VE-PTP participates in Tie receptor clusters at cell–cell contacts (Reinardy et al., 2015, pp. 65–71).

Signalling pathways  
– Rac1 → PAK1 → Tie-1(pThr794) → Rac1 positive-feedback loop controlling cytoskeletal dynamics and migration (Reinardy et al., 2015, pp. 129–137).  
– Modulates Ang1/Tie-2-dependent PI3K–Akt survival signalling (Reinardy et al., 2015, pp. 65–71).  
– Promotes ICAM-1, VCAM-1, and E-selectin expression via p38 MAPK under inflammatory conditions (“The Role of Tie1 Threonine Phosphorylation,” 2015, pp. 59–65).

Biological roles  
– Essential for angiogenic sprouting, capillary morphogenesis, and vessel integrity; Tie-1 knockout mice display mid-gestation haemorrhage and oedema (Reinardy et al., 2015, pp. 54–59).  
– tie1 knockdown in zebrafish abolishes intersegmental vessels; rescue requires wild-type but not T794A mRNA (Reinardy et al., 2015, pp. 137–142).  
– Required for lymphatic valve development and patterning (Reinardy et al., 2015, pp. 54–59).

## Other Comments

Disease associations  
– High Tie-1 expression in atherosclerotic plaques, aneurysms, and inflamed vasculature; endothelial deletion reduces atherosclerosis and inflammatory arthritis (“The Role of Tie1 Threonine Phosphorylation,” 2015, pp. 59–65).  
– Over-expression correlates with poor prognosis in leukaemia and multiple solid tumours (Yang et al., 2015, pp. 3–4).

Notable mutations  
– Missense variant p.V1099G identified within the kinase domain (“The Role of Angiopoietin-2,” 2010, pp. 51–56).  
– T794A acts as a dominant-negative inhibitor of angiogenesis in zebrafish; T794E stabilises Tie receptors but still disrupts vascular development (Reinardy et al., 2015, pp. 97–108, 137–142).

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