1. Phylogeny  
   TIE1 is a receptor tyrosine kinase that is widely conserved among vertebrates and expressed predominantly in endothelial cells, where it plays an essential role in vascular biology (brouillard2024lossoffunctionmutationsof pages 1-2, saharinen2015thetiereceptor pages 1-5). TIE1 is a member of the TIE receptor family and is phylogenetically related to TIE2 (also known as TEK), with both receptors sharing a conserved intracellular tyrosine kinase domain despite differences in their extracellular regions (saharinen2015thetiereceptor pages 28-30, alexander2013theconciseguide pages 24-24). In the context of the human kinome, TIE1 is grouped among the type XII receptor tyrosine kinases, which are characterized by a distinctive set of extracellular immunoglobulin-like, EGF-like, and fibronectin type III domains along with a conserved catalytic core in the intracellular region (alexander2013theconciseguide pages 24-24, brouillard2024lossoffunctionmutationsof pages 13-14). The evolutionary trajectory of TIE1 likely parallels that of TIE2, suggesting that gene duplication and subsequent specialization resulted in two receptors with complementary roles in angiogenesis and vascular maintenance (saharinen2015thetiereceptor pages 1-5, alexander2017theconciseguide pages 31-34).
2. Reaction Catalyzed  
   TIE1 catalyzes the phosphorylation of tyrosine residues on substrate proteins using ATP as a phosphate donor; that is, it transfers the gamma phosphate of ATP to specific tyrosine hydroxyl groups (brouillard2024lossoffunctionmutationsof pages 4-5). The overall reaction can be summarized as: ATP + [protein]-OH → ADP + [protein]-phosphotyrosine + H⁺ (brouillard2024lossoffunctionmutationsof pages 4-5).
3. Cofactor Requirements  
   Similar to other receptor tyrosine kinases, the catalytic activity of TIE1 is dependent on the presence of divalent cations, with Mg²⁺ serving as the critical cofactor required for efficient ATP binding and phosphate transfer during catalysis (boubeva2011understandingtyrosinekinase pages 37-40).
4. Substrate Specificity  
   Although a detailed consensus phosphorylation motif for TIE1 has not been elaborated in the available reports, experimental evidence indicates that TIE1 autophosphorylates on critical tyrosine residues within its activation loop, notably at Y1007, which is essential for its full kinase activity (brouillard2024lossoffunctionmutationsof pages 10-11). Mutations in the kinase domain, such as K870R and R983W, result in markedly reduced autophosphorylation and impair downstream activation of signaling pathways such as the AKT cascade, highlighting that the substrate specificity of TIE1 depends on the integrity of its catalytic and regulatory motifs (brouillard2024lossoffunctionmutationsof pages 5-8, brouillard2024lossoffunctionmutationsof pages 4-5). The disruption of these phosphorylation events underscores the importance of its substrate recognition features in mediating proper endothelial signaling.
5. Structure  
   TIE1 is a transmembrane receptor tyrosine kinase that exhibits a canonical domain organization consisting of an N-terminal extracellular region, a single transmembrane helix, and a C-terminal intracellular kinase domain (brouillard2024lossoffunctionmutationsof pages 1-2, saharinen2015thetiereceptor pages 28-30). The extracellular portion is composed of several immunoglobulin-like domains, multiple epidermal growth factor (EGF)-like motifs, and fibronectin type III repeats; these domains contribute to protein–protein interactions and facilitate potential heterodimerization with TIE2 (brouillard2024lossoffunctionmutationsof pages 1-2, saharinen2015thetiereceptor pages 28-30). The intracellular kinase domain of TIE1 contains an ATP-binding cleft, a flexible activation loop, a conserved C-helix, and regulatory motifs that are characteristic of receptor tyrosine kinases (alexander2013theconciseguide pages 24-24, boubeva2011understandingtyrosinekinase pages 37-40). Structural studies have demonstrated that specific residues such as R983, which is situated near the entrance of the ATP-binding pocket, and M1110 in the C-terminal half of the kinase domain, play critical roles in maintaining kinase activity; substitution of these residues (e.g., R983W or M1110R mutations) disrupts the formation of stabilizing salt bridges and impairs ATP binding, thereby abolishing autophosphorylation (brouillard2024lossoffunctionmutationsof pages 10-11, griffin2021sulfatedglycansengage pages 4-6). In addition, TIE1 is subject to extensive N-linked glycosylation, and the differential glycosylation status observed as a mature 135 kDa cell-surface form versus an immature 125 kDa intracellular form reflects its complex post-translational processing and folding (brouillard2024lossoffunctionmutationsof pages 4-5, griffin2021sulfatedglycansengage pages 12-14). Predicted three-dimensional models, including those based on homology to TIE2 and AlphaFold calculations, affirm the overall receptor tyrosine kinase fold while also highlighting unique structural features that underlie TIE1’s regulatory functions in endothelial signaling (alexander2013theconciseguide pages 24-24).
6. Regulation  
   The activity of TIE1 is controlled by multiple regulatory mechanisms that include ligand-independent autophosphorylation, heterodimerization with TIE2, and post-translational modifications. Although TIE1 is classically considered an orphan receptor with no well-defined endogenous ligand, it modulates TIE2 signaling in endothelial cells through transient heterodimer formation (griffin2021sulfatedglycansengage pages 1-2, griffin2021sulfatedglycansengage pages 8-9). Proteolytic processing also plays a vital role in its regulation; for example, the extracellular domain of TIE1 is cleaved by metalloproteases such as ADAM17, resulting in the release of soluble fragments that may affect receptor availability and signal modulation (brouillard2024lossoffunctionmutationsof pages 4-5, saharinen2015thetiereceptor pages 10-13). In addition, proper receptor trafficking and cell-surface expression are dependent on glycosylation, and mutations that disrupt glycosylation patterns alter the balance between the mature and immature receptor forms (brouillard2024lossoffunctionmutationsof pages 5-8, griffin2021sulfatedglycansengage pages 12-14). Furthermore, specific phosphorylation events within the kinase domain, such as autophosphorylation at Y1007, are crucial for eliciting downstream signaling responses, primarily through the AKT pathway, and disruption of these phosphorylation events via mutation results in compromised receptor function (brouillard2024lossoffunctionmutationsof pages 10-11, brouillard2024lossoffunctionmutationsof pages 8-10). Interactions with sulfated glycosaminoglycans, notably heparan sulfate, further regulate TIE1 by promoting TIE1–TIE2 heterodimer formation and stabilizing receptor complexes at the cell surface (griffin2021sulfatedglycansengage pages 29-34).
7. Function  
   TIE1 is critically involved in vascular development and angiogenesis by modulating the activity of its counterpart TIE2 in endothelial cells (brouillard2024lossoffunctionmutationsof pages 1-2, saharinen2015thetiereceptor pages 1-5). It is expressed predominantly in vascular endothelium, including both blood and lymphatic vessels, and is essential for the maintenance of vascular integrity and remodeling (brouillard2024lossoffunctionmutationsof pages 1-2, saharinen2015thetiereceptor pages 1-5). Functional analyses using CRISPR/Cas9-engineered mouse models have demonstrated that loss-of-function mutations in TIE1 lead to severe lymphatic dysfunction and the development of late-onset primary lymphedema, a phenotype characterized by impaired lymphatic drainage and associated edema (brouillard2024lossoffunctionmutationsof pages 5-8, brouillard2024lossoffunctionmutationsof pages 8-10). In endothelial cells, TIE1 participates in intracellular signaling cascades by activating downstream effectors such as the PI3K/AKT pathway, thereby contributing to cell survival and anti-apoptotic responses (brouillard2024lossoffunctionmutationsof pages 10-11, griffin2021sulfatedglycansengage pages 16-18). Additionally, the interaction of TIE1 with heparan sulfate glycosaminoglycans facilitates the stabilization of TIE1–TIE2 receptor complexes, which is pivotal for fine-tuning angiogenic signaling during both developmental and pathological processes (griffin2021sulfatedglycansengage pages 34-36, khan2014signalingnetworkmap pages 1-2).
8. Other Comments  
   Several notable loss-of-function mutations in TIE1 have been reported that have significant clinical consequences. Specific missense variants, such as R983W and M1110R, disrupt key structural elements within the kinase domain that are critical for ATP binding and autophosphorylation, while a premature stop codon variant (Q682\*) leads to a truncated protein that is rapidly degraded, thereby abrogating receptor function (brouillard2024lossoffunctionmutationsof pages 4-5, brouillard2024lossoffunctionmutationsof pages 5-8). These mutations are directly associated with late-onset primary lymphedema, underscoring the pivotal role of TIE1 in lymphatic vascular homeostasis (brouillard2024lossoffunctionmutationsof pages 8-10, brouillard2024lossoffunctionmutationsof pages 13-14). In addition, alterations in the glycosylation status and proteolytic processing of TIE1 have been observed in experimental systems, highlighting the complex post-translational regulation of this receptor (brouillard2024lossoffunctionmutationsof pages 4-5, griffin2021sulfatedglycansengage pages 12-14). Although specific small molecule inhibitors against TIE1 are not extensively documented, modulation of its activity through interactions with sulfated glycosaminoglycans offers a potential therapeutic avenue in vascular diseases and tumor angiogenesis (griffin2021sulfatedglycansengage pages 29-34, khan2014signalingnetworkmap pages 5-5). Furthermore, the clinical significance of TIE1 mutations has prompted genetic screening in patients with lymphatic disorders, thereby establishing TIE1 as a promising target for therapeutic intervention.
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