1. Phylogeny  
   TIE2 (encoded by the TEK gene) is a receptor tyrosine kinase expressed predominantly in vascular endothelial cells and is a member of the Tie receptor family. Comparative analyses indicate that TIE2 is highly conserved among vertebrates—including mammals, birds, reptiles, amphibians, and fish—underscoring its critical role in vascular biology (du2017reviewofthe pages 1-2, khan2014signalingnetworkmap pages 1-2). In addition, TIE2 shares substantial sequence similarity in its intracellular kinase domain with its paralog TIE1; studies report approximately 76% sequence identity between their cytoplasmic regions, evidence of a common evolutionary origin and a functional relationship in the regulation of angiogenesis and vascular integrity (saharinen2015thetiereceptor pages 27-28, du2017reviewofthe pages 1-2). These evolutionary relationships place TIE2 within the broader receptor tyrosine kinase superfamily and highlight its specialization in endothelial signaling events that date back to early chordate evolution (khan2014signalingnetworkmap pages 1-2).
2. Reaction Catalyzed  
   TIE2 functions as a receptor tyrosine kinase by catalyzing the transfer of the terminal (γ) phosphate group from ATP to specific tyrosine residues on substrate proteins. In its autophosphorylation reaction, TIE2 employs ATP to phosphorylate its own intracellular domain, thereby generating ADP and phosphorylated tyrosine residues within its structure. This reaction is typically represented as:  
     ATP + [protein]-Tyr → ADP + [protein]-Tyr‑phosphate + H⁺  
   Through this mechanism, TIE2 establishes phosphotyrosine motifs that serve as binding sites for downstream signaling proteins, including those containing SH2 or PTB domains such as Dok‑R (jones2003auniqueautophosphorylation pages 2-3, jones1998thetektie2receptor pages 1-3).
3. Cofactor Requirements  
   Like many kinases, the catalytic activity of TIE2 is dependent on the presence of divalent cations. In particular, Mg²⁺ plays an essential role by coordinating with ATP, thereby facilitating the proper positioning of the phosphate group for transfer during the phosphorylation reaction. This cofactor requirement is a well‐established feature of receptor tyrosine kinases and is critical for TIE2’s enzymatic function (jones1998thetektie2receptor pages 1-3, du2017reviewofthe pages 1-2).
4. Substrate Specificity  
   TIE2 exhibits substrate specificity that is largely defined by a set of unique autophosphorylation sites located in its cytoplasmic tail. Notably, tyrosine residues such as Y1106 and Y1100 have been identified as critical for creating docking sites for downstream effectors. Phosphorylation at Y1106, for example, is required for the recruitment of Dok-R through its phosphotyrosine-binding (PTB) domain. Detailed mutagenesis studies have shown that residues flanking Y1106—specifically a leucine at the –1 position and an asparagine at the –4 position—are essential for high-affinity binding of Dok-R, even though this sequence does not conform to the classical NPXY motif commonly recognized by PTB domains (jones2003auniqueautophosphorylation pages 6-7). In addition to autophosphorylation, TIE2 phosphorylates other substrates that contain tyrosine-based motifs, thereby engaging signaling proteins such as rasGAP, Nck, and Crk. These phosphorylation events collectively contribute to the modulation of endothelial cell migration, adhesion, and cytoskeletal reorganization (jones2003auniqueautophosphorylation pages 2-3, jones1998thetektie2receptor pages 7-8).
5. Structure  
   TIE2 is organized as a type I transmembrane receptor with a multidomain architecture. Its extracellular region consists of a series of modules that include two immunoglobulin (Ig)-like loops, several epidermal growth factor (EGF)-like motifs, and three fibronectin type III (FNIII) repeats. These domains are responsible for mediating the high-affinity binding of angiopoietin ligands, which interact with TIE2 to initiate receptor activation (saharinen2015thetiereceptor pages 17-19, jones1998thetektie2receptor pages 1-3). A single transmembrane helix anchors the receptor in the plasma membrane, permitting the extracellular domain to sense ligand concentrations while the intracellular domain transduces signals.

The intracellular portion of TIE2 contains a conserved tyrosine kinase domain that comprises several key structural elements: an activation loop, a nucleotide-binding loop, a catalytic loop, and a C-helix that helps coordinate ATP within the active site. Unique autophosphorylation sites—such as Y1106 and Y1100—are embedded within the carboxy-terminal tail and are crucial for the recruitment of specific adaptor proteins like Dok-R. The three-dimensional organization of the kinase domain, as revealed by crystallographic studies and supported by biochemical data, highlights the presence of a hydrophobic spine and a regulatory C-helix that undergo conformational changes upon activation (jones2003auniqueautophosphorylation pages 2-3, jones2003auniqueautophosphorylation pages 6-7). Furthermore, structural investigations have demonstrated that TIE2 can form higher-order clusters at cell–cell contacts upon binding multimeric angiopoietin-1, a process that is essential for robust downstream signaling (jones2004tektie2signalingnew pages 1-3, saharinen2015thetiereceptor pages 5-7).

1. Regulation  
   The regulation of TIE2 is complex and multifaceted, integrating both extracellular and intracellular mechanisms to modulate its kinase activity. Ligand binding is the principal regulatory mechanism; angiopoietin‑1 (Ang1) is the primary agonist that induces receptor dimerization, autophosphorylation, and activation of downstream signaling pathways such as PI3K/AKT, which are critical for endothelial cell survival and vascular stability (du2017reviewofthe pages 1-2, sack2020theangiopoietintie2pathway pages 3-4). In contrast, angiopoietin‑2 (Ang2) often functions as a context‑dependent antagonist by competing with Ang1 for TIE2 binding, thereby inhibiting receptor phosphorylation and tempering the signaling output (du2017reviewofthe pages 4-6).

In addition to ligand-mediated regulation, TIE2 activity is modulated via interactions with co-receptors and adapter proteins. For instance, heterodimerization with the related receptor TIE1 can suppress basal TIE2 activation and modify its responsiveness to angiopoietins; TIE1 does not directly bind angiopoietins but influences TIE2’s signaling dynamics through its extracellular association (seegar2010tie1tie2interactionsmediate pages 7-9). Moreover, TIE2 undergoes receptor autophosphorylation on specific tyrosine residues, such as Y1106, which establishes docking sites for downstream effectors like Dok-R. These phosphorylation events are reversible and subject to regulation by protein tyrosine phosphatases such as VE‑PTP, which dephosphorylate TIE2 and thus contribute to the fine‑tuning of the receptor’s signaling output (saharinen2015thetiereceptor pages 19-22). Together, these mechanisms ensure that TIE2 activity is precisely controlled within endothelial cells to maintain vascular homeostasis.

1. Function  
   TIE2 plays a central role in controlling key aspects of endothelial cell behavior and vascular function. Its activation by Ang1 leads to a suite of downstream responses that include promoting endothelial cell survival, proliferation, migration, and adhesion. These cellular responses are mediated primarily via the PI3K/AKT signaling cascade, which is activated upon TIE2 autophosphorylation and subsequent recruitment of adapter proteins such as Dok‑R (du2017reviewofthe pages 1-2, jones2003auniqueautophosphorylation pages 2-3). In mature, quiescent vessels, Ang1-bound TIE2 is recruited to cell–cell junctions where it facilitates the formation of receptor clusters, thereby reinforcing endothelial barrier function and reducing vascular permeability. This clustering favors activation of anti‑apoptotic and anti‑inflammatory signaling pathways and helps prevent the leakage of plasma proteins and leukocytes—key processes for maintaining vascular stability (sack2020theangiopoietintie2pathway pages 3-4, saharinen2015thetiereceptor pages 27-28).

During embryogenesis, TIE2 is indispensable for normal angiogenesis and heart development; loss of TIE2 function results in severe vascular defects and embryonic lethality (du2017reviewofthe pages 1-2). In addition to its roles in developmental angiogenesis, TIE2 is involved in post‑natal hematopoiesis and is a critical regulator of adaptive vascular remodeling, modulating the dynamic balance between angiogenesis and vascular quiescence. Furthermore, TIE2-mediated phosphorylation events contribute to the reorganization of the actin cytoskeleton, thus influencing endothelial cell migration and the remodeling of the vascular network (jones1998thetektie2receptor pages 7-8, jones2003auniqueautophosphorylation pages 2-3).

1. Other Comments  
   Dysregulation of TIE2 function is associated with various vascular pathologies, including venous malformations and tumor angiogenesis. Mutations within the TEK gene can lead to aberrant receptor activity and impaired vascular integrity, with such mutations being linked to inherited venous malformations (du2017reviewofthe pages 4-6, saharinen2015thetiereceptor pages 27-28). In the context of cancer, the angiopoietin–TIE2 signaling axis is recognized as a promising therapeutic target; experimental agents, for example the small-molecule inhibitor BAY‑826, have been shown to suppress TIE2 phosphorylation and downstream activation in preclinical models (kraft2025angiopoietin–tie2feedforwardcircuit pages 8-9, gengenbacher2021timedang2targetedtherapy pages 13-14). Furthermore, combination therapies that target both the TIE2 and VEGF pathways are under investigation to counteract the development of resistance to anti‑angiogenic treatments (khan2014signalingnetworkmap pages 4-5, khan2014signalingnetworkmap pages 5-5). In addition to pharmacological inhibitors, protein‑based ligand traps and therapeutic antibodies that modulate the angiopoietin balance are being explored as strategies to restore proper TIE2 signaling and vascular stability in disease settings. TIE2 has therefore emerged as a key node in vascular signaling whose precise modulation is critical for both developmental and pathological angiogenesis.
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