1. Phylogeny  
   Ephrin type‐B receptor 4 (EPHB4) belongs to the large Eph receptor tyrosine kinase family, which is subdivided into EphA and EphB classes. Within the EphB subgroup, receptors EphB1 through EphB6 share structural and functional similarities, with EPHB4 being a well‐conserved member across vertebrate taxa. Comparative sequence analyses reveal that EPHB4 exhibits high amino acid conservation in its intracellular kinase domain with other EphB receptors and is evolutionarily related to paralogous kinases that emerged via gene duplication events early in metazoan evolution. Orthologs of EPHB4 are present in mammals, birds, and amphibians, underscoring its central role in developmental processes such as angiogenesis and cell–cell communication (nakamoto2002diverserolesfor pages 7-8, hughes2006roleofthe pages 3-4, overman2014completingthestructural pages 1-2).
2. Reaction Catalyzed  
   EPHB4 functions as a receptor tyrosine kinase, catalyzing the transfer of a phosphate group from ATP to specific tyrosine residues on target proteins. The chemical reaction can be represented as follows:  
     ATP + [protein]–L‑tyrosine → ADP + [protein]–L‑tyrosine‑phosphate + H⁺  
   This phosphorylation reaction is characteristic of receptor tyrosine kinases and is fundamental to the initiation of downstream signaling pathways (chrencik2006structuralandbiophysical pages 5-6, andolfo2020kinomemultigenicpanel pages 9-11).
3. Cofactor Requirements  
   The enzymatic activity of EPHB4 is dependent on the binding of ATP and requires divalent metal ions as cofactors—most notably Mg²⁺—to stabilize the transition state during catalysis. These Mg²⁺ ions coordinate with ATP within the active site of the kinase domain, facilitating the correct positioning of the phosphate group for transfer. Thus, the presence of Mg²⁺ is essential for efficient phosphorylation by EPHB4 (lafleur2009structurebasedoptimizationof pages 1-2, overman2014completingthestructural pages 2-4).
4. Substrate Specificity  
   As a receptor tyrosine kinase, EPHB4 phosphorylates tyrosine residues within target proteins that participate in various intracellular signaling cascades. While a strict consensus substrate motif for EPHB4 has not been universally defined, available studies indicate that its substrate specificity is, at least in part, determined by the receptor’s ability to interact with specific sites on downstream proteins such as other Eph family members or adaptor proteins that contain SH2 domains. In particular, EPHB4 has been shown to phosphorylate tyrosine residues in the juxtamembrane regions of substrates, including trans‐phosphorylation of related receptors (e.g., EphB6), thereby facilitating the recruitment of SH2-containing signal transducers (liang2021theintracellulardomains pages 14-17, chrencik2006structuralandbiophysical pages 3-4, renuse2021tyrosinephosphoproteomicsof pages 12-14).
5. Structure  
   EPHB4 is a type-I transmembrane receptor that exhibits a modular architecture comprising three principal regions. The extracellular portion features an N-terminal globular ligand-binding domain that is responsible for recognizing and binding transmembrane ephrin-B ligands, particularly ephrin-B2. This extracellular segment further includes a cysteine-rich domain and two fibronectin type III repeats, which collectively facilitate proper ligand presentation and contribute to receptor dimerization and clustering (kertesz2006thesolubleextracellular pages 1-2, chatzikalil2024theclinicalrelevance pages 2-4). The single transmembrane helix anchors the receptor in the plasma membrane, enabling it to engage in contact-dependent cell–cell communication.

The intracellular region is organized into several distinct domains. Immediately following the transmembrane segment lies the juxtamembrane region, which plays a role in autoinhibitory regulation by keeping the kinase domain in an inactive conformation until ligand binding induces a conformational change. This is followed by the conserved catalytic tyrosine kinase domain, which adopts the classic bilobal structure observed among protein kinases: a smaller N-terminal lobe comprised mainly of β-sheets and a larger C-terminal lobe that is predominantly α-helical. Key catalytic features within the kinase domain include the ATP-binding pocket, the C-helix (which helps position catalytic residues), and an activation loop whose phosphorylation is necessary for full catalytic activation (chrencik2006structuralandbiophysical pages 1-2, 7-7, chatzikalil2024theclinicalrelevance pages 2-4). Beyond the kinase domain, the receptor also contains a sterile alpha motif (SAM) domain and a PDZ-binding motif at the very C-terminus. These regions mediate interactions with various cytoplasmic partner proteins, contributing to the assembly of multiprotein signaling complexes and influencing downstream pathways (chrencik2006structuralandbiophysical pages 7-8, overman2014completingthestructural pages 2-4).

High-resolution crystal structures of Eph receptor extracellular domains and kinase domains—along with solution models from AlphaFold—have revealed details of the ligand-binding interfaces, including a flexible J–K loop in the extracellular domain that facilitates accommodation of the ephrin ligand. In the kinase domain, the activation loop’s phosphorylation state and the positioning of the hydrophobic spine are critical regulatory features that determine the active conformation of the enzyme (martinybaron2010thesmallmolecule pages 7-8, lafleur2009structurebasedoptimizationof pages 1-2, overman2014completingthestructural pages 7-9). These structural insights have been instrumental in guiding the design of selective small-molecule inhibitors targeting the ATP-binding pocket of EPHB4 (chrencik2006structuralandbiophysical pages 7-7, martinybaron2010thesmallmolecule pages 9-9).

1. Regulation  
   The regulatory control of EPHB4 is largely mediated via ligand-dependent mechanisms. In its resting state, EPHB4 is maintained in an autoinhibited conformation through intramolecular interactions involving its juxtamembrane region. Binding of its primary ligand, ephrin-B2—which is expressed on adjacent cells—triggers receptor dimerization and clustering. This cell–cell contact-induced clustering facilitates trans-autophosphorylation on key tyrosine residues within the intracellular domain, thereby switching the receptor from an inactive to an active state (andolfo2020kinomemultigenicpanel pages 9-11, hughes2006roleofthe pages 9-9).

Phosphorylation within the activation loop and juxtamembrane region releases autoinhibitory constraints and enables the kinase domain to adopt an active conformation, facilitating substrate phosphorylation. In addition to ligand-induced activation, EPHB4 undergoes other post-translational modifications that influence its signaling output. For instance, receptor internalization and subsequent lysosomal degradation can be triggered by therapeutic antibodies or decoy receptors, such as soluble forms of EPHB4 (sEphB4), which act as competitive antagonists. This mechanism not only attenuates forward signaling but also modulates receptor turnover on the cell surface (merchant2017ephb4isa pages 7-9, stephenson2015antitumoureffectsof pages 1-2).

Furthermore, the phosphorylation status of EPHB4 is intricately linked to downstream signaling pathway activation. Autophosphorylation on specific tyrosine residues creates docking sites for SH2- and PDZ domain-containing adaptor proteins, which then propagate signals to effectors such as members of the PI3K/AKT and Ras/MAPK pathways. Such phosphorylation-dependent recruitment events are central to EPHB4’s ability to regulate cellular repulsion, adhesion, and migration (chrencik2006structuralandbiophysical pages 6-7, chatzikalil2024theclinicalrelevance pages 11-12).

1. Function  
   EPHB4 plays a multifaceted role in mediating cell–cell communication through bidirectional signaling. Upon binding its cognate ligand, ephrin-B2, EPHB4 triggers “forward signaling” that initiates intracellular phosphorylation cascades, whereas ligand-bearing cells simultaneously receive “reverse signaling” through their ephrin cytoplasmic domains. Through these mechanisms, EPHB4 critically influences cell adhesion, migration, and repulsion, all of which are central to tissue patterning and organogenesis (andolfo2020kinomemultigenicpanel pages 9-11, hughes2006roleofthe pages 9-9).

In the context of vascular biology, EPHB4 is involved in heart morphogenesis and angiogenesis. It is predominantly expressed on venous endothelial cells and helps define boundaries between arterial and venous vessels by engaging ephrin-B2—a ligand that is chiefly expressed on arterial endothelial cells. This differential expression and ligand-specific interaction enable EPHB4-mediated forward signaling to control endothelial repulsion and segregation, thereby playing a central role in blood vessel remodeling and permeability (kertesz2006thesolubleextracellular pages 1-2, chatzikalil2024theclinicalrelevance pages 2-4, nakamoto2002diverserolesfor pages 7-8).

EPHB4’s function extends into pathological contexts as well. Overexpression of EPHB4 has been documented in various solid tumors including bladder cancer, mesothelioma, head and neck squamous cell carcinoma, and even in subsets of pediatric malignancies such as neuroblastoma. In tumors, EPHB4 contributes to cell survival, proliferation, and angiogenesis. Elevated levels of EPHB4, often along with aberrant phosphorylation, have been correlated with increased invasiveness and enhanced tumor vascularization. Forward signaling mediated by EPHB4 not only promotes repulsive interactions among tumor cells but also modulates interactions with the tumor microenvironment, thereby influencing metastatic behavior (ferguson2014expressionofthe pages 5-6, xia2006ephb4receptortyrosine pages 2-3, liu2013ephb4asa pages 7-7, chatzikalil2024theclinicalrelevance pages 10-11).

In addition to its roles in angiogenesis and tumor progression, EPHB4 is pivotal in maintaining proper cardiovascular development during embryogenesis. Its signaling ensures the proper segregation of tissues and the establishment of distinct vascular domains necessary for normal heart morphogenesis (hughes2006roleofthe pages 9-9, kertesz2006thesolubleextracellular pages 1-2). This balance of physiological and pathological functions places EPHB4 at a strategic node in cellular signaling networks governing both development and disease (andolfo2020kinomemultigenicpanel pages 9-11, chatzikalil2024theclinicalrelevance pages 11-12).

1. Other Comments  
   Owing to its central role in vascular development and tumor biology, EPHB4 is considered a highly promising therapeutic target. Small-molecule inhibitors, such as NVP-BHG712, have been developed to selectively inhibit the kinase activity of EPHB4 and have demonstrated efficacy in reducing VEGF-driven angiogenesis in in vivo models (martinybaron2010thesmallmolecule pages 9-9, lafleur2009structurebasedoptimizationof pages 1-2). In parallel, biologic approaches using soluble forms of its extracellular domain (sEphB4) have shown the capability to act as decoy receptors that antagonize EPHB4–ephrinB2 interactions, suppressing tumor neovascularization and reducing tumor growth (kertesz2006thesolubleextracellular pages 8-9, stephenson2015antitumoureffectsof pages 1-2).

Genetic analyses have identified somatic mutations in EPHB4 in certain cancers. Notably, the V871I variant has been associated with high-risk neuroblastoma, where it leads to enhanced activation of downstream pathways including the ERK1/2 cascade, ultimately promoting proliferation and migration of neuroblastoma cells (andolfo2020kinomemultigenicpanel pages 9-11). Other mutations, such as the previously reported P257L, have also been identified and are thought to contribute to altered kinase activity. In addition to these mutational events, overexpression of EPHB4 is observed in a range of malignancies, including bladder cancer, where it provides critical survival signals and is associated with both constitutive activation and ligand-independent signaling (xia2006ephb4receptortyrosine pages 2-3, hasina2013criticalrolefor pages 1-2, merchant2017ephb4isa pages 7-9).

The dual functionality of EPHB4—in developmental processes as well as in tumor progression—has spurred significant interest in therapeutically targeting its signaling pathways. Both small-molecule kinase inhibitors and antibody-based strategies are under investigation in preclinical and clinical settings. Antibody-mediated receptor internalization and degradation, as described in studies using monoclonal antibodies such as MAb131, underscore a regulatory approach that not only disrupts ligand-mediated signaling but also decreases receptor levels on the cell surface (merchant2017ephb4isa pages 10-10, stephenson2015antitumoureffectsof pages 1-2). These therapeutic modalities are particularly attractive because normal adult tissue expression of EPHB4 is largely restricted to the vasculature, potentially allowing for a therapeutic window in targeting tumors with minimal toxicity to healthy tissues (chatzikalil2024theclinicalrelevance pages 17-18).

Taken together, the extensive structural, biochemical, and functional characterization of EPHB4 has established its significant role in both physiological vascular remodeling and pathological angiogenesis as well as tumor progression, validating it as an attractive target for future drug development.

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