1. Phylogeny  
   Ephrin type‑B receptor 1 (EPHB1) is a canonical member of the Eph receptor family, a large subfamily within the protein tyrosine kinases that is conserved across metazoans. Eph receptors are phylogenetically divided into two major groups, EphA and EphB receptors, with EPHB1 belonging to the EphB subgroup. Orthologs of EPHB1 are found in all vertebrate species, and its evolutionary lineage can be traced back through early animal evolution, as supported by comparative genomic surveys that identified similar domain architectures in organisms ranging from ascidians to mammals (satou2003agenomewidesurvey pages 4-5, frisen1999ephrinsandtheir pages 1-2). Within the human kinome, EPHB1 is part of a conserved signaling axis that has diversified through gene duplication events occurring early in vertebrate evolution, similar to other receptor tyrosine kinases (chatzikalil2024theclinicalrelevance pages 2-4, frisen1999ephrinsandtheir pages 1-2).
2. Reaction Catalyzed  
   As a receptor tyrosine kinase, EPHB1 catalyzes the transfer of a phosphate group from ATP to specific tyrosine residues on protein substrates. The chemical reaction can be summarized as follows:  
     ATP + [protein]-L-tyrosine → ADP + [protein]-phosphotyrosine + H⁺  
   This autophosphorylation reaction, which occurs on the receptor itself, as well as the phosphorylation of downstream substrates, is essential for propagating the forward signaling cascade initiated upon ephrin binding (chatzikalil2024theclinicalrelevance pages 1-2, chong2000fibroblastgrowthfactor pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of EPHB1, like that of most protein kinases, is dependent on divalent metal ions. In particular, Mg²⁺ is required as a cofactor for optimal ATP binding and phosphate transfer. This cofactor requirement is intrinsic to the kinase function of EPHB1 and is typical for receptor tyrosine kinases (chatzikalil2024theclinicalrelevance pages 1-2, chong2000fibroblastgrowthfactor pages 1-2).
4. Substrate Specificity  
   EPHB1 exhibits substrate specificity that is defined by its ability to recognize and phosphorylate tyrosine residues within particular protein substrates. Although a consensus linear motif is not explicitly detailed in the available context, substrate recognition by EPHB1 is mediated by docking interactions that occur following autophosphorylation of its own juxtamembrane domain. These phosphorylated residues serve as binding sites for SH2 and PDZ domain–containing adaptor proteins, directing downstream signaling events. Thus, the substrate specificity of EPHB1 largely depends on its ability to create and recognize phosphotyrosine motifs that facilitate the recruitment of specific signaling effectors (frisen1999ephrinsandtheir pages 5-6, altamirano2019targetingephb1receptor pages 5-9).
5. Structure  
   EPHB1 conforms to the prototypical domain organization observed for Eph receptors. Its extracellular region contains an N‑terminal ligand‑binding domain that mediates interactions with transmembrane ephrin‑B ligands, followed by a cysteine‑rich domain and two fibronectin type‑III repeats which are critical for receptor dimerization and clustering. This is succeeded by a single transmembrane helix that anchors the receptor in the cell membrane. The intracellular region of EPHB1 is composed of several key modules: a juxtamembrane segment that contains conserved tyrosine residues necessary for autophosphorylation, a tyrosine kinase domain responsible for its catalytic activity, a sterile α motif (SAM) involved in protein–protein interactions and oligomerization, and a short PDZ‑binding motif at the C‑terminus that facilitates the assembly of multi‑protein signaling complexes. High‑resolution structural studies and AlphaFold models have revealed that the kinase domain of EPHB1 possesses the classical bilobed structure with an N‑terminal lobe that mediates ATP binding and a C‑terminal lobe that forms the catalytic core, with the activation loop (A‑loop) containing regulatory phosphorylation sites that are critical for full activation (chatzikalil2024theclinicalrelevance pages 2-4, chong2000fibroblastgrowthfactor pages 1-2, tosato2017ephrinligandsand pages 15-16).
6. Regulation  
   The regulatory mechanisms controlling EPHB1 activity are multifaceted and include both protein–protein interactions and post‑translational modifications. Ligand binding to ephrin‑B ligands on adjacent cells induces receptor dimerization and clustering, a prerequisite for effective autophosphorylation of tyrosine residues located in the juxtamembrane and kinase domains. Autophosphorylation creates docking sites for SH2‑ and PDZ‑domain–containing adaptor proteins, thereby linking EPHB1 to downstream signaling cascades. In addition to ligand‑induced activation, EPHB1 signaling is negatively regulated by several mechanisms. Proteolytic cleavage by metalloproteinases—such as ADAM10—can remove the extracellular portion of the receptor, effectively terminating the signal. Moreover, receptor internalization via clathrin‑dependent endocytosis and subsequent ubiquitination by E3 ligases (e.g., Cbl) serve to decrease receptor levels at the cell surface, thereby attenuating its activity (chatzikalil2024theclinicalrelevance pages 17-18, chong2000fibroblastgrowthfactor pages 4-5, frisen1999ephrinsandtheir pages 5-6). In certain pathological contexts, such as pediatric acute myeloid leukemia, epigenetic modifications like promoter hypermethylation have been shown to reduce EPHB1 expression and downstream phosphorylation events, highlighting an additional layer of regulatory control (chatzikalil2024theclinicalrelevance pages 17-18).
7. Function  
   EPHB1 mediates bidirectional signaling that plays critical roles in both development and adult tissue homeostasis. In the nervous system, forward signaling through EPHB1 is central to retinal axon guidance; for example, it directs the repulsion of ipsilaterally projecting ventrotemporal retinal ganglion cell axons at the optic chiasm midline via interactions with EFNB2. Additionally, in the adult brain, particularly within the hippocampus, EPHB1—together with ephrin‑B3—regulates the chemotaxis, proliferation, and polarity of neural progenitors. This regulation is essential for synaptic plasticity, dendritic spine maturation, and overall synapse formation. Beyond its crucial developmental roles, EPHB1 is also implicated in pathological processes. Aberrant EPHB1 signaling has been associated with various cancers, including pediatric brain tumors such as medulloblastoma and glioma, where its expression levels correlate with invasive potential and treatment response. Moreover, in neuropathic and inflammatory pain models, EPHB1 has been shown to modulate NMDA receptor activity and cytoskeletal dynamics, thereby influencing pain sensitization pathways (chatzikalil2024theclinicalrelevance pages 11-12, king2014ephbandephrinb pages 2-3, altamirano2019targetingephb1receptor pages 13-17). Furthermore, EPHB1 participates in regulating cell adhesion and migration, processes that are critical in both neural connectivity and the architectural organization of developing tissues (chatzikalil2024theclinicalrelevance pages 19-20, frisen1999ephrinsandtheir pages 5-6).
8. Other Comments  
   Several pharmacological approaches have been explored to modulate EPHB1 activity for potential therapeutic benefit. Experimental inhibitors such as recombinant soluble extracellular domain fusion proteins (e.g., EphB‑Fc constructs) and peptidomimetics that mimic ephrin‑B ligands have been developed to competitively block ligand binding and subsequent receptor clustering. In addition, small‑molecule kinase inhibitors that target the ATP‑binding pocket of EPH receptors have been investigated, although their specificity remains a challenge due to the broad conservation of kinase domains among receptor tyrosine kinases. Disease associations for EPHB1 are diverse; its dysregulation has been implicated in developmental disorders of the nervous system, various pediatric malignancies including acute myeloid leukemia and brain tumors, and in pain syndromes where altered forward signaling contributes to hyperalgesic states. Notably, epigenetic silencing via promoter hypermethylation observed in some leukemic cells further underscores the clinical relevance of maintaining appropriate EPHB1 expression for genomic integrity and cell cycle control (chatzikalil2024theclinicalrelevance pages 17-18, herath2010theroleof pages 6-7, bhanumathy2021proteintyrosinekinases pages 6-7).
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