Phylogeny  
Member of the protein-tyrosine kinase group, Eph receptor family, EphB subfamily (Manning et al., 2002). The four catalytically active human EphB kinases arose from vertebrate-specific duplications; closest human paralogs are EPHB1, EPHB2 and EPHB4 (Overman et al., 2014; Unknown Author, 2010). Orthologous receptors in mouse and chicken maintain nanomolar affinity for ephrin-B3 (Bergemann et al., 1998). Following two early whole-genome duplications, a single Eph receptor remained in many invertebrates (e.g., Drosophila, Caenorhabditis), highlighting lineage-specific expansion in jawed vertebrates (Brunet et al., 2016; Manning et al., 2002).

Reaction Catalyzed  
ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine-phosphate (Overman et al., 2014).

Cofactor Requirements  
No metal-ion cofactor requirement has been reported (Overman et al., 2014).

Substrate Specificity  
A definitive consensus phosphorylation motif has not been established; in vitro profiling reveals a subtly altered substrate preference relative to the other EphB kinases (Overman et al., 2013).

Structure  
Extracellular segment: ligand-binding domain, cysteine-rich/EGF module, and two fibronectin type III repeats (Unknown Author, 2005).  
Single-pass transmembrane helix (Unknown Author, 2005).  
Cytoplasmic region: juxtamembrane regulatory tyrosines, protein-tyrosine-kinase domain, sterile-α-motif (SAM) and C-terminal PDZ-binding motif (Unknown Author, 2005).  
Crystal structure of the kinase domain (A899P variant) resolved at 2.2 Å shows a classical bilobed fold with a partially ordered activation loop; an activation-loop tyrosine occupies the substrate groove, supporting a cis-autophosphorylation model (Overman et al., 2014). The catalytic HRD and ATP-binding lysine are intact, whereas the DFG motif adopts an inactive orientation (Overman et al., 2014). A hinge Cys717 (Gly in other EphB kinases) narrows the solvent channel and dictates a distinct inhibitor profile; the A899P mutation also improves stability and eliminates temperature-dependent salting-out (Overman et al., 2013; Overman et al., 2014).

Regulation  
Ligand-induced oligomerisation promotes trans- and cis-autophosphorylation of juxtamembrane, kinase-domain and SAM-domain tyrosines, creating SH2 docking sites (Kung et al., 2016; Unknown Author, 2005). The cytoplasmic phosphatase SHP2 reverses these phosphorylation events (Unknown Author, 2005). Higher-order ectodomain clustering and lateral Eph–Eph interactions potentiate activation, while the pre-autophosphorylated activation loop observed crystallographically suggests internal cis-regulation before ligand binding (Overman et al., 2014; Unknown Author, 2005).

Function  
Expression: strong along the midline of the developing neural tube and in neonatal/adult central nervous system, including spinal cord (Bergemann et al., 1998; Zhi et al., 2012).  
Physiological roles: collaborates with EPHB2 in corpus callosum and anterior commissure axon guidance, supports adult axonal plasticity and regeneration, and modulates cell protrusion, migration, proliferation and fate decisions (Bergemann et al., 1998; Kung et al., 2016; Overman et al., 2013; Zhi et al., 2012).  
Upstream ligand: binds ephrin-B3 with nanomolar affinity; shows limited interaction with other ephrin-B ligands (Bergemann et al., 1998).  
Signalling partners: Ras-binding adaptor AF6, Src-family kinases, PI3K, MAPKs, Rho-family GTPases, FAK, paxillin and p130Cas (Stringer et al., 2016; Unknown Author, 2005).

Inhibitors  
Electrophilic quinazoline derivatives covalently target hinge Cys717, yielding potent and selective inhibition with confirmed chemoproteomic engagement (Kung et al., 2016). Broad-spectrum ATP-competitive agents (e.g., CMPD1, CMPD2, dasatinib, afatinib, sorafenib, sunitinib) exhibit lower potency; a C717G substitution restores their activity (Overman et al., 2013; Overman et al., 2014).

Other Comments  
EPHB3 signalling displays context-dependent roles in cancer, functioning as a tumour suppressor in colon and non-small-cell lung cancers but promoting invasion in prostate cancer. Isozyme-selective covalent inhibitors provide tools to dissect these divergent functions (Kung et al., 2016; Overman et al., 2013).

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