Phylogeny  
• EPHA5 resides in the tyrosine kinase (TK) group, Eph receptor family, EphA subclass that contains nine members (tang2020ephreceptorsas pages 1-4).  
• Vertebrate orthologs are highly conserved; human and mouse EPHA5 share >90 % overall sequence identity (liang2021theintracellulardomains pages 14-17).  
• Within the subclass, EPHA5 shows 74 % identity and 87 % homology to EphA4, indicating close paralogous relatedness (huan2013uniquestructureand pages 1-2).

Reaction Catalyzed  
protein-L-tyrosine + ATP ⇌ protein-L-tyrosine-phosphate + ADP (huan2013uniquestructureand pages 1-2, unknownauthors2021identificationdenouvelles pages 21-25).

Cofactor Requirements  
Catalytic activity is Mg²⁺-dependent, the cation coordinating ATP in the active site (tang2020ephreceptorsas pages 1-4, unknownauthors2021identificationdenouvelles pages 21-25).

Substrate Specificity  
Large-scale phosphotyrosine profiling notes EPHA5 phosphorylation events but a definitive consensus motif has not yet been assigned (huan2013uniquestructureand pages 12-12, tang2020ephreceptorsas pages 1-4).

Structure  
• Domain layout: extracellular ligand-binding domain (LBD), cysteine-rich region, two fibronectin type III repeats, single transmembrane helix, juxtamembrane segment, bilobed kinase domain, sterile α motif (SAM), and a C-terminal PDZ-binding motif (arora2023ephreceptorsin pages 1-3).  
• The isolated LBD crystal structure forms a jelly-roll β-sandwich with an open ephrin-binding pocket even without ligand (huan2013uniquestructureand pages 1-2).  
• NMR and molecular-dynamics analyses reveal markedly reduced millisecond-scale conformational exchange relative to EphA4, underpinning distinct ligand selectivity (huan2013uniquestructureand pages 11-12).  
• Full-length AlphaFold modelling corroborates canonical RTK architecture and positions key catalytic residues within the kinase domain (tang2020ephreceptorsas pages 1-4).  
• Regulatory tyrosines Tyr779, Tyr784 (juxtamembrane) and Tyr833 (activation loop) are positioned to control autoinhibition and catalytic output (unknownauthors2021identificationdenouvelles pages 39-42, huan2013uniquestructureand pages 12-12).

Regulation  
• Autophosphorylation on Tyr779, Tyr784, and Tyr833 increases kinase activity and generates SH2 docking sites (huan2013uniquestructureand pages 12-12).  
• Protein tyrosine phosphatase 1B (PTP1B) dephosphorylates EPHA5, attenuating signalling (huan2013uniquestructureand pages 12-12).  
• The E3 ubiquitin-ligase Cbl ubiquitinates activated receptor, promoting internalisation and degradation (huan2013uniquestructureand pages 12-12).  
• Ligand-induced surface clustering drives higher-order oligomerisation that amplifies autophosphorylation (tang2020ephreceptorsas pages 1-4).  
• SAM-domain self-association contributes an additional layer of activity modulation following phosphorylation (unknownauthors2021identificationdenouvelles pages 39-42).

Function  
• EPHA5 is highly expressed during CNS development in cortex, hippocampus, thalamus, septum, hypothalamus and amygdala, and remains detectable in adult brain (mamiya2008changesinattack pages 1-3).  
• Expression is also reported in retinal ganglion cells, lens epithelial and fibre cells, and pancreatic islet β-cells (vu2022mappingtheuniverse pages 12-12, huan2013uniquestructureand pages 1-2).  
• GPI-anchored ephrin-A ligands activate the receptor, with EFNA5 acting as the primary cognate ligand (arora2023ephreceptorsin pages 1-3, huan2013uniquestructureand pages 1-2).  
• Phosphorylated EPHA5 recruits SH2-adaptors Grb7 and Grb10 linking to downstream pathways (arora2023ephreceptorsin pages 1-3).  
• Interaction with the Rho-specific GEF ephexin activates RhoA, while Vav3 couples the receptor to Rac1 and Cdc42 signalling (arora2023ephreceptorsin pages 1-3, unknownauthors2021identificationdenouvelles pages 39-42).  
• SRC-family and ABL tyrosine kinases bind phospho-EPHA5 to propagate forward signalling cascades (liang2021theintracellulardomains pages 14-17).  
• Biologically, EPHA5 guides axons in retinotectal, entorhino-hippocampal and hippocampo-septal pathways, mediating growth-cone repulsion (mamiya2008changesinattack pages 1-3).  
• The receptor regulates synaptogenesis and synaptic plasticity in adult hippocampus (huan2013uniquestructureand pages 12-12).  
• In pancreatic islets, EPHA5-EFNA5 signalling coordinates glucose-stimulated insulin secretion (huan2013uniquestructureand pages 1-2).  
• EPHA5 also modulates Rac1-dependent endothelial migration and vascular assembly (vu2022mappingtheuniverse pages 12-12).

Inhibitors  
• ALW-II-41-27: ATP-competitive small molecule with activity across EphA kinases including EPHA5 (tang2020ephreceptorsas pages 1-4).  
• Dasatinib: multi-kinase inhibitor that suppresses Eph receptor catalytic function (tang2020ephreceptorsas pages 1-4).  
• UniPR1331: pan-Eph/ephrin antagonist that blocks ligand–receptor interaction (unknownauthors2021identificationdenouvelles pages 21-25).

Other Comments  
• Promoter hypermethylation leads to EPHA5 silencing in breast cancer, whereas elevated expression is documented in pancreatic, colorectal, ovarian and hepatocellular carcinomas; in HCC, co-activation of an ALK-FGFR2-EPHA5 kinase module correlates with poor survival (huan2013uniquestructureand pages 1-2, muhammad2023unravelingthesignificance pages 4-5).  
• EPHA5-null mice exhibit altered aggression and locomotor activity, implicating the receptor in hypothalamic serotonin circuits (mamiya2008changesinattack pages 1-3).  
• Methamphetamine administration changes EPHA5 mRNA levels in mouse brain, indicating stimulus-dependent transcriptional regulation (huan2013uniquestructureand pages 12-12).

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