## Phylogeny

Member of the Tyrosine Kinase (TK) group, Eph receptor family, A-class subgroup. EPHA10 clusters with EphA2, EphA7 and EphA8 in phylogenetic trees and carries the same catalytic-site substitutions found in the kinase-dead receptor EphB6 (Aasheim et al., 2005; Truitt & Freywald, 2011). A single confirmed ortholog is mouse Epha10, which shares 88 % nucleotide and 91 % amino-acid identity with the human gene (Aasheim et al., 2005).

## Reaction catalyzed

ATP + [protein]-L-tyrosyl ⇌ ADP + [protein]-L-tyrosyl-phosphate (Tang et al., 2020).  
Note: the canonical Eph tyrosine-phosphotransfer reaction is listed; EPHA10 itself is catalytically inactive because the VAIK, HRD and DFG motifs are replaced by VAVH, HRG and GFG, respectively (Truitt & Freywald, 2011).

## Cofactor requirements

Active Eph kinases require Mg²⁺ or Mn²⁺ for phosphotransfer (Tang et al., 2020). No divalent-cation dependence has been demonstrated for EPHA10 owing to its lack of catalytic activity (Truitt & Freywald, 2011).

## Substrate specificity

No intrinsic peptide motif or phosphotyrosine preference has been defined for EPHA10; substrate specificity remains undetermined (Truitt & Freywald, 2011; Shin et al., 2020).

## Structure

• Modular organisation: extracellular ligand-binding domain, cysteine-rich/Sushi-EGF module, two fibronectin type-III repeats, single transmembrane helix, juxtamembrane (JM) segment, intracellular pseudokinase domain, SAM domain and C-terminal PDZ-binding motif (Toracchio et al., 2024; Unknown authors, 2016).  
• Catalytic-site substitutions (VAVH/HRG/GFG) abolish enzymatic activity (Truitt & Freywald, 2011).  
• Isoforms: full-length receptor, a transmembrane variant lacking the SAM domain, a soluble ectodomain and additional 48, 50 and 86 kDa species detected in breast cells (Aasheim et al., 2005; Unknown authors, 2016).  
• Biophysical properties: intracellular regions are conformationally flexible; the pseudokinase domain can bind ATP and ATP-competitive small molecules despite being catalytically dead (Liang et al., 2021).  
• No high-resolution crystal or cryo-EM structure is available; current insights rely on domain prediction and solution studies (Liang et al., 2021).

## Regulation

• Forms heterodimers with catalytically active EphA7, resulting in trans-phosphorylation of EPHA10 (Unknown authors, 2016).  
• Phosphorylated JM tyrosines recruit SH2-domain adaptors Abl, Src and Vav3 (Liang et al., 2021).  
• EPHA10 expression elevates p38 MAPK phosphorylation (Unknown authors, 2016).  
• Alternative splicing that removes the SAM domain modulates oligomerisation potential (Aasheim et al., 2005).  
• Specific regulatory phosphorylation or ubiquitination sites have not been mapped.

## Function

Expression: highest in testis; minimal in other normal adult tissues (Aasheim et al., 2005). Over-expressed in breast, pancreatic, prostate and non-small-cell lung cancers (Unknown authors, 2016; Shin et al., 2020; Wang et al., 2024).  
Ligand binding: highest affinity for ephrin-A3, lower affinity for ephrin-A1, A2, A4 and A5 (Aasheim et al., 2005; Truitt & Freywald, 2011).  
Interacting partners: EphA7 (heterodimerisation); SH2 adaptors Abl, Src and Vav3 (Liang et al., 2021; Unknown authors, 2016).  
Signalling outputs: enhanced p38 activation and up-regulation of PD-L1, contributing to tumour immune evasion (Unknown authors, 2016; Shin et al., 2020).

## Inhibitors

Neutralising monoclonal antibodies and antibody–drug conjugates directed against EPHA10 have shown activity in pre-clinical cancer models (Shin et al., 2020).

## Other Comments

• Breast cancer: EPHA10 over-expression correlates with lymph-node metastasis; nuclear localisation in invasive cells is suppressed by EphB6 (Anderton et al., 2021; Unknown authors, 2016).  
• Pancreatic cancer: promotes tumourigenesis in cell and xenograft models (Shin et al., 2020).  
• Non-small-cell lung cancer: high EPHA10 transcript levels associate with poor prognosis and altered immune infiltration (Wang et al., 2024).  
• Isoform-specific modulation of E-cadherin/β-catenin complexes has been reported (Buckens et al., 2020).

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