1. Phylogeny  
   Ephrin type‑A receptor 10 (EPHA10) is a member of the Eph receptor tyrosine kinase family, which represents the largest group of receptor tyrosine kinases in vertebrates. Within this family, EPHA10 is assigned to the EphA subclass, whose members preferentially bind glycosylphosphatidylinositol (GPI)‑anchored ephrin‑A ligands. Comparative integromics analyses reveal that EPHA10 clusters phylogenetically with other EphA receptors, in particular with EPHA7 and EPHA8, underscoring shared evolutionary origins among these paralogous proteins (katoh2006comparativeintegromicsona pages 1-2). Evolutionary studies indicate that the core Eph receptor family emerged early in metazoan evolution, with orthologous sequences present in all mammalian species. In addition, phylogenetic reconstructions place EPHA10 among an evolutionarily conserved cohort of Eph receptors that have maintained a similar domain architecture—from the extracellular ligand‑binding region to the intracellular signaling domains—despite divergence in specific catalytic residues (arcas2020theevolutionaryhistory pages 15-16). These analyses, consistent with the protein kinase complement studies tracing kinase evolution from yeast to man, support EPHA10’s classification within an ancient signaling system that is indispensable for cellular patterning and tissue organization in multicellular organisms (arcas2020theevolutionaryhistory pages 15-16).
2. Reaction Catalyzed  
   In catalytically active receptor tyrosine kinases, the typical chemical reaction involves the transfer of the γ‑phosphate group from ATP to specific tyrosine residues on substrate proteins. This reaction is described as:  
     ATP + [protein]–Tyrosine → ADP + [protein]–phosphotyrosine + H⁺  
   However, EPHA10 is classified as a pseudokinase; alterations in key catalytic residues render its kinase domain essentially inactive for phosphotransfer (arora2023ephreceptorsin pages 11-12, liang2021theintracellulardomains pages 5-6). Although the pseudokinase domain retains the overall architecture of active kinases and is capable of binding ATP, EPHA10 does not efficiently catalyze the phosphorylation reaction under physiological conditions. Consequently, rather than mediating the classic ATP-dependent phosphorylation reaction, EPHA10 is thought to function by adopting alternative regulatory roles in signal transduction.
3. Cofactor Requirements  
   Active protein kinases generally require divalent metal ions—most commonly Mg²⁺—as cofactors to coordinate the phosphate groups of ATP and facilitate the transfer of the phosphate to substrate proteins. In the case of EPHA10, despite its lack of catalytic phosphotransfer activity, its ATP-binding site remains intact, and ATP binding is reported with a moderate affinity (apparent KD of approximately 95 µM) (liang2021theintracellulardomains pages 5-6). This binding would normally be Mg²⁺‑dependent in active kinases; however, due to the mutations affecting key residues within the catalytic loop, no detectable kinase activity is observed. Thus, while the theoretical cofactor requirement of Mg²⁺ persists for any potential ATP binding by the pseudokinase domain, the conventional role of Mg²⁺ in supporting phosphotransfer is not realized in EPHA10.
4. Substrate Specificity  
   The substrate specificity of receptor tyrosine kinases is conventionally determined by the recognition of consensus sequence motifs that position target tyrosine residues for phosphorylation. Active Eph receptors typically phosphorylate substrates following binding to specific ligands, often targeting tyrosine residues within defined sequence contexts. In contrast, EPHA10, as a pseudokinase, does not catalyze the phosphorylation reaction and therefore does not exhibit a canonical substrate motif or intrinsic substrate specificity (liang2021theintracellulardomains pages 5-6). Instead, EPHA10 is proposed to function in a non‐catalytic capacity by serving as a scaffold or adaptor, wherein it may recruit other signaling proteins that are phosphorylated by catalytically active receptors present in heteromeric complexes. As such, no experimentally derived consensus substrate motif has been characterized for EPHA10.
5. Structure  
   EPHA10 retains the overall modular architecture that defines the Eph receptor family. The extracellular region consists of an N‑terminal ephrin‑binding domain that is responsible for binding ephrin‑A ligands (EFNA3, EFNA4, and EFNA5), followed by a cysteine‑rich domain and two fibronectin type III repeats that contribute to receptor dimerization and stabilization of the ligand–receptor interaction (arora2023ephreceptorsin pages 1-3). The receptor is anchored to the plasma membrane by a single transmembrane α‑helix.

The intracellular portion of EPHA10 comprises several distinct domains: a juxtamembrane (JM) segment, a pseudokinase domain, a sterile α‑motif (SAM) domain, and a short PDZ‑binding motif at the extreme C‑terminus (liang2021theintracellulardomains pages 1-2). The pseudokinase domain, while structurally similar to catalytically active kinase domains, is characterized by substitutions in key catalytic residues—such as the conserved lysine in the β3 strand and an aspartate in the catalytic loop—that are essential for phosphotransfer activity (arora2023ephreceptorsin pages 11-12, liang2021theintracellulardomains pages 5-6). Despite these alterations, the pseudokinase domain can still bind ATP, which has been observed to occur with a moderate affinity, suggesting that nucleotide binding may influence the conformation and/or protein–protein interactions mediated by the intracellular region.

Structural studies employing methods such as small‑angle X‑ray scattering (SAXS) and cross‑linking mass spectrometry have demonstrated that the intracellular domains of EPHA10 exhibit a high degree of conformational flexibility, with the pseudokinase and SAM domains connected by an approximately 40‑amino‑acid unstructured linker (liang2021theintracellulardomains pages 1-2, 6-8). This dynamic organization is thought to enable EPHA10 to function as a signaling hub by facilitating transient interactions with downstream effectors and catalytically active partner receptors. In addition, predictions from AlphaFold and comparative analyses with related Eph receptors suggest that although EPHA10’s activation loop and hydrophobic spine regions are present, they are disordered or altered due to the loss of essential catalytic residues, thereby impairing typical kinase activation mechanisms (arora2023ephreceptorsin pages 11-12). The presence of a PDZ‑binding motif at the C‑terminus further implies that EPHA10 may interact with PDZ domain‑containing scaffold proteins, contributing to the assembly of multiprotein signaling complexes at the plasma membrane (liang2021theintracellulardomains pages 17-19, katoh2006comparativeintegromicsona pages 1-2).

1. Regulation  
   Regulation of EPHA10 deviates from the canonical mechanisms employed by active receptor tyrosine kinases, due primarily to its classification as a pseudokinase. In active Eph receptors, autophosphorylation of conserved tyrosine residues in the juxtamembrane (JM) segment is a critical step that relieves autoinhibition and promotes full kinase activation. However, EPHA10 lacks the requisite phosphorylatable tyrosine residues in its JM region—specifically, substitutions at positions corresponding to the conserved JX1 and JX2 sites—resulting in an absence of intrinsic autophosphorylation activity (liang2021theintracellulardomains pages 14-17).

Despite this, EPHA10 is not inert; rather, it appears to function as a dynamic regulatory scaffold that can assemble signaling complexes through protein–protein interactions. The ATP-binding ability retained by its pseudokinase domain, despite the absence of phosphotransfer, may induce conformational changes that modulate these interactions (liang2021theintracellulardomains pages 5-6). Additionally, the SAM domain is known to facilitate dimerization and higher‑order oligomerization, processes that are important in the spatial organization of signaling cascades in other Eph receptors (arora2023ephreceptorsin pages 11-12). Although post‑translational modifications such as ubiquitination and redox‑based cysteine modifications have been reported for other Eph receptors, such modifications have not been well characterized for EPHA10. Instead, EPHA10’s regulatory mechanisms seem to rely predominantly on conformational dynamics and the formation of heteromeric complexes with catalytically active Eph receptors—such as EphA7—which are capable of trans‑phosphorylating downstream substrates (shin2020thecatalyticallydefective pages 10-11, liang2021theintracellulardomains pages 14-17). No single modifying enzyme has been conclusively identified as directly regulating EPHA10, and thus its regulation remains an active area of investigation.

1. Function  
   EPHA10 functions as a receptor for members of the ephrin‑A family, binding specifically to EFNA3, EFNA4, and EFNA5 via its extracellular ephrin‑binding domain (arora2023ephreceptorsin pages 1-3). Although it lacks intrinsic catalytic kinase activity due to alterations in key active site residues, EPHA10 plays a pivotal role in mediating cell–cell communication by operating as a signaling adaptor or scaffold. By forming heterodimeric or higher‑order complexes with catalytically active Eph receptors—such as EphA7—EPHA10 is capable of participating in trans‑phosphorylation events that initiate downstream signaling cascades (arora2023ephreceptorsin pages 11-12, liang2021theintracellulardomains pages 14-17).

Functionally, EPHA10 has been implicated in several physiological processes. In developmental contexts, Eph receptors are well known for their roles in tissue patterning, axon guidance, and the regulation of cell adhesion. EPHA10 is believed to contribute to these processes through its ability to bind ephrin‑A ligands and modulate intercellular interactions. In addition, differential gene expression studies have revealed that EPHA10 is variably expressed across tissue types, with marked upregulation in certain cancers. For example, expression profiling indicates that EPHA10 levels correlate with lymph node metastasis in breast cancer, and functional studies in pancreatic cancer cell lines have linked EPHA10 to increased proliferation, migration, and invasive behavior (shin2020thecatalyticallydefective pages 9-10, zhang2021theexpressionprofile pages 10-12). Such observations support the notion that, despite its lack of kinase activity, EPHA10 contributes to oncogenic processes by functioning in a scaffolding capacity that modulates the activity of neighboring catalytically active receptors. Moreover, the involvement of EPHA10 in these pathways suggests that it may indirectly influence key cellular behaviors such as alterations in cell adhesion, regulation of the actin cytoskeleton, and engagement of downstream signaling effectors involved in cell growth and survival (hughes2020harnessingthepower pages 1-3, arora2023ephreceptorsin pages 11-12).

1. Other Comments  
   Therapeutic interest in EPHA10 is rising particularly because of its emerging role in cancer. Recent developments have focused on targeting EPHA10 with monoclonal antibodies and antibody–drug conjugates (ADCs) as potential treatments for aggressive cancers such as triple‑negative breast cancer. Preclinical studies have demonstrated that bispecific antibodies directed against EPHA10, sometimes in combination with ligands that engage CD3 on T cells, exhibit antitumor activity in relevant cancer models (arora2023ephreceptorsin pages 23-24, hughes2020harnessingthepower pages 11-13). To date, there are no reported small‑molecule inhibitors specifically developed for EPHA10, likely due to its pseudokinase nature and absence of intrinsic phosphotransferase activity. In the context of disease, aberrant expression patterns of EPHA10 have been associated with tumor progression and metastasis in both breast and pancreatic cancers, suggesting that EPHA10 has potential as a diagnostic marker and therapeutic target (zhang2021theexpressionprofile pages 10-12, shin2020thecatalyticallydefective pages 9-10). In addition, while classical post‑translational modifications—such as phosphorylation within the activation loop—are not well characterized for EPHA10, its regulation via conformational dynamics and heteromeric receptor interactions highlights a non‑canonical mode of signal modulation that distinguishes it from active kinases. The gaps in understanding regarding specific redox sensor functions or cysteine modifications present an opportunity for further detailed investigation, and ongoing research is expected to help delineate the full spectrum of EPHA10’s biological roles.
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