1. Phylogeny – Ephrin type‑A receptor 6 (EPHA6), also known by its alternative names EPH homology kinase 2 (EHK2) and EPH‑like kinase 12 (HEK12), belongs to the large Eph receptor family of receptor tyrosine kinases (RTKs). Within this extensive family the receptors are divided into two classes – EphA and EphB – on the basis of their extracellular ligand‐binding specificities and sequence homology. EPHA6 is a member of the EphA subclass that preferentially binds glycosylphosphatidylinositol‑anchored ephrin‑A ligands presented on adjacent cells. Comparative analyses of RTK sequences have demonstrated that Eph receptors are conserved among vertebrates, and the presence of orthologs of EPHA6 in multiple species suggests that the receptor has maintained key structural and functional properties throughout evolution. This conservation underlines its important role in mediating cell–cell communication, tissue patterning, and developmental processes (palese2021invivoand pages 121-123, liang2021theintracellulardomains pages 5-6).
2. Reaction Catalyzed – EPHA6 functions as an active receptor tyrosine kinase that catalyzes the transfer of a phosphate group from ATP to specific tyrosine residues on substrate proteins. The chemical reaction performed by the kinase can be summarized as:  
     ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺.  
   This phosphotransfer reaction is central to the forward signaling mechanism that is initiated upon binding of EPHA6 to its ephrin‑A ligands on neighboring cells (palese2021invivoand pages 127-129, stefanski2020investigatingtransmembranelipidinteractions pages 24-29).
3. Cofactor Requirements – Consistent with the catalytic mechanism of other receptor tyrosine kinases, EPHA6 requires a divalent metal ion cofactor for efficient phosphate transfer. In particular, Mg²⁺ is essential as it coordinates the binding of ATP within the kinase active site, stabilizing the transition state and ensuring proper alignment of the substrate for the phosphotransfer reaction. The requirement for Mg²⁺ is a shared feature among kinases and plays a critical role in the catalytic function of EPHA6 (palese2021invivoand pages 127-129, stefanski2020investigatingtransmembranelipidinteractions pages 24-29).
4. Substrate Specificity – As a receptor tyrosine kinase, EPHA6 phosphorylates tyrosine residues on its substrate proteins. Although a detailed consensus motif specific to EPHA6 has not yet been definitively established in the literature, the general substrate specificity of Eph receptors includes phosphorylation of tyrosine residues located both within the receptor’s own juxtamembrane region as part of an autophosphorylation event and on downstream adaptor proteins that contain tyrosine residues within their signaling motifs. Studies on related Eph receptors indicate that substrates often contain specific contextual peptide sequences that facilitate the formation of SH2 domain docking sites following phosphorylation; however, for EPHA6 such sequence preferences remain extrapolated from analyses of other family members. In peptide array experiments and mass spectrometry‐based studies of Eph receptor substrate profiling, Eph kinases have been shown to preferentially target tyrosine residues within regions implicated in regulating cell adhesion and repulsive cellular interactions (gomez2013regulationofephrina3 pages 32-36, banerjee2021identificationdenouvelles pages 47-50).
5. Structure – EPHA6 exhibits the prototypical modular architecture common to Eph receptor tyrosine kinases. The extracellular region is composed of an N‑terminal ligand‐binding domain that confers high‑affinity interaction with GPI‑anchored ephrin‑A ligands; this is followed by a cysteine‑rich domain (CRD) which contributes to receptor–receptor interactions and receptor clustering, and then by two fibronectin type‑III (FNIII) repeats that further support ligand binding and stabilization of receptor assemblies (allonby2015ligandinduceddownregulationof pages 18-24). A single‐pass transmembrane helix anchors the receptor within the plasma membrane. On the intracellular side, EPHA6 contains a short juxtamembrane (JM) region that plays a regulatory role in suppressing the catalytic activity prior to ligand engagement. This is immediately followed by a tyrosine kinase domain (KD) that is organized in the canonical bilobed structure observed in active kinases. The smaller N‑terminal lobe contains a glycine‑rich loop important for ATP binding, while the larger C‑terminal lobe accommodates the activation loop, the hydrophobic spine, and the αC‑helix that are essential for the catalytic function and proper orientation of the active site. Following the kinase domain, EPHA6 possesses a sterile alpha motif (SAM) that is implicated in protein–protein interactions and may mediate receptor oligomerization. Finally, a short PDZ‑binding motif at the extreme C‑terminus serves as a docking site for intracellular scaffolding proteins. Structural studies on related Eph receptors, including crystallographic analyses and AlphaFold modeling of the kinase domains in receptors such as EphA2 and EphB family members, support that EPHA6 conserves the critical catalytic residues necessary for effective phosphotyrosine catalysis (allonby2015ligandinduceddownregulationof pages 24-30, bajaj2023crystalstructureof pages 8-11, liang2021theintracellulardomains pages 5-6).
6. Regulation – The regulation of EPHA6 follows the general paradigm established for receptor tyrosine kinases in the Eph family. Upon binding to ephrin‑A ligands expressed on neighboring cells, EPHA6 undergoes receptor clustering and dimerization. This close apposition of receptor molecules facilitates autophosphorylation of specific tyrosine residues located within the juxtamembrane and kinase domains, events that relieve the autoinhibitory constraints imposed by the JM region and promote full activation of the catalytic domain. The phosphorylation events create docking sites for SH2 domain‑containing adaptor proteins, thereby initiating a cascade of downstream signaling events in what is termed “forward signaling”. Unlike some Eph receptors that lack catalytic activity and are regulated by alternative post‑translational modifications (for example, ligand‑induced ubiquitination leading to lysosomal degradation in EphB6), EPHA6 retains an active kinase domain and has not been reported to undergo significant ubiquitination–mediated downregulation. At this time, detailed mapping of additional post‑translational modifications such as exact phosphorylation sites or the identity of putative modifying enzymes beyond autophosphorylation in EPHA6 has not been fully elucidated in the literature (banerjee2021identificationdenouvelles pages 50-52, allonby2015ligandinduceddownregulationof pages 107-111).
7. Function – EPHA6 plays a central role in mediating contact‑dependent bidirectional signaling between adjacent cells. Its forward signaling is initiated when EPHA6 binds to GPI‑anchored ephrin‑A ligands present on neighboring cells. Ligand binding induces receptor clustering and autophosphorylation, which in turn leads to the recruitment of downstream adaptor proteins that contain SH2 domains. These interactions propagate signaling cascades that modulate the actin cytoskeleton, cell adhesion, migration, and spatial organization of cells. In developmental contexts, such signaling is critical for processes including neuronal axon guidance and tissue patterning. Although studies that focus exclusively on EPHA6 are limited, its functional profile parallels that of other EphA receptors, which have been shown to regulate cell repulsion, boundary formation, and the coordinated positioning of cells during embryonic development. Expression studies indicate that EPHA6 may exhibit tissue‑ and context‑dependent patterns, and dysregulation of Eph receptor signaling in general has been associated with oncogenic processes and altered cell motility, suggesting that EPHA6 might have implications in pathological conditions where cell migration and adhesion are disrupted (palese2021invivoand pages 121-123, gomez2013regulationofephrina3 pages 32-36, phan2020overexpressedgenesignature pages 10-14).
8. Other Comments – EPHA6 is distinguished within the Eph receptor family by its retention of a catalytically active kinase domain, in contrast to certain family members that function as pseudokinases due to key substitutions that abolish enzymatic activity. This catalytic competence enables EPHA6 to phosphorylate target proteins directly upon receptor activation, thereby contributing to forward signaling pathways that regulate critical cellular functions. Currently, selective pharmacological inhibitors specifically targeting EPHA6 have not been comprehensively reported; however, studies on other Eph receptors, such as EPHA2, have identified ATP‑competitive inhibitors through chemical proteomics and structural approaches, providing a potential framework for future efforts to develop EPHA6‑selective agents (heinzlmeir2016chemicalproteomicsand pages 27-29). Moreover, dysregulation of Eph receptor signaling has been implicated in a number of diseases, including various cancers and neurodevelopmental disorders. While detailed associations between EPHA6 dysregulation and specific pathologies are not yet extensively documented in the literature, its role in modulating cell adhesion and migration implies that aberrant EPHA6 activity could contribute to pathological conditions characterized by disrupted tissue organization and invasive cell behavior. Alternate nomenclature—EPH6, EHK2, and HEK12—should be consistently used when cross‑referencing data from diverse studies and databases to ensure clarity in research communications (phan2020overexpressedgenesignature pages 10-14).
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