1. Phylogeny  
   PTK7 is an evolutionarily conserved receptor tyrosine pseudokinase that appears in a broad range of metazoans. Orthologs of PTK7 have been documented in vertebrates—including mouse, chick, frog, and zebrafish—and in invertebrates, where Drosophila homologs such as off‐track (otk) and off‐track2 (otk2) have been identified (dunn2016ptk7andmcc pages 1-3). Its widespread conservation throughout evolution places PTK7 within the receptor tyrosine kinase (RTK) superfamily, although its catalytic domain lacks key residues required for ATP binding and phosphotransfer activity (golubkov2014proteintyrosinepseudokinase7 pages 1-1). Phylogenetically, PTK7 is grouped with other pseudokinases that, despite low or absent catalytic activity, are maintained as part of core signaling modules operating in developmental and cell polarity processes. The evolutionary lineage of PTK7 can be traced back to early metazoans, and its conservation reflects its essential noncatalytic roles in modulating developmental signaling cascades such as the Wnt pathways (berger2017ptk7facesthe pages 1-2, dunn2016ptk7andmcc pages 1-3).
2. Reaction Catalyzed  
   Unlike catalytically active kinases that mediate the transfer of a phosphate group from ATP to a substrate protein (i.e., ATP + [protein] → ADP + [protein]-phosphotyrosine + H⁺), PTK7 has been classified as an inactive or pseudokinase and does not perform phosphotransfer activity (golubkov2014proteintyrosinepseudokinase7 pages 1-1). No detectable phosphorylation reaction occurs because key residues in the ATP-binding site and active loop are substituted or absent, rendering the kinase domain catalytically inert (dunn2016ptk7andmcc pages 1-3).
3. Cofactor Requirements  
   Catalytically active kinases generally require divalent metal ions, most commonly Mg²⁺, to coordinate and bind ATP during the phosphorylation reaction. However, PTK7 is unique in that its intracellular pseudokinase domain does not exhibit ATP binding or catalytic activity; accordingly, it does not display a requirement for typical cofactors such as Mg²⁺ for enzymatic function (dunn2016ptk7andmcc pages 1-3, golubkov2014proteintyrosinepseudokinase7 pages 1-1).
4. Substrate Specificity  
   Due to the absence of intrinsic kinase activity, no consensus substrate phosphorylation motif has been delineated for PTK7. In contrast to active tyrosine kinases that preferentially phosphorylate substrates with defined motifs, PTK7 functions as a scaffolding or regulatory protein. Its intracellular domain, although structurally similar to that of active kinases, is unable to catalyze phosphotransfer and consequently does not exhibit substrate specificity in the canonical sense (golubkov2014proteintyrosinepseudokinase7 pages 1-1, dunn2016ptk7andmcc pages 3-5, mendrola2013receptortyrosinekinases pages 6-7).
5. Structure  
   PTK7 exhibits a classical receptor architecture comprising three major regions. The protein has a long extracellular domain that contains seven immunoglobulin-like (Ig) C2-type repeats, which are encoded by a series of exons and mediate protein–protein interactions with ligands and co-receptors (berger2017ptk7facesthe pages 1-2, martinez2015theptk7and pages 1-2). This is followed by a single-pass transmembrane domain that anchors PTK7 in the plasma membrane. The intracellular portion is comprised of a pseudokinase domain that retains the overall tertiary fold of active kinases but lacks catalytic activity due to alterations in critical motifs such as the glycine-rich loop and the DFG motif (golubkov2014proteintyrosinepseudokinase7 pages 1-1, dunn2016ptk7andmcc pages 3-5). Recent structural modeling, including insights obtained from crystallographic studies and AlphaFold predictions, indicates that the intracellular pseudokinase domain adopts a conformation similar to that of active kinases, with a recognizable C-helix and a configuration that permits formation of a salt bridge between residues analogous to those typically involved in kinase activation; however, ATP binding is sterically hindered by substitutions in the kinase active site (hueber2021laëtitiaganier pages 61-65, frenster2023ptk7isa pages 3-5). Unique structural features of PTK7 also include specific cleavage sites within its extracellular region that render it susceptible to proteolytic processing. For instance, membrane type-1 matrix metalloproteinase (MT1-MMP) has been shown to cleave PTK7 within the seventh Ig-like domain, generating soluble ectodomain fragments and membrane-associated fragments that contribute to differential signaling outcomes (golubkov2012insightsintoectodomain pages 8-9, golubkov2014proteintyrosinepseudokinase7 pages 3-4).
6. Regulation  
   PTK7 is regulated predominantly through post-translational proteolytic processing rather than by classical phosphorylation events. Its extracellular domain is subject to cleavage by metalloproteinases such as MT1-MMP and members of the ADAM family; these enzymatic events produce soluble N-terminal fragments (for example, approximately 65–70 kDa species) as well as membrane-bound C-terminal fragments (approximately 45–50 kDa) (golubkov2012insightsintoectodomain pages 8-9, golubkov2014proteintyrosinepseudokinase7 pages 10-10). This regulated ectodomain shedding is essential for modulating PTK7’s function in cellular migration and invasion, as the balance between full-length and proteolytically processed forms affects actin cytoskeletal contractility. In addition, the intracellular fragment resulting from sequential γ-secretase cleavage has been implicated in enhancing cell proliferation and migration in cancer contexts (dunn2016ptk7andmcc pages 9-11). Beyond proteolysis, PTK7 functions in regulatory complexes through its extracellular interactions with ligands such as Wnt proteins and with other receptor partners like ROR2, contributing to the fine-tuning of both canonical and non-canonical Wnt signaling. In glioblastoma, PTK7 has also been shown to interact with the adhesion G protein-coupled receptor GPR133 and act as a positive allosteric modulator of its signaling (frenster2023ptk7isa pages 23-28).
7. Function  
   Despite its inability to catalyze phosphotransfer reactions, PTK7 plays several critical roles in cellular signaling. It is a key component of both the canonical Wnt/β-catenin and non-canonical Wnt/planar cell polarity (PCP) pathways, where it functions as a co-receptor and regulatory scaffold rather than an enzyme (berger2017ptk7facesthe pages 1-2, dunn2016ptk7andmcc pages 1-3). Through its extracellular domain, PTK7 binds a range of Wnt ligands—including Wnt3a, Wnt5a, and Wnt8—and can interact with Frizzled receptors to modulate downstream signaling events that regulate cell adhesion, migration, and polarity (dunn2016ptk7andmcc pages 3-5, martinez2015theptk7and pages 10-12). The importance of PTK7 in establishing planar cell polarity is underscored by its involvement in processes such as neural tube closure, convergent extension during gastrulation, and coordinated cell migration during embryonic development (berger2017ptk7facesthe pages 1-2). In addition to its developmental roles, PTK7 is implicated in several cancers; aberrant expression and proteolytic processing of PTK7 have been correlated with enhanced cell motility, invasion, and metastasis in tumors such as colon, lung, and esophageal carcinomas (golubkov2014proteintyrosinepseudokinase7 pages 10-10, miao2022wholeexomesequencingidentifies pages 20-20). In glioblastoma, PTK7 enhances GPR133 signaling, thereby influencing tumor cell behavior (frenster2023ptk7isa pages 23-28). The protein also contributes to actin cytoskeletal reorganization, impacting cell shape and polarity through its regulation of adhesive and migratory processes as part of the non-canonical Wnt/PCP pathway.
8. Other Comments  
   Due to its catalytically inactive kinase domain, conventional kinase inhibitors that target ATP binding are not readily applicable to PTK7. Consequently, research efforts are focusing on modulating PTK7 function through its proteolytic processing and interactions with other cell surface receptors. The ratio of full-length to cleaved PTK7 forms has been proposed as a potential predictive biomarker in cancer, as altered proteolysis correlates with invasive behavior and metastasis (golubkov2014proteintyrosinepseudokinase7 pages 10-10, dunn2016ptk7andmcc pages 9-11). Furthermore, microRNA-mediated regulation—for example, via miR-205-5p in colorectal cancer—has been reported to affect PTK7 expression and downstream signaling (miao2022wholeexomesequencingidentifies pages 20-20). PTK7 is also associated with developmental disorders including neural tube defects and scoliosis, reflecting its central role in tissue morphogenesis and cellular polarity. In addition, its function as a modulator of signaling via interactions with receptors such as ROR2 and GPR133 underscores its emerging status as a therapeutic target in both developmental pathologies and cancer (dunn2016ptk7andmcc pages 1-3, frenster2023ptk7isa pages 23-28).
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