1. Phylogeny  
   Cyclin-dependent kinase 17 (CDK17), also known as PCTAIRE2 or PCTK2, belongs to the PCTAIRE subfamily within the CDK family and is classified as an atypical serine/threonine kinase. CDK17 is evolutionarily conserved in higher eukaryotes and is absent in yeast genomes, consistent with an evolutionary specialization in multicellular organisms. It shares high sequence homology in its catalytic domain with other PCTAIRE kinases (CDK16 and CDK18) and displays unique N-terminal extensions that distinguish it from canonical cell cycle CDKs. These features place CDK17 within the CMGC group of kinases, whose evolutionary relationships have been documented from yeast to man (karimbayli2024insightsintothe pages 1-2, mikolcevic2012orphankinasesturn pages 1-2).
2. Reaction Catalyzed  
   CDK17 catalyzes the transfer of a phosphate group from ATP to a serine or threonine residue on its substrate. The chemical reaction can be represented as follows:  
   ATP + [substrate protein] → ADP + [substrate protein]-phospho-serine/threonine + H⁺ (karimbayli2024insightsintothe pages 1-2).
3. Cofactor Requirements  
   The enzymatic activity of CDK17 depends on the presence of divalent metal ions, with Mg²⁺ being required as a cofactor to facilitate ATP binding and proper catalysis (karimbayli2024insightsintothe pages 1-2).
4. Substrate Specificity  
   CDK17 is known by similarity to exhibit serine/threonine-phosphorylating activity, with histone H1 cited as a substrate. The preferred substrate motif is not comprehensively defined; however, evidence from related PCTAIRE kinases indicates that a proline residue following the phosphorylation site and basic residues at certain positions may contribute to substrate recognition (shehata2012analysisofsubstrate pages 1-2, karimbayli2024insightsintothe pages 2-4).
5. Structure  
   CDK17 contains a central catalytic kinase domain that is flanked by unique N-terminal and C-terminal extensions. The catalytic domain displays the typical bilobal structure found in CDKs, comprising an N-terminal lobe responsible for ATP binding and a C-terminal lobe that accommodates the substrate. A distinguishing structural feature of CDK17 is the presence of a PCTAIRE box within its αC helix region, which replaces the canonical PSTAIRE sequence found in other cell cycle CDKs; this domain is critical for the regulation of kinase activity via cyclin binding (endicott2013structuralcharacterizationof pages 2-3, karimbayli2024insightsintothe pages 13-14). Although a high-resolution crystal structure of CDK17 has not been reported, homology models based on related PCTAIRE kinases such as CDK16 indicate conservation of key structural elements, including the activation loop, DFG motif, and hydrophobic spine, which are essential for catalysis and regulation (mikolcevic2012orphankinasesturn pages 2-3, karimbayli2024insightsintothe pages 4-6).
6. Regulation  
   Regulation of CDK17 activity involves mechanisms that are similar to those described for other members of the PCTAIRE subfamily. These regulatory mechanisms include activation through binding to cyclin partners, most notably cyclin Y and potentially other cyclin variants, as well as phosphorylation events at key residues within the activation loop. Phosphorylation by CDK-activating kinases (CAKs) is presumed necessary to induce conformational changes from an inactive to active state, although the precise cyclin partners and phosphorylation sites for CDK17 remain to be fully characterized (karimbayli2024insightsintothe pages 15-17, endicott2013structuralcharacterizationof pages 3-5). Additionally, CDK17 activity may be modulated by intracellular localization signals and binding of regulatory proteins, as observed in related PCTAIRE kinases (karimbayli2022dissectingtherole pages 68-71).
7. Function  
   CDK17 is predominantly expressed in terminally differentiated neurons and in a limited set of other tissues such as the kidney, testis, and intestine, indicating a specialized role outside the conventional cell cycle regulation seen in other CDKs. It is implicated in neuronal functions, including processes related to neurite outgrowth and intracellular trafficking, and is reported to phosphorylate histone H1 in a manner similar to other serine/threonine kinases. This tissue-specific expression pattern suggests that CDK17 may play a role in the regulation of neuronal differentiation and possibly in the modulation of chromatin structure through histone phosphorylation (karimbayli2024insightsintothe pages 1-2, karimbayli2022dissectingtherole pages 68-71, cole2009pctkproteinsthe pages 2-4).
8. Other Comments  
   Specific inhibitors targeting CDK17 are not well established, and most available inhibitors tend to target multiple CDKs, including members of the PCTAIRE subfamily. CDK17 has been associated with disease contexts including neurodegenerative disorders and various cancers, with alterations in its expression observed in tumor types such as glioblastoma and ovarian cancer. However, detailed functional studies are still required to fully establish its role in these diseases and to develop selective therapeutic agents. Notable studies have identified potential regulatory interactions with proteins such as TRAP and components involved in vesicular trafficking, which may further influence its cellular functions (karimbayli2024insightsintothe pages 10-13, karimbayli2022dissectingtherole pages 57-62, cole2009pctkproteinsthe pages 8-10).
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