1. Phylogeny  
   CDK17 (also known as PCTAIRE2 or PCTK2) is a member of the PCTAIRE subfamily of cyclin‐dependent kinases. It is grouped together with related kinases CDK16 (PCTAIRE1) and CDK18 (PCTAIRE3), which share a conserved catalytic domain and unique N‐ and C‐terminal extensions that are less conserved compared to classical cell cycle CDKs. Orthologs of CDK17 are found across eumetazoans and its phylogenetic placement is consistent with the evolution of specialized kinase functions in terminally differentiated tissues, particularly in the nervous system (alonso2021caracterizacióndecdk1418 pages 114-118, mikolcevic2012orphankinasesturn pages 1-2).
2. Reaction Catalyzed  
   CDK17 catalyzes the phosphorylation reaction using ATP as a substrate. The chemical reaction involved is:  
   ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This reaction underlies the essential kinase activity observed in serine/threonine protein kinases (alonso2021caracterizacióndecdk1418 pages 29-32).
3. Cofactor Requirements  
   The enzymatic activity of CDK17 is dependent on the presence of divalent metal ions. In particular, Mg²⁺ is required as a cofactor to facilitate proper binding of ATP within the catalytic site (alonso2021caracterizacióndecdk1418 pages 29-32).
4. Substrate Specificity  
   CDK17 exhibits substrate specificity characteristic of proline‐directed serine/threonine kinases. Experimental profiling using high‐throughput peptide substrate phosphorylation assays has demonstrated that the kinase preferentially phosphorylates serine or threonine residues when these residues are immediately followed by a proline in the peptide sequence. This indicates that the consensus phosphorylation motif for CDK17 is defined by (S/T)-P preference, a feature shared with other cyclin‐dependent kinases in the CMGC group (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 4-4, johnson2023anatlasof pages 7-7).
5. Structure  
   CDK17 contains a central catalytic kinase domain approximating 250 amino acids in length that displays the common bi-lobal architecture observed for CDKs. The N-terminal lobe is predominantly composed of β-sheets and a glycine-rich (G-) loop, whereas the C-terminal lobe is mainly α-helical and includes the activation loop whose conformation is critical for enzymatic activity. A distinctive feature of CDK17 is the replacement of the canonical PSTAIRE motif found in many CDKs by a PCTAIRE sequence in the C-helix, which is important for cyclin binding and dictates part of its functional specificity. Flanking the kinase domain are less conserved N-terminal and C-terminal extensions that are thought to mediate interactions with regulatory partners and may contribute to subcellular localization. Additionally, the kinase domain harbors the conserved HRD and DFG motifs essential for catalysis and has been modeled to share structural similarities with other active forms of CDKs despite limited direct crystallographic data on CDK17 itself (alonso2021caracterizacióndecdk1418 pages 32-35, endicott2013structuralcharacterizationof pages 3-5).
6. Regulation  
   The regulation of CDK17 involves a combination of cyclin binding, phosphorylation events, and potential interactions with regulatory proteins such as 14-3-3. Although the specific cyclin partner for CDK17 remains less definitively characterized compared to classical cell cycle CDKs, evidence supports that cyclin Y may function in its activation, analogous to observations made for other PCTAIRE kinases. Activation typically requires the formation of a CDK-cyclin complex that induces conformational changes exposing the active site; in the case of CDK17, phosphorylation on key amino acid residues by upstream kinases (including protein kinase A in some cellular contexts) has been noted to modulate its kinase activity and subcellular distribution. Moreover, interaction with 14-3-3 proteins can influence the localization and stability of the kinase, further contributing to its regulatory control in terminally differentiated neurons (alonso2021caracterizacióndecdk1418 pages 118-121, karimbayli2024insightsintothe pages 17-18).
7. Function  
   CDK17 is primarily expressed in terminally differentiated neurons, and its biological role is thought to be distinct from the classical cell cycle regulatory functions of many other CDKs. It has been characterized as a serine/threonine kinase based on its ability to phosphorylate substrates such as histone H1, by similarity to other kinases of the CDK family. The neuronal expression pattern implies a role in neuronal differentiation and possibly in the regulation of chromatin dynamics within post-mitotic cells. Furthermore, although detailed downstream signaling pathways remain to be fully elucidated, CDK17 is implicated in processes intrinsic to neuronal function and may participate in specialized signaling pathways that differ from those governing cell proliferation (alonso2021caracterizacióndecdk1418 pages 114-118, johnson2023anatlasof pages 7-7, karimbayli2024insightsintothe pages 17-18).
8. Other Comments  
   Selective inhibitors that exclusively target CDK17 have not yet been comprehensively characterized; existing pan-CDK inhibitors may affect its activity, albeit without established specificity. In addition, although bioinformatic analyses and limited experimental data have linked CDK17 expression with neurodegenerative conditions, particularly given its neuronal enrichment, definitive disease associations and the clinical relevance of CDK17 mutations or dysregulation are still under investigation. Further detailed biochemical studies and high-resolution structural analyses are needed to clarify its precise substrates, inhibitor sensitivity, and the full spectrum of its physiological functions (amrhein2022discoveryof3amino1hpyrazolebased pages 1-3, karimbayli2024insightsintothe pages 17-17).
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