1. Phylogeny  
   Cyclin-dependent kinase 17 (CDK17), also known as PCTAIRE2, belongs to the atypical subfamily of cyclin-dependent kinases comprising CDK14–18. Phylogenetic analyses have grouped CDK17 together with CDK16 (PCTAIRE1) and CDK18 (PCTAIRE3), and these kinases are closely related to the cell cycle–related CDK5 despite their divergent regulatory features. CDK17 is evolutionarily conserved and appears to have emerged during eumetazoan evolution concomitant with the development of the nervous system; its expression is particularly noted in terminally differentiated neurons, indicating a role that is distinct from canonical cell cycle regulators (alonso2021caracterizacióndecdk1418b pages 29-32, karimbayli2024insightsintothe pages 17-18). In several species, orthologs of CDK17 can be found among the PCTAIRE kinases. Its conservation even extends to early diverging metazoans, although some organisms (such as insects in particular contexts) might lack a direct CDK17 homolog, suggesting that its specialized function in neuronal differentiation may be linked to more complex nervous systems (alonso2021caracterizacióndecdk1418c pages 29-32, karimbayli2022dissectingtherole pages 57-62). The kinome group classification places CDK17 within the CMGC group, sharing high sequence homology in its kinase domain with other serine/threonine kinases in this family. Overall, the phylogenetic context of CDK17 underscores its close evolutionary relationship with other PCTAIRE members and hints at functional specialization in differentiated, nonproliferative tissues such as the brain (karimbayli2024insightsintothe pages 17-18).
2. Reaction Catalyzed  
   CDK17 is a serine/threonine kinase that catalyzes the phosphorylation reaction typical of cyclin-dependent kinases. The general biochemical reaction it facilitates can be described as follows: ATP + a target protein containing serine and/or threonine residues yields ADP, inorganic phosphate, and the phosphorylated target protein. Although the complete substrate repertoire of CDK17 is not yet fully elucidated, by similarity to other CDKs its activity has been associated with the phosphorylation of histone H1, suggesting its potential involvement in chromatin regulation. This reaction mechanism, which transfers the γ-phosphate from ATP to the hydroxyl group of serine or threonine residues on protein substrates, is a canonical feature of CDK enzymes. The reaction is dependent on the proper alignment of ATP in the catalytic pocket, engagement of conserved residues such as those within the DFG and HRD motifs, and typically an induced-fit activation through cyclin binding or phosphorylation events (klenor2021rationaldesignofa pages 1-8, shah2020cdksfamilya pages 4-5).
3. Cofactor Requirements  
   The catalytic activity of CDK17, like all protein kinases of the CDK family, is dependent on the binding of adenosine triphosphate (ATP) as the phosphate donor. Additionally, most serine/threonine kinases require divalent metal ions as cofactors to stabilize the negative charges of ATP’s phosphate groups and to facilitate the phosphoryl transfer reaction. In the case of CDK17, Mg²⁺ is the most commonly required metal ion cofactor, ensuring proper coordination within its ATP-binding pocket. Although direct biochemical characterization of CDK17’s cofactor requirements is limited, parallels with closely related CDKs strongly support the necessity for ATP and Mg²⁺ for catalytic activity. In some cellular contexts, additional regulatory molecules may be involved—such as cyclin binding partners or regulatory proteins like 14-3-3 proteins—but the primary cofactors remain ATP and Mg²⁺ (klenor2021rationaldesignofa pages 1-8, karimbayli2024insightsintothe pages 2-4).
4. Substrate Specificity  
   CDK17’s substrate specificity centers on its ability to phosphorylate serine/threonine residues on target proteins. One of the few identified substrates, delivered by similarity to other CDKs, is histone H1; this suggests that CDK17 may have a role in modulating chromatin structure and regulating gene expression within terminally differentiated neurons. In general, CDKs recognize substrates through specific amino acid motifs; while classical CDKs such as CDK2 favor motifs with basic residues surrounding the phosphoacceptor site, the substrate motif for CDK17 remains less clearly defined. However, the fact that CDK17 is expressed predominantly in post-mitotic neuronal cells indicates that its substrates are likely to be proteins essential for neuronal differentiation, synaptic function, or maintenance of the differentiated state. In addition, several reports have hinted that the substrate specificity of PCTAIRE kinases, in general, may rely on unique interactions mediated by their distinct N‐ and C‐terminal sequences, potentially guiding them towards substrates that are not typically recognized by the canonical PSTAIRE kinases (pepino2021overviewofpctk3cdk18 pages 17-18, karimbayli2024insightsintothe pages 17-18). At present, no consensus phosphorylation sequence specific for CDK17 has been firmly established, and further proteomic studies are required to map its full substrate spectrum.
5. Structure  
   The structural architecture of CDK17 comprises a central kinase domain that is highly conserved among CDK family members and flanked by unique N-terminal and C-terminal extensions. These terminal extensions, while less conserved than the catalytic core, are thought to contain important regulatory motifs involved in cyclin binding, subcellular targeting, and protein–protein interactions. Unlike canonical CDKs that harbor the PSTAIRE motif for cyclin recruitment, CDK17 is characterized by a PCTAIRE motif that distinguishes it both structurally and functionally from other CDKs (alonso2021caracterizacióndecdk1418b pages 29-32, alonso2021caracterizacióndecdk1418d pages 29-32). Although no crystal structure of CDK17 has yet been solved, homology modeling based on the available structure of CDK16 has provided insights into its 3D conformation. The conserved kinase domain includes the characteristic glycine-rich loop, an αC-helix, and a catalytic cleft that houses key catalytic motifs such as the DFG and HRD sequences. The ATP-binding pocket is highly conserved and is presumed to exhibit similar interactions with ATP and Mg²⁺ as observed in other CDKs (karimbayli2024insightsintothe pages 2-4). Moreover, the absence of extensive structural data for its regulatory regions leaves open questions regarding the precise mode of cyclin binding. Some studies suggest that while CDK17 may interact with cyclin Y, this interaction is either transient or localized to specific cellular compartments, given that its reported subcellular localization is predominantly cytoplasmic with hints of mitochondrial association in certain cell types (alonso2021caracterizacióndecdk1418c pages 29-32, alonso2021caracterizacióndecdk1418d pages 32-35). The unique sequence features in the N- and C-terminal regions potentially confer specialized regulatory properties that differentiate CDK17’s activity from that of its canonical counterparts.
6. Regulation  
   The regulation of CDK17 appears to rely on multiple layers of control that are characteristic of cyclin-dependent kinases, albeit with several atypical features. A key regulatory mechanism for CDK17 likely involves binding to an activating cyclin partner. Although several PCTAIRE kinases, such as CDK16 and CDK18, are known to interact with cyclin Y and cyclin Y–like proteins, the specific cyclin partner for CDK17 has yet to be conclusively identified. In several reports, cyclin Y is implicated in the activation of related kinases, and by extension CDK17 may also use this interaction for proper activation (alonso2021caracterizacióndecdk1418b pages 29-32, karimbayli2022dissectingtherole pages 57-62). In addition, CDK17 contains a conserved N-terminal PKA binding motif (R–R–X–S) that suggests regulation by phosphorylation events mediated by protein kinase A. Such phosphorylation may modulate its kinase activity either directly by altering conformational stability or indirectly by influencing interactions with regulatory proteins such as 14-3-3 proteins (karimbayli2024insightsintothe pages 17-18). Post-translational modifications, including phosphorylation on activation loop residues, may be necessary for full catalytic activity. While the detailed identification of the phosphorylation sites remains incomplete for CDK17, the presence of conserved residues analogous to those in canonical CDKs implies that similar mechanisms—such as phosphorylation by CDK-activating kinases (CAKs) or regulatory kinases—could be operative. Finally, subcellular localization plays a crucial role in its regulation; CDK17 is predominantly cytoplasmic and has been reported to localize to mitochondria in COS7 cells, suggesting that compartmentalization may influence its accessibility to substrates and regulatory partners (alonso2021caracterizacióndecdk1418c pages 29-32, karimbayli2024insightsintothe pages 7-9).
7. Function  
   CDK17 is primarily expressed in terminally differentiated neurons and is associated with specialized functions in the nervous system. Its expression pattern—peaking during brain development and being predominantly found in post-mitotic neural tissues such as the hippocampus and olfactory bulbs—suggests a role in neuronal differentiation and function (alonso2021caracterizacióndecdk1418b pages 29-32, karimbayli2024insightsintothe pages 7-9). One of its putative functions, inferred by similarity to other CDKs, is the phosphorylation of histone H1. This activity could implicate CDK17 in chromatin remodeling and transcriptional regulation, thereby influencing the gene expression programs necessary for the maintenance of the differentiated state in neurons. In addition to its nuclear effects, CDK17 has been implicated in noncanonical signaling pathways that may affect vesicular trafficking and receptor-mediated signaling, especially considering its proposed roles in phosphorylation of substrates involved in endocytosis such as EPS15 and AP2 complex proteins observed in epithelial ovarian cancer models (karimbayli2022dissectingtherole pages 57-62). Such functions suggest that beyond its classical kinase activity, CDK17 might impact cellular processes related to neuronal survival, synaptic plasticity, and potentially even the cellular response to chemotherapeutic agents, as evidenced by its influence on Gefitinib sensitivity in cancer cells. Although much of its precise physiological role remains to be fully elucidated, the data currently available indicate that CDK17 participates in both chromatin-associated and cytoplasmic signaling processes, reinforcing its classification as an atypical CDK with a unique biological niche in differentiated cells (alonso2021caracterizacióndecdk1418c pages 29-32, karimbayli2022dissectingtherolea pages 19-22).
8. Other Comments  
   As an understudied member of the CDK family, CDK17 has attracted increasing research interest due to its potential roles in both neurobiology and oncology. Notably, its predominant expression in terminally differentiated neuronal cells raises the possibility that dysregulation of CDK17 activity could contribute to neurodegenerative diseases such as Alzheimer’s disease, a hypothesis that is supported by some experimental models showing increased CDK17 expression in Alzheimer’s mouse models (karimbayli2024insightsintothe pages 7-9). In the context of cancer, particularly epithelial ovarian cancer, emerging evidence suggests that CDK17 may modulate cell survival and influence the efficacy of targeted therapies like EGFR inhibitors; silencing of CDK17 has been shown to sensitize cancer cells to drugs such as Gefitinib, thereby lowering the effective IC50 and potentially overcoming drug resistance mechanisms (karimbayli2022dissectingtherole pages 57-62). Additionally, while no selective inhibitors for CDK17 are currently well established, several pan-CDK inhibitors have been reported to affect PCTAIRE kinases, and structure-based design efforts continue with the aim of developing compounds that efficiently target CDK17. Furthermore, there are no widely reported disease-associated mutations or polymorphisms for CDK17 at present, which might be due to its relatively restricted expression profile and specialized biological function. Research into its interactome, particularly the identification of its regulating cyclin partner(s) and specific substrates, remains an active area of investigation that may provide further insights into its regulatory mechanisms and therapeutic potential (alonso2021caracterizacióndecdk1418b pages 29-32, karimbayli2024insightsintothe pages 17-18).
9. References  
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