## Phylogeny

Cyclin-dependent kinase 17 (CDK17, also known as PCTAIRE2/PCTK2) is an atypical serine/threonine kinase that belongs to the PCTAIRE branch of the CDK family within the CMGC kinase group. It is evolutionarily conserved in multicellular animals but absent from yeast genomes, suggesting a role that emerged after the divergence of unicellular fungi. CDK17 shares high catalytic-domain sequence identity with its paralogues CDK16 and CDK18 and contains distinctive N-terminal extensions not present in canonical cell-cycle CDKs (Karimbayli et al., 2024, pp. 1-2; Mikolcevic et al., 2012, pp. 1-2).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + H⁺ + [protein]-phospho-Ser/Thr (Karimbayli et al., 2024, pp. 1-2).

## Cofactor Requirements

Mg²⁺ is required for ATP binding and catalysis (Karimbayli et al., 2024, pp. 1-2).

## Substrate Specificity

CDK17 phosphorylates serine or threonine residues and, by similarity with other PCTAIRE kinases, favours a Pro residue at the +1 position and basic residues at defined downstream sites. Histone H1 has been reported as a substrate, but a comprehensive motif definition remains unresolved (Shehata et al., 2012, pp. 1-2; Karimbayli et al., 2024, pp. 2-4).

## Structure

The protein comprises an N-terminal extension, a bilobal catalytic kinase domain, and a short C-terminal tail. Within the αC helix of the kinase fold, the canonical PSTAIRE sequence is replaced by a PCTAIRE motif that governs cyclin interaction. Although no crystal structure is available, homology models based on CDK16 show conservation of the activation loop, DFG motif, and hydrophobic spine typical of active kinases (Endicott & Noble, 2013, pp. 2-3; Karimbayli et al., 2024, pp. 4-6, 13-14).

## Regulation

CDK17 activity is stimulated by binding to cyclin partners—cyclin Y is the best-documented—and by phosphorylation of key residues in the activation segment, most likely by CDK-activating kinases (CAKs). Additional control may involve subcellular localisation cues and association with regulatory proteins, paralleling mechanisms described for CDK16 and CDK18 (Karimbayli et al., 2024, pp. 15-17; Endicott & Noble, 2013, pp. 3-5; Karimbayli, 2022, pp. 68-71).

## Function

CDK17 is most abundant in terminally differentiated neurons and, at lower levels, in kidney, testis, and intestine. Reported roles include promotion of neurite outgrowth, regulation of intracellular trafficking, and phosphorylation of histone H1, suggesting contributions to neuronal differentiation and chromatin modulation. Altered CDK17 expression has been observed in several cancers, including glioblastoma and ovarian tumours (Karimbayli et al., 2024, pp. 1-2; Cole, 2009, pp. 2-4; Karimbayli, 2022, pp. 57-62).

## Inhibitors

No selective CDK17 inhibitors have been described. Available small-molecule CDK inhibitors generally display broad activity across CDK family members, including PCTAIRE kinases (Karimbayli et al., 2024, pp. 10-13; Klenor, 2021, pp. 16-19).

## Other Comments

CDK17 has been linked to neurodegenerative conditions and interacts with trafficking-related proteins such as TRAP complexes, but detailed functional studies are still needed to clarify these associations (Karimbayli et al., 2024, pp. 10-13; Cole, 2009, pp. 8-10).

## 9. References

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