1. Phylogeny  
   Cyclin‐dependent kinase 10 (CDK10) is a serine/threonine protein kinase that belongs to the cyclin‐dependent kinase family and is classified within the Cdk10/Cdk11 subfamily. It is evolutionarily conserved among mammals and other vertebrates, and its emergence appears to have occurred after the divergence from yeast, as no clear orthologs exist in budding yeast. (duster2022functionalcharacterizationof pages 1-2)  
   CDK10 shares approximately 53% sequence identity over its catalytic region with its closest paralog CDK11, a finding that supports a common ancestral origin within the metazoan lineage. (guen2013cdk10cyclinmis pages 1-1)  
   Phylogenetic analyses based on the human kinome reveal that CDK10 is one of the later evolutionary additions, found only in higher eukaryotes, and it demonstrates significant conservation across species such as zebrafish, mouse, and human, indicating a vital role in vertebrate cellular regulation. (malumbres2014cyclindependentkinases pages 7-8)  
   The identification of CDK10 orthologs in zebrafish and other vertebrates further confirms that it forms part of an evolutionarily conserved set of cyclin‐dependent kinases that regulate essential processes such as cell cycle progression and transcription, although its yeast counterparts are either absent or highly divergent. (yeh2013knockdownofcyclindependent pages 4-6)
2. Reaction Catalyzed  
   CDK10 catalyzes the transfer of the γ‐phosphate group from ATP to specific serine/threonine residues on substrate proteins, following the canonical reaction scheme:  
     ATP + [protein]–(L‐serine or L‐threonine) → ADP + [protein]–(L‐serine/threonine)‐phosphate + H⁺. (duster2022functionalcharacterizationof pages 4-4)  
   This phosphoryl transfer reaction is typical of serine/threonine kinases and results in a conformational change of the substrate, which may ultimately signal for its degradation or modulate its activity. (duster2022functionalcharacterizationof pages 4-5)
3. Cofactor Requirements  
   The catalytic activity of CDK10 depends on the presence of divalent metal ions, with Mg²⁺ being the primary cofactor required for effective ATP binding and the stabilization of the nucleotide within its active site. (sun2005homologymodelingand pages 4-5)  
   The requirement for Mg²⁺ is critical, as it coordinates with the phosphate groups of ATP, thereby allowing the proper positioning of the substrate within the catalytic cleft for efficient phosphoryl transfer. (malumbres2014cyclindependentkinases pages 9-10)
4. Substrate Specificity  
   CDK10 exhibits substrate specificity for serine/threonine residues in a manner characteristic of cyclin‐dependent kinases, with a notable preference for phosphorylation events occurring in a proline-directed context. (duster2022functionalcharacterizationof pages 2-3)  
   One of the best‐characterized substrates of CDK10 is the transcription factor ETS2; phosphorylation of ETS2 by CDK10 marks it for proteasomal degradation, thereby functioning as a regulatory mechanism to limit ETS2’s transcriptional activity. (guen2013cdk10cyclinmis pages 1-1)  
   In addition to ETS2, CDK10 phosphorylates actin dynamics regulators such as protein kinase N2 (PKN2), and through this activity it modulates the organization of the actin cytoskeleton. (duster2022functionalcharacterizationof pages 15-16)  
   Furthermore, CDK10 appears to act on substrates that conform to a minimal consensus motif comprising a serine or threonine residue followed by a proline, although comprehensive consensus sequences have not yet been fully delineated. (guen2017theawakeningof pages 7-8)
5. Structure  
   CDK10 is a protein of 360 amino acids featuring a central kinase domain that is highly conserved among cyclin‐dependent kinases. (duster2022functionalcharacterizationof pages 1-2)  
   Within this domain, the catalytic center includes a critical aspartate residue (D163) that is essential for the phosphoryl transfer reaction, and the activation loop contains a conserved threonine residue (T196) whose phosphorylation is required for full catalytic activation. (duster2022functionalcharacterizationof pages 2-2)  
   A notable structural hallmark of CDK10 is the presence of a gatekeeper methionine at position 117, along with a variant of the classic CDK PSTAIRE motif—specifically, the PISSLRE motif—necessary for cyclin binding and proper positioning of the catalytic elements. (guen2017theawakeningof pages 1-2)  
   Although no experimental crystal structure of CDK10 is currently available, homology modeling studies using CDK2 as a template suggest that CDK10 adopts the canonical bilobal kinase fold. The N-terminal lobe is predominantly composed of beta sheets, whereas the C-terminal lobe is rich in alpha helices; this organization is critical for forming the ATP-binding cleft and for mediating substrate interactions. (sun2005homologymodelingand pages 1-2, sun2005homologymodelingand pages 2-4)  
   The regulatory interaction with its cyclin partner, cyclin Q, is facilitated by conserved cyclin-binding motifs within CDK10, and this interface plays a major role in stabilizing the active conformation of the kinase. (guen2013cdk10cyclinmis pages 2-3)
6. Regulation  
   CDK10’s enzymatic activity is tightly regulated by its association with cyclin Q, which is essential for both its activation and stability in the cellular environment. (duster2022functionalcharacterizationof pages 1-2)  
   A key regulatory mechanism involves the phosphorylation of the activation loop at threonine 196; this phosphorylation event is indispensable for achieving full catalytic activity, as mutations of this residue have been shown to abolish activity without disrupting the formation of the CDK10/cyclin Q complex. (duster2022functionalcharacterizationof pages 2-3)  
   Additional post-translational modifications, such as phosphorylation at threonine 133 and serine 276, have been identified on CDK10; these modifications may affect the protein’s stability and its susceptibility to proteasomal degradation, although the precise enzymes responsible for these modifications have not been conclusively identified. (duster2022functionalcharacterizationof pages 8-9)  
   Moreover, CDK10 itself can be phosphorylated by other cyclin-dependent kinases including CDK1 and CDK5, with these phosphorylation events potentially contributing to cross-talk between different CDK-mediated signaling pathways. (guen2013cdk10cyclinmis pages 5-6)
7. Function  
   CDK10 plays an important role in controlling cellular processes by phosphorylating specific protein substrates. A primary function of CDK10 is the phosphorylation of the transcription factor ETS2, which leads to its proteasomal degradation; this activity positions CDK10 as a negative regulator of ETS2-mediated transcription. (guen2013cdk10cyclinmis pages 1-1)  
   Through its action on ETS2, CDK10 is implicated in the regulation of the MAPK signaling pathway, since degradation of ETS2 can affect the expression of downstream oncogenes, including c-Raf, thereby influencing cell proliferation and survival. (guen2013cdk10cyclinmis pages 2-3)  
   In parallel, CDK10 phosphorylates actin regulatory proteins such as PKN2. This phosphorylation event is associated with the modulation of actin cytoskeleton organization and serves as a mechanism to negatively regulate ciliogenesis by promoting RhoA signaling. (duster2022functionalcharacterizationof pages 15-16)  
   Expression studies have revealed that CDK10 is broadly expressed in various tissues, and its activity has been linked to developmental processes—including aspects of neural development—and to the maintenance of cellular structural integrity. (yeh2013knockdownofcyclindependent pages 4-6)
8. Other Comments  
   A number of small-molecule inhibitors have been explored for their capacity to inhibit CDK10 activity. For example, compounds such as flavopiridol, dinaciclib, SNS-032, and NVP-2 have been tested in biochemical assays, although these inhibitors tend to display higher potency against other cyclin-dependent kinases such as CDK9 and are not entirely selective for CDK10. (duster2022functionalcharacterizationof pages 4-5)  
   Additionally, the inhibitor OTS964, which has been predominantly characterized as a CDK11 inhibitor, also exhibits moderate inhibitory activity against CDK10 in vitro; this observation has fueled interest in developing more selective inhibitors that target CDK10 specifically. (duster2022functionalcharacterizationof pages 5-6)  
   Mutations and alterations in the expression levels of CDK10 or its cyclin partner, cyclin Q, have been linked to significant clinical phenotypes. In particular, loss-of-function mutations in cyclin Q have been associated with STAR syndrome, a developmental disorder characterized by syndactyly, telecanthus, and anogenital as well as renal malformations. (guen2013cdk10cyclinmis pages 2-3, guen2017theawakeningof pages 9-10)  
   Furthermore, aberrant CDK10 expression has been implicated in cancer biology; for instance, reduced CDK10 activity has been correlated with tamoxifen resistance in breast cancer cells, an observation that underscores its potential role as a tumor suppressor and as a therapeutic target. (guen2013cdk10cyclinmis pages 2-3, duster2022functionalcharacterizationof pages 6-7)
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