1. Phylogeny  
   Cyclin-dependent kinase 10 (CDK10) belongs to the large family of serine/threonine protein kinases that regulate cell cycle progression and transcription. It is evolutionarily conserved in metazoans and appears to be closely related to CDK11, sharing 53% sequence identity and 82% sequence similarity within its kinase domain, which positions it within the transcriptional CDKs that expanded during the evolution of higher eukaryotes (duster2022functionalcharacterizationof pages 1-2, malumbres2014cyclindependentkinases pages 3-5). Comparative analyses across species indicate that CDK10 and its cyclin partner, Cyclin Q (also known as Cyclin M), are conserved in mammals, underscoring their maintenance as part of the core regulatory circuitry in cellular signaling (duster2022functionalcharacterizationof pages 1-2).
2. Reaction Catalyzed  
   CDK10 catalyzes a phosphorylation reaction in which ATP and a target protein substrate are converted into ADP, a phosphorylated protein on serine or threonine residues, and a proton. In formulaic terms, this reaction is represented as:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (duster2022functionalcharacterizationof pages 1-2).
3. Cofactor Requirements  
   The kinase activity of CDK10 is dependent on the presence of divalent cations, most notably Mg²⁺. Magnesium ions coordinate ATP binding in the catalytic cleft of CDK10 and facilitate the phosphotransfer reaction to its protein substrates (duster2022functionalcharacterizationof pages 1-2).
4. Substrate Specificity  
   CDK10 phosphorylates key regulators involved in cell cycle and transcriptional control. Experimentally, substrates identified in vitro include components such as the C-terminal domain (CTD) of RNA polymerase II, c-MYC, and the retinoblastoma-associated protein (RB1) (duster2022functionalcharacterizationof pages 1-2). In additional studies, CDK10 has been shown to modify the transcription factor ETS2; phosphorylation of ETS2 by CDK10 promotes its proteasomal degradation, thereby regulating ETS2-dependent transcription (guen2017theawakeningof pages 1-2, malumbres2014cyclindependentkinases pages 7-8). Furthermore, CDK10 phosphorylates protein kinase N2 (PKN2), a key regulator of actin dynamics, which in turn affects both actin cytoskeleton organization and ciliogenesis through modulation of RhoA signaling (guen2017theawakeningof pages 2-3, duster2022functionalcharacterizationof pages 4-4). When employing CTD peptides as substrates, phosphorylation efficiency is significantly enhanced by a substitution of serine residue at position 7 with lysine, indicating a substrate preference that disfavors pre-phosphorylation and may require a positively charged residue at this position (duster2022functionalcharacterizationof pages 4-4).
5. Structure  
   The human CDK10 protein is composed of 360 amino acids and features a canonical kinase domain that is characteristic of the CDK family. Its domain organization is relatively compact, lacking the large N- or C-terminal extensions found in some other CDKs, thus corresponding to a central catalytic core responsible for its serine/threonine kinase activity (duster2022functionalcharacterizationof pages 1-2). Within this kinase domain, key structural elements include an N-terminal lobe, primarily consisting of β-sheets, and a C-terminal lobe that is predominantly α-helical; these two lobes form a cleft that accommodates ATP binding and subsequent phosphotransfer. A critical regulatory feature is the activation loop (T-loop), which contains residue Thr196—this threonine is essential for the activation of CDK10; phosphorylation at Thr196 is required for full catalytic activity, yet it is not necessary for cyclin binding (duster2022functionalcharacterizationof pages 2-3). Mass spectrometry studies have further confirmed additional phosphorylation at Ser276 along with Thr196, suggesting possible layers of regulation within the kinase domain. CDK10 interacts stoichiometrically with its activating partner Cyclin Q (also known as Cyclin M), a cyclin that contains structured cyclin box domains and bipartite nuclear localization signals. Cyclin Q is necessary for facilitating a proper conformation of CDK10 and may assist in substrate recognition by stabilizing the active conformation of the kinase (duster2022functionalcharacterizationof pages 1-2, guen2017theawakeningof pages 1-2).
6. Regulation  
   Regulation of CDK10 activity is multifaceted. A key regulatory mechanism is the phosphorylation of the activation loop at Thr196, a modification essential for catalytic activity without affecting cyclin binding; mutation of Thr196 eliminates kinase activity despite stable association with Cyclin Q (duster2022functionalcharacterizationof pages 2-3, duster2022functionalcharacterizationof pages 5-6). Additionally, CDK10 is phosphorylated at other residues such as Ser276, although the precise functional outcome of this modification remains to be fully elucidated. Beyond direct phosphorylation, CDK10 activity is controlled by its interaction with Cyclin Q, which not only stabilizes the kinase but also protects it from ubiquitin-mediated degradation (guen2017theawakeningof pages 3-4). In cellular contexts, regulatory cross-talk with other CDKs has been suggested by evidence indicating that CDK1 and CDK5 can phosphorylate CDK10 in vitro, implying an integration of CDK10 regulation within broader cell cycle and signaling networks (duster2022functionalcharacterizationof pages 5-6). Finally, the phosphorylation of its substrates—most notably ETS2—serves as an indirect regulatory mechanism, as CDK10-mediated phosphorylation triggers proteasomal degradation of ETS2, thereby modulating transcriptional outcomes (guen2017theawakeningof pages 10-12).
7. Function  
   CDK10 plays critical biological roles through its kinase activity. One of its primary functions is the phosphorylation of ETS2, a transcription factor; this post-translational modification facilitates ETS2 proteasomal degradation, thereby acting as a negative regulator of ETS2-dependent transcription (guen2017theawakeningof pages 1-2, malumbres2014cyclindependentkinases pages 7-8). In addition to ETS2, CDK10 phosphorylates substrates involved in cell cycle and transcriptional regulation, including the CTD of RNA polymerase II, c-MYC, and RB1. These phosphorylation events position CDK10 as a hybrid regulator that bridges cell cycle control and transcription. Furthermore, CDK10 phosphorylates PKN2, which plays a key role in actin cytoskeleton organization. This modification impacts RhoA signaling and serves as a negative regulator of ciliogenesis by promoting actin stress fiber formation, a process important for maintaining the normal balance between ciliogenesis and cell cycle re-entry (guen2017theawakeningof pages 2-3, duster2022functionalcharacterizationof pages 1-2). CDK10 has also been implicated in neural development processes and appears to exert tumor-suppressive effects in certain cancers, although its role may vary according to the cellular context (duster2022functionalcharacterizationof pages 1-2, robert2020developmentofa pages 1-2).
8. Other Comments  
   Several studies have evaluated the chemical inhibition profile of CDK10, highlighting its partial responsiveness to established pan-CDK inhibitors. For instance, compounds such as flavopiridol, dinaciclib, SNS-032, and NVP-2 inhibit CDK10 but with considerably lower potency compared to their activity against CDK9; the measured IC₅₀ values for CDK10 range from submicromolar to low micromolar levels, whereas these compounds exhibit 5- to 20-fold greater potency against CDK9 (duster2022functionalcharacterizationof pages 4-5, duster2022functionalcharacterizationof pages 5-6). In contrast, the CDK11 inhibitor OTS964 shows a unique selectivity advantage, although its potency against CDK10 remains modest. These results underscore the current lack of highly potent and selective inhibitors targeting CDK10 and indicate a need for further structure-guided drug design to overcome these challenges (robert2020developmentofa pages 5-8). In the disease context, perturbations in CDK10 function have been linked with developmental disorders such as STAR syndrome, which is associated with mutations in Cyclin M, and with endocrine therapy resistance in breast cancer, where altered CDK10 activity and expression levels correlate with clinical outcomes (guen2017theawakeningof pages 9-10, duster2022functionalcharacterizationof pages 1-2).
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