1. Phylogeny  
   Cyclin-dependent kinase 10 (CDK10) is a member of the cyclin-dependent kinase family that emerged early in eukaryotic evolution. It is classified within the transcriptional CDK subfamily as opposed to the cell cycle–oriented CDKs. CDK10 was discovered by virtue of its sequence homology to the yeast Cdc2 PSTAIRE domain and shares approximately 38–45% sequence identity with other CDKs, positioning it phylogenetically among kinases that regulate transcription rather than direct cell division (bazzi2021cdk10ingastrointestinal pages 2-4, colas2020cyclindependentkinasesand pages 1-2). Its evolutionary relationship with other CDKs is further underscored by conserved catalytic motifs that are found among many eukaryotic serine/threonine kinases. Although detailed studies on orthologs have not been as extensive as for some other family members, available data suggest that CDK10 orthologs with a similar domain organization exist in several metazoans, and its close evolutionary relatives include members of the CDK11 subgroup (chowdhury2023cmgckinasesin pages 21-22). Furthermore, alternative splicing generating both a full-length active isoform and a truncated inactive variant appears conserved in higher eukaryotes, reflecting an evolutionary mechanism for tuning kinase activity.
2. Reaction Catalyzed  
   CDK10 catalyzes a prototypical kinase reaction in which the γ-phosphate transferred from ATP is covalently attached to the hydroxyl group of serine or threonine residues on substrate proteins. Its catalytic reaction can be summarized as: ATP + [protein]-(L‑serine or L‑threonine) → ADP + [protein]-(L‑serine/threonine‑phosphate) + H⁺ (duster2021biochemicalcharacterizationof pages 86-89, duster2022functionalcharacterizationof pages 9-10). One of the best characterized substrates is the transcription factor ETS2; CDK10 phosphorylates ETS2, promoting its proteasomal degradation and thereby acting as a negative regulator of ETS2-driven transcription (guen2017theawakeningof pages 1-2). In addition, CDK10 phosphorylates protein kinase C–like 2 (PKN2); this phosphorylation regulates actin cytoskeleton organization by modulating RhoA signaling and ultimately suppresses ciliogenesis (guen2017theawakeningof pages 1-2, pluta2024investigatingtherole pages 62-63). The reaction mechanism, typical of serine/threonine kinases, involves binding both ATP and the substrate via the catalytic cleft in the kinase domain followed by nucleophilic attack from the substrate hydroxyl group on the γ-phosphate of ATP, releasing ADP as a byproduct (duster2021biochemicalcharacterizationof pages 93-97).
3. Cofactor Requirements  
   The catalytic activity of CDK10, as with most protein kinases, is dependent on the presence of divalent metal ions. Magnesium (Mg²⁺) is required for optimal kinase activity as it coordinates the ATP molecule within the active site, facilitating correct positioning of the γ-phosphate for transfer (duster2021biochemicalcharacterizationof pages 86-89). Although not explicitly detailed in every study, this requirement is a common feature among cyclin-dependent kinases, and no alternative metal cofactor (such as Mn²⁺) has been distinctly reported for CDK10. Thus, Mg²⁺ is the primary and essential cofactor for catalysis.
4. Substrate Specificity  
   The substrate specificity of CDK10 is defined both by the presence of consensus phosphorylation motifs and by its protein–protein interactions that are mediated through binding partners such as Cyclin M. One well‐established substrate is ETS2, where CDK10 phosphorylates specific serine residues that form a phosphodegron, tagging ETS2 for ubiquitin‐mediated degradation (guen2017theawakeningof pages 2-3). Additionally, the kinase phosphorylates PKN2, a regulator of actin dynamics; this modification contributes to the control of the RhoA signaling pathway, indirectly impacting cytoskeletal organization and ciliogenesis (pluta2024investigatingtherole pages 62-63). While the minimal consensus sequence for many cyclin-dependent kinases is often characterized by an (S/T)P motif, evidence suggests that CDK10’s substrate recognition might be similarly centered on serine/threonine residues followed by proline (duster2022functionalcharacterizationof pages 6-7). However, studies employing analogue-sensitive mutants and mass spectrometry have indicated that CDK10 may also phosphorylate non-canonical sites in context-dependent manners, likely influenced by distal regions and the tertiary structure of the substrate (duster2022functionalcharacterizationof pages 6-7, duster2022functionalcharacterizationof pages 8-9). Therefore, while ETS2 and PKN2 remain the primary physiological substrates, its substrate specificity may extend to additional proteins involved in transcription regulation, cell cycle progression, and cytoskeletal organization.
5. Structure  
   CDK10 is a 360–amino acid protein in its full-length active form, characterized by a central kinase domain that is flanked by regulatory regions. The active isoform contains conserved motifs common to cyclin-dependent kinases, such as the PISSLRE motif—an atypical variation of the PSTAIRE helix that is important for the association with its cyclin partner, Cyclin M (bazzi2021cdk10ingastrointestinal pages 2-4, duster2021biochemicalcharacterizationof pages 86-89). Key catalytic residues include an essential aspartate (often around position 163) that functions as a proton acceptor during phosphoryl transfer (duster2021biochemicalcharacterizationof pages 86-89). Additionally, a conserved threonine residue within the activation loop (commonly identified as Thr196) is critical for kinase activation; phosphorylation at this site is a prerequisite for full activity, although the kinase may form a complex with Cyclin M even in the absence of this modification (duster2022functionalcharacterizationof pages 2-3). The structural organization in CDK10 resembles that seen in other CDKs, with an N-terminal lobe primarily involved in ATP binding and a larger C-terminal lobe containing substrate recognition elements. Alternative splicing of the CDK10 gene produces a shorter, 272–amino acid isoform that lacks the ATP-binding domain, rendering it catalytically inactive, which underscores the importance of full-length structure for kinase function (bazzi2021cdk10ingastrointestinal pages 2-4, colas2020cyclindependentkinasesand pages 1-2). Structural models generated via homology modeling and recent AlphaFold predictions have provided additional insight into the three-dimensional conformation of CDK10, revealing the spatial arrangement of the catalytic and regulatory regions that are essential for its interaction with Cyclin M and for substrate binding (duster2021biochemicalcharacterizationof pages 112-116, duster2022functionalcharacterizationof pages 1-2).
6. Regulation  
   CDK10 is regulated by several converging mechanisms that modulate both its abundance and catalytic activity. The primary mode of regulation is through its association with Cyclin M, which is mandatory for the kinase activity of CDK10; in the absence of Cyclin M, the kinase remains inactive and is more susceptible to ubiquitin-mediated degradation (guen2017theawakeningof pages 1-2, duster2022functionalcharacterizationof pages 2-2). Furthermore, alternative splicing of the CDK10 mRNA results in the production of isoforms with distinct regulatory properties, such as the full-length enzymatically active variant and a truncated, inactive form lacking the ATP-binding domain (bazzi2021cdk10ingastrointestinal pages 2-4, colas2020cyclindependentkinasesand pages 1-2). Post-translational modifications play a crucial role in its regulation as well. Phosphorylation of Thr196 in the activation loop is critical for activation, a modification that is necessary for catalytic function, though the upstream kinase responsible for this phosphorylation event has not been definitively identified in the literature (duster2021biochemicalcharacterizationof pages 86-89, duster2022functionalcharacterizationof pages 2-3). In addition, CDK10 interacts with the prolyl isomerase Pin1, which has been reported to affect its function in estrogen receptor–positive breast cancer by influencing its stability and degradation (guen2017theawakeningof pages 2-3). CDK10 is also subject to regulatory degradation via the ubiquitin-proteasome system, and Cyclin M binding serves to stabilize CDK10, thereby protecting it from degradation (guen2017theawakeningof pages 2-3). Such multi-layered regulation ensures that CDK10 activity is tightly controlled, with its levels and activity being modulated in response to developmental cues and cellular stress, as well as in the context of tumor progression and drug resistance (pluta2024investigatingtherole pages 62-63, łukasik2021cyclindependentkinases(cdk) pages 18-19).
7. Function  
   Functionally, CDK10 is involved in a diverse array of cellular processes that extend from transcription regulation to the control of cytoskeletal dynamics. One of its best characterized functions is the phosphorylation of the transcription factor ETS2. By phosphorylating ETS2, CDK10 facilitates its proteasomal degradation, thereby modulating transcriptional programs that are critical for cell proliferation and differentiation. This function of CDK10 in ETS2 regulation positions it as a tumor suppressor in certain contexts, although its functional role may vary with tissue type and subcellular context (guen2017theawakeningof pages 1-2, bazzi2021cdk10ingastrointestinal pages 2-4). In parallel, CDK10 phosphorylates PKN2, a kinase involved in actin cytoskeleton organization. Phosphorylation of PKN2 by CDK10 is linked to the regulation of RhoA signaling, which in turn controls the formation and maintenance of actin stress fibers and represses ciliogenesis. This negative regulation of ciliogenesis is significant given that alterations in primary cilium dynamics are implicated in developmental disorders such as STAR syndrome and may influence tumor progression (pluta2024investigatingtherole pages 62-63, duster2022functionalcharacterizationof pages 3-4). CDK10 has also been implicated in cell cycle regulation, particularly in the promotion of the G2/M transition, and alterations in its expression have been correlated with differences in cell proliferation rates in various cancers (colas2020cyclindependentkinasesand pages 1-2, bazzi2021cdk10ingastrointestinal pages 2-4). Collectively, the functions of CDK10 span the regulation of transcription through degradation of key transcription factors, control of cytoskeletal and ciliogenesis pathways via phosphorylation of actin-regulatory kinases, and modulation of cell cycle progression, thereby impacting developmental processes and oncogenic signaling pathways.
8. Other Comments  
   Despite its critical roles in regulating ETS2 degradation, actin dynamics, and ciliogenesis, specific pharmacological inhibitors targeting CDK10 have not been as well developed or characterized as those for other CDKs. The absence of selective inhibitors continues to pose a challenge in fully dissecting its functions in normal and pathological contexts, although the dual role of CDK10 as both a tumor suppressor and an oncogenic driver in different tissues makes it an attractive target for future therapeutic development (guen2017theawakeningof pages 1-2, pluta2024investigatingtherole pages 62-63). Additionally, mutations in the CDK10 gene or alterations in its splicing that result in the production of inactive isoforms have been associated with developmental disorders such as Al Kaissi syndrome and may overlap with features seen in STAR syndrome due to defects in Cyclin M (colas2020cyclindependentkinasesand pages 1-2, łukasik2021cyclindependentkinases(cdk) pages 18-19). Ongoing research continues to explore the substrate spectrum of CDK10 and its broader roles in transcriptional control as well as in the maintenance of cellular architecture. Given its involvement in a wide array of cellular processes—from transcription regulation to the actin cytoskeleton and ciliary dynamics—CDK10 remains a focus of active research with potential implications for the development of novel diagnostic and therapeutic strategies.
9. References  
   bazzi2021cdk10ingastrointestinal pages 2-4, chowdhury2023cmgckinasesin pages 21-22, colas2020cyclindependentkinasesand pages 1-2, dai2019cellcycleregulation pages 6-7, duster2021biochemicalcharacterizationof pages 86-89, duster2021biochemicalcharacterizationof pages 93-97, duster2022functionalcharacterizationof pages 1-2, duster2022functionalcharacterizationof pages 2-3, duster2022functionalcharacterizationof pages 3-4, duster2022functionalcharacterizationof pages 6-7, duster2022functionalcharacterizationof pages 8-9, guen2017theawakeningof pages 1-2, guen2017theawakeningof pages 2-3, pluta2024investigatingtherole pages 62-63, łukasik2021cyclindependentkinases(cdk) pages 18-19

References

1. (bazzi2021cdk10ingastrointestinal pages 2-4): Zainab A. Bazzi and Isabella T. Tai. Cdk10 in gastrointestinal cancers: dual roles as a tumor suppressor and oncogene. Frontiers in Oncology, Jun 2021. URL: https://doi.org/10.3389/fonc.2021.655479, doi:10.3389/fonc.2021.655479. This article has 17 citations and is from a peer-reviewed journal.
2. (chowdhury2023cmgckinasesin pages 21-22): Iftekhar Chowdhury, Giovanna Dashi, and Salla Keskitalo. Cmgc kinases in health and cancer. Cancers, 15:3838, Jul 2023. URL: https://doi.org/10.3390/cancers15153838, doi:10.3390/cancers15153838. This article has 18 citations and is from a peer-reviewed journal.
3. (colas2020cyclindependentkinasesand pages 1-2): Pierre Colas. Cyclin-dependent kinases and rare developmental disorders. Orphanet Journal of Rare Diseases, Aug 2020. URL: https://doi.org/10.1186/s13023-020-01472-y, doi:10.1186/s13023-020-01472-y. This article has 33 citations and is from a peer-reviewed journal.
4. (dai2019cellcycleregulation pages 6-7): Yun Dai, Fengyan Jin, Wei Wu, and Shaji K. Kumar. Cell cycle regulation and hematologic malignancies. Blood Science, 1:34-43, Aug 2019. URL: https://doi.org/10.1097/bs9.0000000000000009, doi:10.1097/bs9.0000000000000009. This article has 33 citations.
5. (duster2021biochemicalcharacterizationof pages 112-116): RS Düster. Biochemical characterization of the human cyclin-dependent kinases cdk7 and cdk10. Unknown journal, 2021.
6. (duster2021biochemicalcharacterizationof pages 86-89): RS Düster. Biochemical characterization of the human cyclin-dependent kinases cdk7 and cdk10. Unknown journal, 2021.
7. (duster2021biochemicalcharacterizationof pages 93-97): RS Düster. Biochemical characterization of the human cyclin-dependent kinases cdk7 and cdk10. Unknown journal, 2021.
8. (duster2022functionalcharacterizationof pages 1-2): Robert Düster, Yanlong Ji, Kuan-Ting Pan, Henning Urlaub, and Matthias Geyer. Functional characterization of the human cdk10/cyclin q complex. Open Biology, Mar 2022. URL: https://doi.org/10.1098/rsob.210381, doi:10.1098/rsob.210381. This article has 12 citations and is from a peer-reviewed journal.
9. (duster2022functionalcharacterizationof pages 2-2): Robert Düster, Yanlong Ji, Kuan-Ting Pan, Henning Urlaub, and Matthias Geyer. Functional characterization of the human cdk10/cyclin q complex. Open Biology, Mar 2022. URL: https://doi.org/10.1098/rsob.210381, doi:10.1098/rsob.210381. This article has 12 citations and is from a peer-reviewed journal.
10. (duster2022functionalcharacterizationof pages 2-3): Robert Düster, Yanlong Ji, Kuan-Ting Pan, Henning Urlaub, and Matthias Geyer. Functional characterization of the human cdk10/cyclin q complex. Open Biology, Mar 2022. URL: https://doi.org/10.1098/rsob.210381, doi:10.1098/rsob.210381. This article has 12 citations and is from a peer-reviewed journal.
11. (duster2022functionalcharacterizationof pages 3-4): Robert Düster, Yanlong Ji, Kuan-Ting Pan, Henning Urlaub, and Matthias Geyer. Functional characterization of the human cdk10/cyclin q complex. Open Biology, Mar 2022. URL: https://doi.org/10.1098/rsob.210381, doi:10.1098/rsob.210381. This article has 12 citations and is from a peer-reviewed journal.
12. (duster2022functionalcharacterizationof pages 6-7): Robert Düster, Yanlong Ji, Kuan-Ting Pan, Henning Urlaub, and Matthias Geyer. Functional characterization of the human cdk10/cyclin q complex. Open Biology, Mar 2022. URL: https://doi.org/10.1098/rsob.210381, doi:10.1098/rsob.210381. This article has 12 citations and is from a peer-reviewed journal.
13. (duster2022functionalcharacterizationof pages 8-9): Robert Düster, Yanlong Ji, Kuan-Ting Pan, Henning Urlaub, and Matthias Geyer. Functional characterization of the human cdk10/cyclin q complex. Open Biology, Mar 2022. URL: https://doi.org/10.1098/rsob.210381, doi:10.1098/rsob.210381. This article has 12 citations and is from a peer-reviewed journal.
14. (duster2022functionalcharacterizationof pages 9-10): Robert Düster, Yanlong Ji, Kuan-Ting Pan, Henning Urlaub, and Matthias Geyer. Functional characterization of the human cdk10/cyclin q complex. Open Biology, Mar 2022. URL: https://doi.org/10.1098/rsob.210381, doi:10.1098/rsob.210381. This article has 12 citations and is from a peer-reviewed journal.
15. (guen2017theawakeningof pages 1-2): Vincent J Guen, C. Gamble, J. Lees, and P. Colas. The awakening of the cdk10/cyclin m protein kinase. Oncotarget, 8:50174-50186, Feb 2017. URL: https://doi.org/10.18632/oncotarget.15024, doi:10.18632/oncotarget.15024. This article has 42 citations and is from a poor quality or predatory journal.
16. (guen2017theawakeningof pages 2-3): Vincent J Guen, C. Gamble, J. Lees, and P. Colas. The awakening of the cdk10/cyclin m protein kinase. Oncotarget, 8:50174-50186, Feb 2017. URL: https://doi.org/10.18632/oncotarget.15024, doi:10.18632/oncotarget.15024. This article has 42 citations and is from a poor quality or predatory journal.
17. (pluta2024investigatingtherole pages 62-63): AJ Pluta. Investigating the role of cdk1 in governing the transcriptional landscape in cancer cells. Unknown journal, 2024.
18. (łukasik2021cyclindependentkinases(cdk) pages 18-19): Paweł Łukasik, Michał Załuski, and Izabela Gutowska. Cyclin-dependent kinases (cdk) and their role in diseases development–review. International Journal of Molecular Sciences, 22:2935, Mar 2021. URL: https://doi.org/10.3390/ijms22062935, doi:10.3390/ijms22062935. This article has 198 citations and is from a peer-reviewed journal.