## Phylogeny

Cyclin-dependent kinase 10 (CDK10) is a member of the CMGC group of serine/threonine protein kinases, which also includes MAPKs, GSK3, and CLKs (unknownauthors2021biochemicalcharacterizationof pages 23-28, wood2018structuralinsightsinto pages 1-2). Within the kinome, it is classified as a member of the cyclin-dependent kinase (CDK) family and is assigned to the transcriptional CDK subfamily, which includes CDK7, 8, 9, 11, 12, and 13 (malumbres2014cyclindependentkinases pages 1-2, pellarin2025cyclindependentproteinkinases pages 2-4, unknownauthors2021biochemicalcharacterizationof pages 23-28). According to the classification by Manning et al. 2002, CDK10 forms a distinct subfamily with its closest paralog, CDK11 (malumbres2014cyclindependentkinases pages 1-2). Human CDK10 shares 53% sequence identity and 82% similarity with human CDK11 (duster2022functionalcharacterizationof pages 2-2, duster2022functionalcharacterizationof pages 1-2). CDK10 orthologs have been identified in *Drosophila* (cdc2rk), but are absent in yeast and *Caenorhabditis elegans* (guen2017theawakeningof pages 8-9, duster2022functionalcharacterizationof pages 1-2).

## Reaction Catalyzed

As a serine/threonine-specific protein kinase, CDK10 catalyzes the transfer of the γ-phosphate group from ATP to a serine or threonine residue on a protein substrate (peyressatre2015targetingcyclindependentkinases pages 6-8, unknownauthors2021biochemicalcharacterizationof pages 23-28, wood2018structuralinsightsinto pages 3-4). The reaction is: ATP + [a protein] → ADP + [a phosphoprotein] (malumbres2014cyclindependentkinases pages 1-2).

## Cofactor Requirements

The catalytic activity of CDK10 requires ATP as the phosphate donor (guen2013cdk10cyclinmis pages 1-2, peyressatre2015targetingcyclindependentkinases pages 6-8, malumbres2014cyclindependentkinases pages 1-2). The kinase reaction also requires Mg²⁺ for ATP coordination (guen2017theawakeningof pages 1-2).

## Substrate Specificity

The consensus substrate specificity motif for CDK10 is described with some contradiction in the literature. One comprehensive analysis of the human kinome classifies CDK10 as a Pro-directed kinase, preferentially phosphorylating serine or threonine residues immediately followed by a proline residue in the +1 position (S/T-P motif) (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 4-4). However, another study reports that the consensus motif is not strictly proline-directed (duster2022functionalcharacterizationof pages 9-10).

CDK10 phosphorylates the C-terminal domain (CTD) of RNA polymerase II at Ser2, Ser5, and Ser7 of the heptad repeats (unknownauthors2021biochemicalcharacterizationof pages 89-93). The efficiency of CTD phosphorylation is enhanced approximately fourfold when Ser7 is substituted with a lysine residue (duster2022functionalcharacterizationof pages 4-4). CDK10 also phosphorylates the transcription factor c-Myc at multiple (Ser/Thr)Pro motifs, including Thr58, Ser62, Ser67, Ser71, and Thr78 (unknownauthors2021biochemicalcharacterizationof pages 89-93).

## Structure

Human CDK10 is a 360-amino acid protein that exists as at least two splice isoforms: a full-length, enzymatically active form and a truncated, inactive variant lacking the ATP-binding domain (bazzi2021cdk10ingastrointestinal pages 2-4, duster2022functionalcharacterizationof pages 1-2). It possesses a canonical bilobal kinase domain architecture typical of CDKs, with a smaller N-terminal lobe for ATP binding and a larger C-terminal lobe containing the catalytic site (malumbres2014cyclindependentkinases pages 1-2, peyressatre2015targetingcyclindependentkinases pages 6-8). Key catalytic and regulatory residues include the gatekeeper methionine M117, catalytic aspartate D163, and regulatory threonines T133 and T196 (duster2022functionalcharacterizationof pages 2-3). A kinase-dead mutant can be generated by a D181A substitution (guen2013cdk10cyclinmis pages 1-2).

A unique structural feature is the PISSLRE motif, a variant of the canonical PSTAIRE αC-helix that is critical for cyclin interaction (duster2022functionalcharacterizationof pages 2-2, unknownauthors2021biochemicalcharacterizationof pages 86-89). The full-length isoform also contains a bipartite nuclear localization signal at its C-terminus (guen2017theawakeningof pages 2-3, unknownauthors2021biochemicalcharacterizationof pages 86-89). No experimentally determined 3D structure of the CDK10/Cyclin M complex has been resolved by crystallography; however, AlphaFold structural predictions confirm the typical domain organization and kinase fold (duster2022functionalcharacterizationof pages 2-3, guen2017theawakeningof pages 8-9, unknownauthors2021biochemicalcharacterizationof pages 86-89).

## Regulation

CDK10 activity is controlled by cyclin binding, post-translational modifications, and protein-protein interactions.

**Cyclin Binding**: The kinase activity of CDK10 is strictly dependent on forming a stoichiometric heterodimeric complex with its regulatory partner, Cyclin M (also known as Cyclin Q or FAM58A) (duster2022functionalcharacterizationof pages 2-2, guen2013cdk10cyclinmis pages 1-2, unknownauthors2021biochemicalcharacterizationof pages 89-93). Cyclin M binding also stabilizes CDK10 by protecting it from ubiquitin-mediated proteasomal degradation (guen2017theawakeningof pages 2-3, pellarin2025cyclindependentproteinkinases pages 13-14).

**Phosphorylation**: - **Activation**: Full kinase activation requires phosphorylation at Thr196 in the activation T-loop (duster2022functionalcharacterizationof pages 2-2, guen2017theawakeningof pages 2-3). This phosphorylation is essential for catalytic function but is not required for complex formation with Cyclin M (duster2022functionalcharacterizationof pages 2-3). - **Degradation**: Phosphorylation at Thr133 promotes Pin1-mediated ubiquitin-proteasome degradation of CDK10 (duster2022functionalcharacterizationof pages 2-2, pellarin2025cyclindependentproteinkinases pages 13-14). - **Other Sites**: CDK10 is also phosphorylated on tyrosine residues 50 and 54 (guen2017theawakeningof pages 2-3). - **Upstream Kinases**: CDK10 is a substrate for other CDKs, including Cdk1/CycB1 and Cdk5/p35, which phosphorylate it at sites other than Thr196 (duster2022functionalcharacterizationof pages 9-10).

**Other Interactions**: CDK10 interacts with the chaperone protein HSP90, which may be required for its stability, and with the prolyl-isomerase Pin1, which modulates its function and stability (bazzi2021cdk10ingastrointestinal pages 2-4, unknownauthors2021biochemicalcharacterizationof pages 112-116).

## Function

CDK10 is a multifunctional kinase that regulates transcription, cell cycle progression, cytoskeletal dynamics, and ciliogenesis (bazzi2021cdk10ingastrointestinal pages 2-4, guen2017theawakeningof pages 1-2). Its kinase activity peaks during the G2/M phase of the cell cycle (guen2017theawakeningof pages 1-2).

**Substrates and Signaling Pathways**: - **ETS2**: CDK10 phosphorylates the transcription factor ETS2, which inhibits its transactivation potential and promotes its degradation via the COP1/DET1 ubiquitin ligase complex (bazzi2021cdk10ingastrointestinal pages 2-4, guen2017theawakeningof pages 3-4). This suppresses MAPK signaling by reducing the expression of ETS2 targets like c-RAF (duster2022functionalcharacterizationof pages 2-2, guen2013cdk10cyclinmis pages 1-2). - **PKN2**: CDK10 phosphorylates protein kinase N2 (PKN2) at residues Thr121 and Thr124 (bazzi2021cdk10ingastrointestinal pages 2-4). This phosphorylation event represses ciliogenesis in a RhoA-dependent manner and regulates actin cytoskeleton dynamics (bazzi2021cdk10ingastrointestinal pages 2-4, guen2017theawakeningof pages 3-4). - **Other Substrates**: Additional substrates include retinoblastoma protein (RB1), c-MYC, RNA polymerase II CTD, HDGF, and ARGLU1 (duster2022functionalcharacterizationof pages 1-2, duster2022functionalcharacterizationof pages 9-10).

**Cellular Roles**: - **Ciliogenesis and Cytoskeleton**: The CDK10/Cyclin M complex localizes to the basal body of primary cilia and acts as a negative regulator of ciliogenesis (bazzi2021cdk10ingastrointestinal pages 2-4, guen2017theawakeningof pages 3-4). Knockdown of CDK10 leads to the formation of elongated primary cilia and a decrease in actin stress fibers (bazzi2021cdk10ingastrointestinal pages 2-4, duster2022functionalcharacterizationof pages 2-3). - **Transcription**: CDK10 is involved in transcription elongation and pre-mRNA splicing and is found within spliceosomal C complexes (guen2017theawakeningof pages 7-8, pellarin2025cyclindependentproteinkinases pages 13-14). - **Localization**: Cyclin M lacks a nuclear localization signal (NLS), and its nuclear import depends on binding to CDK10, which possesses a C-terminal NLS (duster2022functionalcharacterizationof pages 2-2, guen2017theawakeningof pages 2-3).

## Inhibitors

Several ATP-competitive small molecule inhibitors target CDK10, though none are selective. - The pan-CDK inhibitors flavopiridol (IC50 ≈ 298 nM), dinaciclib, SNS-032, and NVP-2 inhibit CDK10 but are generally more potent against CDK9 (duster2022functionalcharacterizationof pages 4-4, duster2022functionalcharacterizationof pages 9-10). - OTS964, a CDK11 inhibitor, also inhibits CDK10 (IC50 ≈ 1491 nM) (duster2022functionalcharacterizationof pages 4-4, duster2022functionalcharacterizationof pages 9-10). - No low-molecular-weight selective inhibitors for CDK10 are currently available (duster2022functionalcharacterizationof pages 9-10).

## Other Comments

**Disease Associations**: - **STAR Syndrome**: Loss-of-function mutations in *FAM58A*, the gene encoding Cyclin M, cause STAR (Towler-Scott) syndrome, a rare X-linked developmental disorder (guen2013cdk10cyclinmis pages 1-2, unknownauthors2021biochemicalcharacterizationof pages 81-86, wood2018structuralinsightsinto pages 1-2). These mutations impair CDK10/Cyclin M kinase activity, leading to developmental abnormalities linked to ciliogenesis defects (guen2013cdk10cyclinmis pages 1-2, guen2017theawakeningof pages 4-6). - **Developmental Defects**: Pathogenic splice-site mutations in the *CDK10* gene are associated with human developmental defects (duster2022functionalcharacterizationof pages 2-2). Complete knockout of *Cdk10* in mice is embryonically lethal (duster2022functionalcharacterizationof pages 2-2, unknownauthors2021biochemicalcharacterizationof pages 81-86). - **Cancer**: CDK10 has dual, context-dependent roles in cancer. It acts as a tumor suppressor in breast, gastric, and liver cancers, as well as glioma, but can be oncogenic in colorectal cancer (duster2022functionalcharacterizationof pages 2-2). In estrogen receptor (ER)-positive breast cancer, low CDK10 expression is associated with increased ETS-2 levels, MAPK pathway activation, and tamoxifen resistance (duster2022functionalcharacterizationof pages 2-2, guen2013cdk10cyclinmis pages 1-2).

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