## Phylogeny

Cyclin-dependent kinase 3 (CDK3) is classified in the CMGC group of protein kinases, within the CDK family (manning2002theproteinkinase pages 3-3, malumbres2014cyclindependentkinases pages 1-2, caenepeel2004themousekinome pages 1-2). Phylogenetically, CDK3 is part of the cell-cycle-related CDK subfamily and is closely related to CDK1 and CDK2, sharing high sequence identity (malumbres2014cyclindependentkinases pages 1-2, braun1998investigationofthe pages 1-2, manning2002theproteinkinase pages 3-3). Multiple sequence alignments and phylogenetic analyses confirm that CDK3 clusters with CDK1 and CDK2 (pellarin2025cyclindependentproteinkinases pages 2-4). CDK3 emerged via divergence within the mammalian lineage and does not have a direct yeast ortholog (malumbres2014cyclindependentkinases pages 1-2). Mouse orthologs for human kinases, including CDKs, have been identified, and CDK3 orthologs are found across metazoans (caenepeel2004themousekinome pages 1-2, manning2002theproteinkinase pages 3-3).

## Reaction Catalyzed

CDK3 is a serine/threonine kinase that catalyzes the transfer of a phosphate group from ATP to a serine or threonine residue on a protein substrate (johnson2023anatlasof pages 3-4, malumbres2014cyclindependentkinases pages 1-2).

## Cofactor Requirements

The catalytic activity of CDK3 depends on Mg²⁺ as an essential divalent cation cofactor to coordinate ATP binding and phosphoryl transfer (johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 2-3).

## Substrate Specificity

CDK3 is a proline-directed kinase that preferentially phosphorylates serine or threonine residues followed immediately by a proline at the +1 position, conforming to the canonical [S/T]P motif (johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 2-3). Substrate recognition is enhanced by a preference for basic residues, particularly arginine or lysine, at positions upstream of the phosphorylation site, such as -2 and -1 (johnson2023anatlasof pages 3-4).

## Structure

The structure of CDK3 contains a conserved bilobal catalytic core typical of protein kinases, which consists of a small N-terminal lobe composed mostly of β-sheets and a larger C-terminal lobe primarily made of α-helices (joubes2000cdkrelatedproteinkinases pages 2-3). The ATP molecule binds in a catalytic cleft located between these two lobes (joubes2000cdkrelatedproteinkinases pages 2-3). Key structural and regulatory features include the C-helix and hydrophobic spine, which are important for catalytic activity (pellarin2025cyclindependentproteinkinases pages 2-4). The active site contains conserved residues essential for ATP binding and catalysis, including a glycine-rich loop, Lys-33, and Glu-51, which is located in the C-helix (joubes2000cdkrelatedproteinkinases pages 2-3). The structure also features a T-loop, which plays a critical role in regulation via phosphorylation (joubes2000cdkrelatedproteinkinases pages 2-3, pellarin2025cyclindependentproteinkinases pages 9-10).

## Regulation

CDK3 activity is regulated by multiple mechanisms, including cyclin binding, phosphorylation, and interaction with inhibitors (braun1998investigationofthe pages 1-2, pellarin2025cyclindependentproteinkinases pages 9-10). For activation, CDK3 requires association with cyclin subunits; it interacts with cyclins E, A, and C (pellarin2025cyclindependentproteinkinases pages 9-10). Cyclin binding induces a conformational change that rotates the C-helix into the catalytic cleft, realigning active site residues for catalysis (joubes2000cdkrelatedproteinkinases pages 2-3). Full activation requires phosphorylation within the T-loop by the CDK-activating kinase (CAK) complex, which consists of CDK7, cyclin H, and MAT1 (pellarin2025cyclindependentproteinkinases pages 9-10, joubes2000cdkrelatedproteinkinases pages 2-3). Although CDK3 protein is constitutively expressed, its kinase activity fluctuates during the cell cycle and is modulated by CDK inhibitors (CKIs) p21 and p27, which bind to CDK3 (braun1998investigationofthe pages 1-2).

## Function

CDK3 is predominantly localized in the cytosol and shows high expression in the respiratory tract (pellarin2025cyclindependentproteinkinases pages 9-10). It plays a critical role in cell cycle progression, particularly in the G1 to S phase transition and in promoting exit from the G0 phase (braun1998investigationofthe pages 1-2, zhang2024cdkl3isa pages 17-18). CDK3 phosphorylates key substrates, including Histone H1, activating transcription factor 1 (ATF1), the retinoblastoma protein (pRb), and CABLES1 (pellarin2025cyclindependentproteinkinases pages 9-10, braun1998investigationofthe pages 1-2, sato2002ik32arelative pages 6-7). Phosphorylation of pRb by the CDK3/cyclin C complex is required for the G0-G1 transition (pellarin2025cyclindependentproteinkinases pages 9-10). CDK3 also regulates the transcriptional activity of E2F family members (E2F1, E2F2, E2F3) in an RB-independent manner (pellarin2025cyclindependentproteinkinases pages 9-10). It interacts with cyclins A, C, and E, CDK inhibitors p21 and p27, and the protein ik3-2 (pellarin2025cyclindependentproteinkinases pages 9-10, braun1998investigationofthe pages 1-2, sato2002ik32arelative pages 6-7).

## Inhibitors

The kinase activity of CDK3 is inhibited by the endogenous cyclin-dependent kinase inhibitors p21 and p27, which bind to CDK3 to regulate its function during the cell cycle (braun1998investigationofthe pages 1-2). In contrast, CDK3 activity is not affected by the inhibitor p16 (braun1998investigationofthe pages 1-2).

## Other Comments

Although CDK3’s role in cell cycle progression links it to cancer biology, it does not cooperate with Ras in fibroblast transformation or demonstrate oncogenic activity in certain models (braun1998investigationofthe pages 1-2, zhang2024cdkl3isa pages 17-18). However, it does enhance Myc-induced proliferation and anchorage-independent growth (braun1998investigationofthe pages 1-2).

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