## Phylogeny

Cyclin-dependent kinase 3 (CDK3; UniProt Q00526) belongs to the CDK1/2/3 sub-family of classical cell-cycle kinases. Phylogenetic analyses (maximum-likelihood and Bayesian) place CDK3 closer to CDK2 than to CDK1; a metazoan gene-duplication yielded separate CDK1 and CDK2/3 clades (Cao et al., 2014; Liu & Kipreos, 2000). Orthologs occur from basal metazoans (e.g., Amphimedon queenslandica, Trichoplax adhaerens) to mammals, whereas unicellular eukaryotes retain a single ancestral CDK1/2/3 gene (Cao et al., 2014; Malumbres, 2014).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Malumbres, 2014).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Huwe et al., 2003).

## Substrate Specificity

CDK3 phosphorylates serine/threonine sites in histone H1, activating transcription factor 1 (ATF1), retinoblastoma protein (RB1) and CABLES1. A strict consensus sequence has not been defined, but specificity resembles that of other cell-cycle CDKs (Peyressatre et al., 2015; Pluta et al., 2024).

## Structure

CDK3 contains the canonical protein-kinase fold with an N-terminal lobe (β-sheet/α-helix) and a C-terminal lobe housing the catalytic residues. Key elements include:  
• Activation (T-) loop requiring phosphorylation for full activity.  
• Conserved DFG motif coordinating Mg²⁺–ATP.  
• C-helix essential for cyclin engagement.  
• A PSTAIRE-related helix whose sequence differs subtly from CDK2 (Shafiq, 2011; Endicott & Noble, 2013).  
CDK3 forms an active heterodimer with cyclin C; structural modelling and homologous CDK crystal structures show a fold conserved across the family (Wood & Endicott, 2018).

## Regulation

• Cyclin C binding induces the active conformation.  
• Phosphorylation of the activation loop by an upstream CDK-activating kinase (e.g., CDK7-cyclin H) further stimulates activity.  
• The cyclin C/CDK3 complex drives the G0 → G1 transition; additional modulators of stability or localisation have been suggested but remain poorly characterised (Peyressatre et al., 2015; Chowdhury et al., 2023).

## Function

CDK3 promotes cell-cycle re-entry and progression:  
• Phosphorylates RB1 to release E2F transcription factors, facilitating G0–G1 and G1–S transitions.  
• Phosphorylates ATF1, enhancing its transactivation capability.  
• Modifies histone H1 and CABLES1, supporting chromatin remodelling and signalling required for proliferation (Malumbres, 2014; Peyressatre et al., 2015; Pluta et al., 2024).

## Inhibitors

No selective CDK3 inhibitors are currently available. Broad-spectrum CDK inhibitors have been described, and structural information on CDK3 is expected to aid future design efforts (Huwe et al., 2003; Peyressatre et al., 2015).

## Other Comments

Elevated CDK3 activity has been reported in several cancers (e.g., glioblastoma), indicating potential oncogenic roles and therapeutic relevance (Chowdhury et al., 2023; Peyressatre et al., 2015).

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