## Phylogeny

CDK1 is a member of the CMGC protein-kinase group and the founding enzyme of the cyclin-dependent kinase (CDK) family (Manning et al., 2002a). It is highly conserved in all eukaryotes; key yeast orthologues are Cdc28 in Saccharomyces cerevisiae and Cdc2 in Schizosaccharomyces pombe (Manning et al., 2002a; Sánchez & Dynlacht, 2005; Enserink & Kolodner, 2010; Lim & Kaldis, 2013). In mammals CDK1 is the only CDK whose loss is lethal, underscoring its unique, non-redundant role (Brown et al., 2015).

## Reaction Catalyzed

ATP + [protein]-L-serine ⇌ ADP + [protein]-L-serine phosphate  
ATP + [protein]-L-threonine ⇌ ADP + [protein]-L-threonine phosphate (Lim & Kaldis, 2013; Wang et al., 2023).

## Cofactor Requirements

Requires Mg²⁺ for catalytic activity (Wang et al., 2023).

## Substrate Specificity

CDK1 is a proline-directed Ser/Thr kinase. The minimal consensus sequence is S/T-P; a basic residue (Lys/Arg) or, less frequently, Gly at the +3 position can enhance recognition, giving the expanded motif [S/T]-P-X-[K/R] (Johnson et al., 2023; Sánchez & Dynlacht, 2005).

## Structure

The enzyme displays the canonical bilobal kinase fold (~200 aa catalytic core) with an N-terminal ATP-binding lobe and a predominantly helical C-terminal lobe (Brown et al., 2015; Fischer & Lane, 2000). Key regulatory elements include:  
• PSTAIRE helix (cyclin-binding)  
• Activation (T) loop containing Thr161  
Crystal structures of human CDK1 bound to cyclin B reveal conformational plasticity that can be exploited for inhibitor design (Brown et al., 2015).

## Regulation

• Cyclin binding – mainly cyclins A and B – is required for activity; binding repositions the T-loop (Brown et al., 2015; Lim & Kaldis, 2013).  
• Activating phosphorylation of Thr161 by CDK-activating kinase (CAK; CDK7 complex) completes activation (Brown et al., 2015; Enserink & Kolodner, 2010).  
• Inhibitory phosphorylation at Thr14 and Tyr15 by Wee1 and Myt1 blocks ATP binding (Brown et al., 2015; Lim & Kaldis, 2013; Wang et al., 2023).  
• Cdc25 phosphatases (CDC25A/B/C) remove the inhibitory phosphates to trigger mitotic entry (Enserink & Kolodner, 2010; Wang et al., 2023).  
• Accessory proteins Cks1/2 facilitate docking of primed substrates (Brown et al., 2015).  
• Additional control occurs via transcription, translation (e.g., NSUN2-mediated mRNA methylation) and proteolysis (Wang et al., 2023).

## Function

CDK1 is the master regulator of the eukaryotic cell cycle. In complex with cyclins A/B it drives the G2/M transition and many mitotic events; it also contributes to the G1/S transition (Brown et al., 2015; Lim & Kaldis, 2013; Wang et al., 2023). Hundreds of substrates are phosphorylated to coordinate chromosome condensation (Histone H1), nuclear-envelope breakdown (lamins A/B), spindle assembly (KIF4A, CENPA, SKA3), checkpoint control (CDC20, CDC25C, WEE1) and cytokinesis (Enserink & Kolodner, 2010; Payton et al., 2006; Wang et al., 2023). CDK1 also participates in DNA replication, DNA-damage repair, genome stability and, in a kinase-independent manner, transcriptional regulation via proteasome recruitment (Enserink & Kolodner, 2010).

## Inhibitors

ATP-competitive small molecules include the pan-CDK inhibitor roscovitine (CYC202); more selective agents are RO-3306 and CGP-74514A (Brown et al., 2015; Wang et al., 2023). Additional pan-CDK drugs with CDK1 activity are flavopiridol, dinaciclib and roniciclib (Wang et al., 2023). Natural protein inhibitors such as p16^INK4 and p21^WAF1 also antagonize CDK1 (Fischer & Lane, 2000).

## Other Comments

CDK1 overexpression or dysregulation is common in many cancers and correlates with aggressive disease and poor prognosis, making it an attractive therapeutic target (Brown et al., 2015; Wang et al., 2023). Complete genetic ablation of CDK1 is embryonically lethal in mammals, reflecting its essential role (Payton et al., 2006).

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