## Phylogeny

Cyclin-dependent kinase 2 (CDK2) belongs to the CMGC group of serine/threonine kinases. It is highly conserved across eukaryotes, with close sequence and structural similarity to CDK1 and CDK3 and orthologs detected from yeast to mammals (Equinet, 2004; Karimbayli et al., 2024; Wood & Endicott, 2018). Its widespread conservation highlights an essential role in cell-cycle control (Equinet, 2004; Pellarin et al., 2025).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Meschini, 2011; Pellarin et al., 2025).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity, coordinating ATP in the active site (Meschini, 2011; Wood & Endicott, 2018).

## Substrate Specificity

CDK2 phosphorylates serine or threonine residues that are immediately followed by proline (S/T-P motif). Additional determinants such as RXL docking motifs on substrates enhance recognition and binding. Well-characterised targets include the retinoblastoma protein (RB) and NPAT (Meschini, 2011; Pellarin et al., 2025; Wood & Endicott, 2018).

## Structure

CDK2 (~33 kDa) adopts the canonical bilobal protein-kinase fold: a β-sheet-rich N-lobe and an α-helical C-lobe with the active site in the inter-lobe cleft. Key elements include the glycine-rich loop, the hinge region, and the activation loop containing Thr160. Cyclin binding (cyclin E in G1/S, cyclin A in S phase) repositions the αC-helix and orders the activation loop, enabling catalysis. The extensive CDK2–cyclin interface ensures proper ATP alignment and substrate selection (Meschini, 2011; Pellarin et al., 2025; Wood & Endicott, 2018).

## Regulation

• Cyclin binding: association with cyclin E (early cell cycle) or cyclin A (later phases) is obligatory for activation (Equinet, 2004; Pellarin et al., 2025).  
• Activating phosphorylation: CDK-activating kinase (CDK7–cyclin H–MAT1) phosphorylates Thr160, stabilising the active conformation (Pellarin et al., 2025; Wood & Endicott, 2018).  
• Inhibitory phosphorylation: Wee1 and Myt1 add phosphates to Thr14 and Tyr15; Cdc25 phosphatases remove them (Meschini, 2011; Pellarin et al., 2025).  
• CKIs: Cip/Kip family members (p21^Cip1, p27^Kip1, p57^Kip2) bind CDK2–cyclin complexes and block ATP or substrate access (Meschini, 2011; Pellarin et al., 2025).

## Function

CDK2 drives the G1/S transition and S-phase progression by phosphorylating RB, thereby releasing E2F transcription factors that promote DNA-replication gene expression. Additional roles include centrosome duplication, homologous-recombination DNA repair, regulation of histone gene transcription via NPAT, and phosphorylation of DNA-damage response proteins (e.g., BRCA2, NBN). In embryonic stem cells, CDK2 activity influences proliferation and pluripotency. Its activity peaks during S and G2 phases and contributes to timely activation of cyclin B/CDK1 complexes (Equinet, 2004; Meschini, 2011; Pellarin et al., 2025).

## Inhibitors

Numerous ATP-competitive small molecules, including dual CDK2/CDK7 inhibitors, have been reported and show nanomolar potency in pre-clinical studies (Meschini, 2011; Wood & Endicott, 2018; Pellarin et al., 2025).

## Other Comments

CDK2 dysregulation is linked to many cancers (breast, glioblastoma, colorectal) and to meiotic defects causing infertility. It also modulates transcription factors such as MYC and EZH2, influencing epigenetic gene silencing. Although activating-loop mutations are uncommon, altered regulation of CDK2 or its partners is frequent in disease, making selective CDK2 targeting a continuing therapeutic focus (Colas, 2020; Karimbayli et al., 2024; Meschini, 2011; Pellarin et al., 2025).

## 9. References

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