## Phylogeny

Cyclin-dependent kinase 6 (CDK6) is a serine/threonine protein kinase that belongs to the CDK family within the CMGC group of the kinome (Choi & Anders, 2014; Fassl et al., 2022; Nebenführ et al., 2020; Tadesse et al., 2015). It forms part of the CDK4 sub-family (Malumbres, 2014) and is evolutionarily conserved across eukaryotes, with orthologues identified in vertebrates and other metazoans (Choi & Anders, 2014; Fassl et al., 2022). CDK6 shares high sequence identity with CDK4 (≈ 71 %) and shows additional homology to CDK2 (Grossel & Hinds, 2006; Tadesse et al., 2015).

## Reaction Catalyzed

ATP + protein ⇌ ADP + phospho-protein (Choi & Anders, 2014; Nebenführ et al., 2020)

## Cofactor Requirements

Catalysis requires divalent cations, primarily Mg²⁺; Mn²⁺ can substitute (Choi & Anders, 2014; Fassl et al., 2022; Nebenführ et al., 2020; Tadesse et al., 2015).

## Substrate Specificity

CDK6 is a proline-directed kinase that phosphorylates Ser/Thr residues followed immediately by Pro (+1). Peptide library analyses show additional preference for Gly or Ala at positions −5 to −3, with tolerances for positively charged or polar residues at other flanking sites (Fassl et al., 2022; Johnson et al., 2023).

## Structure

The enzyme adopts the conserved bilobal protein-kinase fold.  
• N-terminal lobe (residues 1–100): five antiparallel β-strands, a glycine-rich loop, and the regulatory αC-helix containing the PLSTIRE motif (Malumbres, 2014; Tadesse et al., 2015).  
• C-terminal lobe (residues 101–326): predominantly α-helical and includes the activation (T-) loop, residues 163–189, harbouring the regulatory phosphosite Thr177 (Tadesse et al., 2015).  
In the inactive monomer, the T-loop blocks the catalytic cleft and misaligns Lys43, Glu61 and Asp163. Crystal structures such as PDB 2EUF depict inhibitor binding and alternative conformations (Nebenführ et al., 2020; Tadesse et al., 2015).

## Regulation

Positive control  
• Binding of cyclin D1/D2/D3 re-positions the αC-helix and permits phosphorylation of Thr177 by CDK-activating kinase (CDK7–cyclin H–MAT1), stabilising the active state (Choi & Anders, 2014; Tadesse et al., 2015).

Negative control  
• INK4 proteins (p15, p16, p18, p19) bind CDK6 monomers, distort the ATP site and block cyclin binding (Choi & Anders, 2014; Nebenführ et al., 2020).  
• Cip/Kip proteins (p21, p27, p57) inhibit assembled CDK6–cyclin D complexes by occluding substrate access; phosphorylation of Cip/Kip tyrosines can convert them to assembly factors (Choi & Anders, 2014; Malumbres, 2014).  
• Wee1/Myt1 phosphorylate Tyr24, reducing ATP binding; Cdc25 phosphatases reverse this modification (Tadesse et al., 2015).

## Function

CDK6 drives the G1-to-S phase transition by forming complexes with D-type cyclins that phosphorylate retinoblastoma family proteins (pRB/RB1, p107, p130), thereby releasing E2F transcription factors and inducing S-phase gene expression (Choi & Anders, 2014; Tadesse et al., 2015; Fassl et al., 2022). Additional substrates include FOXM1, SMAD2/3 and WDR77 (Choi & Anders, 2014).

Expression is highest in proliferating cells, notably in haematopoietic tissues, thymocytes, breast tissue and melanoma (Nebenführ et al., 2020). Beyond cell-cycle control, CDK6 participates in differentiation, neurogenesis, haematopoietic stem-cell proliferation, and kinase-independent transcriptional programmes regulating angiogenesis and NF-κB signalling (Malumbres, 2014; Nebenführ et al., 2020).

## Inhibitors

Clinically used ATP-competitive dual CDK4/6 inhibitors include palbociclib, ribociclib and abemaciclib, which block RB phosphorylation and impose G1 arrest (Lu et al., 2005; Tadesse et al., 2015). The flavonol fisetin also binds and inhibits CDK6 (Lu et al., 2005).

## Other Comments

CDK6 over-expression or amplification is frequent in hormone-receptor-positive breast cancer, lymphomas, gliomas and leukaemias (Fassl et al., 2022; Tadesse et al., 2015). No recurrent pathogenic point mutations have been reported in humans (Nebenführ et al., 2020). Mouse models: kinase-dead Cdk6^K43M reduces proliferation, whereas hyperactive Cdk6^R31C resists INK4 inhibition and expands progenitor pools (Nebenführ et al., 2020). Sporadic chromosomal translocations involving CDK6 occur in some tumours (Nebenführ et al., 2020).

## References

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