## Phylogeny

Cyclin-dependent kinase 7 (CDK7) belongs to the CMGC group of protein kinases and sits within the CDK family (Manning et al., 2002). Phylogenetic analyses place CDK7—together with CDK8 and CDK9—in a “CTD-clade” that co-evolved with the C-terminal domain of RNA polymerase II (Guo & Stiller, 2004). CDK7 is distinct from the monomeric yeast CAK Cak1 (Liu & Kipreos, 2000). Orthologues are highly conserved across eukaryotes, for example Kin28 (Saccharomyces cerevisiae), DmCdk7 (Drosophila melanogaster), cdk-7 (Caenorhabditis elegans), and several CdkD isoforms in Arabidopsis thaliana (Guo & Stiller, 2004; Inzé, 2007).

## Reaction Catalyzed

ATP + [protein] ⇌ ADP + [phospho-protein] (Galbraith et al., 2019; Lolli et al., 2004).

## Cofactor Requirements

ATP is required as the phosphate donor (Galbraith et al., 2019; Lolli et al., 2004; Sava et al., 2020).

## Substrate Specificity

CDK7 is a proline-directed Ser/Thr kinase. Optimal sites contain a Ser/Thr phospho-acceptor, Pro at +1, and a basic residue (Lys/Arg) at –3 (Johnson et al., 2023). Confirmed protein substrates include:  
• RNA polymerase II CTD (Ser5/Ser7 of YSPTSPS) (Galbraith et al., 2019; Song et al., 2024).  
• T-loops of CDK1 (Thr161), CDK2 (Thr160), CDK4, CDK6, and CDK9 (Sava et al., 2020).  
• Transcription factors p53, estrogen receptor, androgen receptor, and E2F1 (Sava et al., 2020).  
• SPT5 C-terminal repeat (Düster et al., 2024).

## Structure

Human CDK7 is a 346-residue kinase with the canonical bilobal fold: an N-terminal β-sheet-rich lobe (res. 13–96) and α-helical C-lobe (res. 97–311). The ATP pocket lies between the lobes (Lolli et al., 2004; Song et al., 2024). A 2.15 Å structure of the active CDK7–Cyclin H–MAT1 complex is available (Düster et al., 2024).  
Key features  
• Activation (T)-loop, res. 155–182, phosphorylated at Ser164 and Thr170 (Düster et al., 2024).  
• αC-helix (res. 56–62, NRTALRE motif); Arg61 forms salt bridges with pThr170 and Cyclin H Glu117 (Düster et al., 2024).  
• Hydrophobic spine stabilises the active conformation (Düster et al., 2024).  
• ATP site is unusually hydrophobic (e.g., Val100 in place of Lys89 of CDK2), aiding selective inhibitor design (Lolli et al., 2004).  
• L14 loop limits dephosphorylation by KAP phosphatase (Lolli et al., 2004).

## Regulation

Activity depends on assembly with Cyclin H and MAT1; MAT1 also anchors the complex to TFIIH (Kumar et al., 2021; Song et al., 2024). Dual phosphorylation of Ser164 (priming) and Thr170 (activation) locks the T-loop in an active conformation (Düster et al., 2024). PKCι can phosphorylate Thr170 (Sava et al., 2020). The p53 tumour suppressor binds Cyclin H and inhibits CDK7 activity (Schneider et al., 1998).

## Function

CDK7 is a nuclear CAK that couples cell-cycle control with transcription (Lolli et al., 2004; Song et al., 2024).  
Cell-cycle role – as the catalytic core of CAK, CDK7 phosphorylates and activates CDK1/2/4/6, driving G1/S and G2/M transitions (Song et al., 2024; Sava et al., 2020).  
Transcription role – within TFIIH, CDK7 phosphorylates RNAP II CTD (Ser5/Ser7) to promote initiation, promoter clearance, and pausing; it also activates CDK9 to stimulate elongation (Galbraith et al., 2019; Sava et al., 2020).  
Interacting partners – Cyclin H, MAT1, p53, RNAP II, multiple CDKs, and transcription factors noted above (Kumar et al., 2021; Schneider et al., 1998; Sava et al., 2020).

## Inhibitors

Covalent inhibitors THZ1 and THZ2 target Cys312. Additional selective agents include SY-1365, YKL-1-116, BS-181, ICEC0942, SY-5609, and LY3405105, several of which are in Phase I/II trials (Galbraith et al., 2019; Sava et al., 2020).

## Other Comments

CDK7 is overexpressed in multiple malignancies (e.g., triple-negative breast, small-cell lung, ovarian, gastric, pancreatic cancers) and high levels correlate with poor prognosis, supporting CDK7 as a therapeutic target (Galbraith et al., 2019; Kumar et al., 2021). Although pathogenic CDK7 mutations are rare, defects in TFIIH subunits can impair CDK7-dependent transcription (Galbraith et al., 2019; Sava et al., 2020).

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