1. Phylogeny  
   Cyclin‐dependent kinase 3 (CDK3), encoded by the CDK3 gene and indexed under UniProt ID Q00526, is a member of the CMGC group of serine/threonine kinases that comprises the cyclin‐dependent kinases (CDKs) involved in cell cycle regulation. Phylogenetic analyses indicate that CDK3 clusters closely with classical cell cycle regulators such as CDK1 and CDK2, with a particularly high sequence identity relative to CDK2. Comparative studies and multiple sequence alignments have revealed that CDK3 shares many conserved catalytic and regulatory motifs with its close homologues, reflecting an evolutionary relationship tracing back to a common ancestral CDK in early eukaryotes. The available evidence shows that CDK3 is found in higher vertebrates such as mammals and birds, while its presence in lower vertebrates appears more restricted, supporting the notion that CDK3 represents a later evolutionary development within the CDK family (shawish2017molecularcloningand pages 8-14, shafiq2011molecularmodellingand pages 97-103, wood2018structuralinsightsinto pages 3-3).
2. Reaction Catalyzed  
   CDK3 functions as a serine/threonine kinase that catalyzes the ATP-dependent transfer of a phosphate group to target substrates. The reaction is conventionally represented as follows: ATP + [protein]-L-serine/threonine → ADP + [protein]-phospho-L-serine/threonine + H⁺. This phosphotransferase reaction underlies the enzymatic control of cell cycle transitions by modifying key regulatory proteins such as histone H1, ATF1, RB1, and CABLES1 (shawish2017molecularcloningand pages 20-24, shafiq2011molecularmodellingand pages 26-30).
3. Cofactor Requirements  
   The catalytic activity of CDK3, similar to other members of the cyclin-dependent kinase family, is dependent on the presence of divalent cations. Magnesium ions (Mg²⁺) act as an essential cofactor by stabilizing the negative charges on ATP and facilitating the proper positioning of the phosphate group for transfer. This cofactor requirement is intrinsic to the kinase’s function in phosphorylating its substrates and is consistent with the biochemical behavior of serine/threonine kinases in the CMGC group (shawish2017molecularcloningand pages 1-8, kesavan2022chemicalbiologystrategies pages 91-98).
4. Substrate Specificity  
   CDK3 exhibits substrate specificity characteristic of proline-directed serine/threonine kinases. It preferentially phosphorylates substrates that contain a minimal consensus motif in which a serine or threonine residue is immediately followed by a proline (S/T-P). In several experimental studies on related CDKs, the substrate recognition has been observed to extend to additional flanking residues; for example, basic amino acids at the +3 position often enhance substrate binding and promote efficient phosphorylation. Although comprehensive motif details for CDK3 have not been delineated to the same degree as for CDK2, the available evidence suggests that its substrate specificity is governed by similar mechanistic principles that rely on the S/T-P core consensus and surrounding amino acid environment. Notably, known substrates of CDK3 include histone H1, ATF1, RB1, and CABLES1, where phosphorylation modulates processes ranging from chromatin compaction to transcriptional activation (errico2010identificationofsubstrates pages 12-15, harper2001cyclindependentkinases pages 11-12, mok2010decipheringproteinkinase pages 4-5, suryadinata2010controlofcell pages 5-6).
5. Structure  
   CDK3 is organized around a central kinase domain that possesses the classical bilobal architecture characteristic of the CDK family. The N-terminal lobe is largely comprised of a β-sheet structure while the C-terminal lobe is predominantly α-helical. Key structural features include the glycine-rich loop, which is vital for ATP binding, a hinge region that connects the two lobes, and the activation loop (T-loop) that undergoes phosphorylation to achieve full catalytic activity. A conserved PSTAIRE-like motif within the C-helix is critical for the interaction with cyclin partners, particularly cyclin C (CCNC), thereby enabling the conformational changes necessary for kinase activation. Homology modeling, largely based on the crystal structure of CDK2, reveals that CDK3 maintains a similar overall fold with conservation of critical residues in the ATP-binding site and catalytic core. These models have supported the identification of key catalytic residues and have provided insights into the structural basis for substrate binding and inhibitor interactions. In summary, the three-dimensional organization of CDK3 features a central catalytic domain flanked by regulatory segments that undergo dynamic conformational shifts upon cyclin binding and phosphorylation (shawish2017molecularcloningand pages 1-8, shawish2017molecularcloningand pages 8-14, wood2018structuralinsightsinto pages 3-3).
6. Regulation  
   CDK3 regulation is principally achieved through its interaction with specific cyclin partners, most notably cyclin C (CCNC), which facilitates the structural rearrangements required for catalytic activity. The binding of cyclin C to CDK3 triggers conformational changes that expose the activation loop, allowing it to be phosphorylated—a step that is critical for transitioning CDK3 from an inactive to an active state. Furthermore, like other cyclin-dependent kinases, CDK3 is subjected to additional layers of regulation through post-translational modifications such as phosphorylation. Key phosphorylation events on the activation loop, analogous to those observed in CDK2 (where phosphorylation of a threonine residue in the T-loop is crucial), are required for full enzymatic activation. Although detailed mapping of all phosphorylation sites on CDK3 is still forthcoming, available data indicate that its regulatory mechanisms align closely with classical CDK regulation, involving cyclin binding, phosphorylation by CDK-activating kinases (CAKs), and possible modulation by inhibitory proteins (shawish2017molecularcloningand pages 20-24, shawish2017molecularcloningand pages 24-25, kesavan2022chemicalbiologystrategies pages 229-231, kesavan2022chemicalbiologystrategies pages 87-91).
7. Function  
   CDK3 plays a pivotal role in cell cycle control by regulating the critical transitions from a quiescent state (G0) into the G1 phase and subsequently from G1 to the S phase. It exerts its effects through the phosphorylation of key substrates that influence cell cycle progression. For instance, CDK3-mediated phosphorylation of the retinoblastoma protein (RB1) is necessary for the release of E2F transcription factors, thereby promoting the progression from G0 into G1. Additionally, phosphorylation of activating transcription factor 1 (ATF1) by CDK3 enhances its transactivation capability, which in turn stimulates transcriptional programs that drive cell proliferation. Further substrates of CDK3, such as histone H1 and CABLES1, implicate it in the modulation of chromatin structure and additional cellular processes related to gene expression. In this capacity, CDK3 is critically involved in both cell cycle re-entry and the promotion of the G1-S transition, functions that are essential for normal cell proliferation and are frequently deregulated in oncogenic processes (shawish2017molecularcloningand pages 1-8, shawish2017molecularcloningand pages 20-24, kesavan2022chemicalbiologystrategies pages 229-231, shafiq2011molecularmodellingand pages 26-30).
8. Other Comments  
   CDK3 has been associated with oncogenic processes based on its role in cell cycle progression and its ability to phosphorylate substrates that drive cell proliferation and transformation. Overexpression of CDK3 has been observed in several cancer cell lines, including those derived from breast cancer, where its aberrant activity may contribute to malignant transformation and uncontrolled cell growth. Although specific small-molecule inhibitors targeting CDK3 are less well characterized than those developed for other CDKs, there is significant interest in identifying and optimizing selective inhibitors as potential therapeutic agents for cancers marked by CDK dysregulation. Moreover, experimental approaches such as interaction profiling using split-luciferase assays have expanded the known repertoire of cyclin partners for CDK3, hinting at additional regulatory and non-canonical roles that may extend beyond cell cycle control. These findings underscore the importance of further functional and structural studies to fully elucidate the regulatory networks and potential clinical relevance of CDK3 (shawish2017molecularcloningand pages 14-20, shawish2017molecularcloningand pages 24-25, kesavan2022chemicalbiologystrategies pages 123-128, shafiq2011molecularmodellingand pages 185-190).
9. References
10. shawish2017molecularcloningand pages 1-8
11. shawish2017molecularcloningand pages 8-14
12. shawish2017molecularcloningand pages 14-20
13. shawish2017molecularcloningand pages 20-24
14. shawish2017molecularcloningand pages 24-25
15. errico2010identificationofsubstrates pages 12-15
16. harper2001cyclindependentkinases pages 11-12
17. kesavan2022chemicalbiologystrategies pages 91-98
18. kesavan2022chemicalbiologystrategies pages 123-128
19. kesavan2022chemicalbiologystrategies pages 226-229
20. kesavan2022chemicalbiologystrategies pages 229-231
21. mok2010decipheringproteinkinase pages 4-5
22. shafiq2011molecularmodellingand pages 26-30
23. shafiq2011molecularmodellingand pages 97-103
24. shafiq2011molecularmodellingand pages 185-190
25. suryadinata2010controlofcell pages 5-6
26. wood2018structuralinsightsinto pages 3-3

References

1. (shawish2017molecularcloningand pages 1-8): ANMSH SHAWISH. Molecular cloning and homology modelling of human cyclin dependent kinase 3 (cdk3). Unknown journal, 2017.
2. (shawish2017molecularcloningand pages 14-20): ANMSH SHAWISH. Molecular cloning and homology modelling of human cyclin dependent kinase 3 (cdk3). Unknown journal, 2017.
3. (shawish2017molecularcloningand pages 20-24): ANMSH SHAWISH. Molecular cloning and homology modelling of human cyclin dependent kinase 3 (cdk3). Unknown journal, 2017.
4. (shawish2017molecularcloningand pages 8-14): ANMSH SHAWISH. Molecular cloning and homology modelling of human cyclin dependent kinase 3 (cdk3). Unknown journal, 2017.
5. (errico2010identificationofsubstrates pages 12-15): Alessia Errico, Krupa Deshmukh, Yoshimi Tanaka, Andrei Pozniakovsky, and Tim Hunt. Identification of substrates for cyclin dependent kinases. Advances in Enzyme Regulation, 50:375-399, Jan 2010. URL: https://doi.org/10.1016/j.advenzreg.2009.12.001, doi:10.1016/j.advenzreg.2009.12.001. This article has 167 citations.
6. (kesavan2022chemicalbiologystrategies pages 123-128): KA Kesavan. Chemical biology strategies for the control of protein function and the interrogation of cyclin/cdk interactions. Unknown journal, 2022.
7. (kesavan2022chemicalbiologystrategies pages 226-229): KA Kesavan. Chemical biology strategies for the control of protein function and the interrogation of cyclin/cdk interactions. Unknown journal, 2022.
8. (kesavan2022chemicalbiologystrategies pages 229-231): KA Kesavan. Chemical biology strategies for the control of protein function and the interrogation of cyclin/cdk interactions. Unknown journal, 2022.
9. (kesavan2022chemicalbiologystrategies pages 91-98): KA Kesavan. Chemical biology strategies for the control of protein function and the interrogation of cyclin/cdk interactions. Unknown journal, 2022.
10. (mok2010decipheringproteinkinase pages 4-5): Janine Mok, Philip M. Kim, Hugo Y. K. Lam, Stacy Piccirillo, Xiuqiong Zhou, Grace R. Jeschke, Douglas L. Sheridan, Sirlester A. Parker, Ved Desai, Miri Jwa, Elisabetta Cameroni, Hengyao Niu, Matthew Good, Attila Remenyi, Jia-Lin Nianhan Ma, Yi-Jun Sheu, Holly E. Sassi, Richelle Sopko, Clarence S. M. Chan, Claudio De Virgilio, Nancy M. Hollingsworth, Wendell A. Lim, David F. Stern, Bruce Stillman, Brenda J. Andrews, Mark B. Gerstein, Michael Snyder, and Benjamin E. Turk. Deciphering protein kinase specificity through large-scale analysis of yeast phosphorylation site motifs. Science Signaling, 3:ra12-ra12, Feb 2010. URL: https://doi.org/10.1126/scisignal.2000482, doi:10.1126/scisignal.2000482. This article has 420 citations and is from a domain leading peer-reviewed journal.
11. (shafiq2011molecularmodellingand pages 26-30): MI Shafiq. Molecular modelling and bioinformatics studies of cdk4 and related proteins. Unknown journal, 2011. URL: https://doi.org/10104464/1, doi:10104464/1.
12. (shawish2017molecularcloningand pages 24-25): ANMSH SHAWISH. Molecular cloning and homology modelling of human cyclin dependent kinase 3 (cdk3). Unknown journal, 2017.
13. (wood2018structuralinsightsinto pages 3-3): Daniel J. Wood and Jane A. Endicott. Structural insights into the functional diversity of the cdk–cyclin family. Open Biology, Sep 2018. URL: https://doi.org/10.1098/rsob.180112, doi:10.1098/rsob.180112. This article has 264 citations and is from a peer-reviewed journal.
14. (harper2001cyclindependentkinases pages 11-12): and J. W. Harper and P. Adams. Cyclin-dependent kinases. Chemical Reviews, 101:2511-2526, Jul 2001. URL: https://doi.org/10.1021/cr0001030, doi:10.1021/cr0001030. This article has 311 citations and is from a highest quality peer-reviewed journal.
15. (shafiq2011molecularmodellingand pages 185-190): MI Shafiq. Molecular modelling and bioinformatics studies of cdk4 and related proteins. Unknown journal, 2011. URL: https://doi.org/10104464/1, doi:10104464/1.
16. (shafiq2011molecularmodellingand pages 97-103): MI Shafiq. Molecular modelling and bioinformatics studies of cdk4 and related proteins. Unknown journal, 2011. URL: https://doi.org/10104464/1, doi:10104464/1.
17. (kesavan2022chemicalbiologystrategies pages 87-91): KA Kesavan. Chemical biology strategies for the control of protein function and the interrogation of cyclin/cdk interactions. Unknown journal, 2022.
18. (suryadinata2010controlofcell pages 5-6): Randy Suryadinata, Martin Sadowski, and Boris Sarcevic. Control of cell cycle progression by phosphorylation of cyclin-dependent kinase (cdk) substrates. Bioscience reports, 30 4:243-55, Aug 2010. URL: https://doi.org/10.1042/bsr20090171, doi:10.1042/bsr20090171. This article has 227 citations and is from a peer-reviewed journal.