## 1. Phylogeny

Cyclin‐dependent kinase 15 (CDK15), also known by alternative names PFTK2 and ALS2CR7, is classified within the cyclin‐dependent kinase family. Unlike the canonical cell cycle CDKs (e.g., CDK1, CDK2) or the transcriptional CDKs (e.g., CDK7, CDK9), CDK15 belongs to an atypical subgroup that includes several kinases with less‐defined roles, sometimes grouped together with the PCTAIRE kinases (CDK14, CDK16–18) (karimbayli2024insightsintothe pages 1-2, karimbayli2024insightsintothe pages 2-4). Although extensive phylogenetic trees have not been published specifically for CDK15, available evidence based on its sequence homology supports its inclusion within the broader CMGC kinase group, which encompasses serine/threonine kinases involved in cell cycle regulation and transcription. Orthologs of CDK15 can be identified in various mammalian species, indicating that this kinase is an evolutionarily conserved component of the metazoan kinome. Its evolutionary trajectory suggests that while the common ancestor of eukaryotes possessed a core set of CDKs, subsequent gene duplications and divergence have given rise to atypical kinases such as CDK15 with specialized or even tissue‐specific roles (karimbayli2024insightsintothe pages 1-2, malumbres2014cyclindependentkinases pages 1-2).

## 2. Reaction Catalyzed

CDK15 functions as a serine/threonine protein kinase whose classical catalytic activity involves transferring a phosphate group from ATP to the hydroxyl group of serine or threonine residues on target substrates. In the case of CDK15, a well‐documented substrate is the antiapoptotic protein survivin (also known as BIRC5). CDK15 phosphorylates survivin at threonine 34 (Thr34), an event that has been shown to counteract TRAIL/TNFSF10-induced apoptosis. Thus, the overall reaction catalyzed by CDK15 can be summarized as follows:  
  ATP + survivin (protein with a free –OH on Thr34) → ADP + survivin phosphorylated on Thr34 + H⁺  
This phosphorylation event is thought to enhance the antiapoptotic function of survivin, thereby promoting cell survival under apoptotic stress (liao2016therolesand pages 12-13, karimbayli2024insightsintothe pages 1-2).

## 3. Cofactor Requirements

As with most cyclin-dependent kinases, CDK15 requires divalent metal ions to support its catalytic activity. The prevailing evidence from studies on related serine/threonine kinases suggests that the kinase domain of CDK15 relies on Mg²⁺ ions to coordinate ATP binding and facilitate phosphoryl transfer (karimbayli2024insightsintothe pages 1-2, malumbres2014cyclindependentkinases pages 3-5). Although specific experimental data for CDK15’s cofactor dependency have not been detailed separately, the conserved nature of the catalytic mechanism among CDKs implies that Mg²⁺ is the essential cofactor. Additional regulatory molecules such as specific cyclin partners (if present for CDK15) may also modulate its activity, although direct evidence for such regulatory cofactors in the case of CDK15 remains limited (duster2021biochemicalcharacterizationof pages 23-28).

## 4. Substrate Specificity

CDK15 exhibits substrate specificity characteristic of serine/threonine kinases in the CDK family. Its most well-characterized substrate is survivin (BIRC5), which is phosphorylated at Thr34. This post-translational modification is crucial for CDK15’s antiapoptotic activity: by phosphorylating survivin at Thr34, CDK15 contributes to resistance against TRAIL/TNFSF10-induced apoptotic signaling (liao2016therolesand pages 12-13). Although broad consensus motifs for substrate recognition by CDK15 have not been firmly established, the mechanistic details are expected to share similarities with other CDKs that rely on docking interactions mediated by cyclin binding and conserved kinase domain motifs such as the DFG and HRD motifs. In the absence of detailed studies defining a full consensus sequence for CDK15 substrates, the functional data currently underscores a selective role in modifying survivin’s antiapoptotic properties rather than engaging a wide spectrum of substrates (karimbayli2024insightsintothe pages 15-17, pluta2024cyclin‐dependentkinasesmasters pages 41-42).

## 5. Structure

The three-dimensional structure of CDK15 has not yet been determined using high-resolution crystallography; however, homology with other CDKs provides meaningful insight into its likely organization. CDK15 is expected to possess a conserved kinase domain of approximately 250 amino acids that forms a bilobal architecture typical of serine/threonine kinases. The N-terminal lobe would largely consist of β-sheets and a glycine-rich loop involved in ATP binding, while the C-terminal lobe is characterized by α-helical regions that contribute to substrate recognition and catalysis (wood2018structuralinsightsinto pages 2-3, karimbayli2024insightsintothe pages 2-4). Conserved motifs that are hallmarks of CDK catalytic domains, such as the HRD motif in the catalytic loop and the DFG motif at the start of the activation loop, are presumed to be present in CDK15. Additionally, predictive models and sequence analysis suggest that CDK15 may harbor unique regulatory sequences—potentially an extended N-terminal region—that could influence its interactions with partner proteins, similar to other atypical CDKs within the PCTAIRE or PFTK subgroups (wood2018structuralinsightsinto pages 2-3, pluta2024cyclin‐dependentkinasesmasters pages 12-14). Although experimental structural data remain scarce, these inferred features are expected to underpin both the catalytic function and regulatory controls of CDK15.

## 6. Regulation

Regulation of CDK15, while not as comprehensively characterized as for other more canonical CDKs, appears to follow several principles common to the family. CDKs are often regulated by phosphorylation events and through interactions with cyclin proteins, which aid in substrate selection and activation. Specific to CDK15, its antiapoptotic function via survivin phosphorylation suggests that its activity must be tightly controlled within the cell. One reported mechanism involves modulation by proteasome activator complexes; for example, in breast cancer, downregulation of CDK15 by PA28α/β has been correlated with increased invasion and metastasis, suggesting that reduced CDK15 activity may contribute to tumorigenesis (ding2020therolesof pages 21-23). Post-translational modifications such as phosphorylation are likely to influence CDK15’s conformation and interactions, although the precise regulatory phosphorylation sites have not been explicitly mapped in the literature. In contrast to classical CDK activation, which typically depends on cyclin binding and subsequent activation loop phosphorylation by CDK-activating kinases (CAKs), the regulatory pathway for CDK15 remains less defined and is a subject of ongoing research (karimbayli2024insightsintothe pages 15-17, malumbres2014cyclindependentkinases pages 6-7). Thus, while CDK15’s modulation by phosphorylation and protein-protein interactions is anticipated to be similar to its CDK counterparts, specific details—including potential cyclin partners or regulatory co-factors—await further experimental validation.

## 7. Function

The primary function attributed to CDK15 is its role as an antiapoptotic kinase. It achieves this by phosphorylating survivin (BIRC5) at threonine 34, an event that counterbalances apoptosis induced by the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/TNFSF10) (liao2016therolesand pages 12-13). Survivin is a well-known inhibitor of apoptosis, and its phosphorylation at Thr34 is closely linked to enhanced cell survival mechanisms. Consequently, CDK15 is thought to contribute to the regulation of cellular apoptosis, and by extension, may influence tumor cell survival and resistance to apoptosis in certain cancer contexts (ding2020therolesof pages 21-23, pluta2024cyclin‐dependentkinasesmasters pages 41-42). Although the full spectrum of CDK15’s biological roles has not been exhaustively delineated, its antiapoptotic activity positions it as a potential modulator in both normal cellular homeostasis and disease conditions, including cancer and possibly other stress-related pathologies. Furthermore, genetic association data (as integrated by platforms such as OpenTargets) have hinted at a moderate link between CDK15 and depressive disorder, suggesting that it might play roles in neurological pathways or stress responses, although such associations require further detailed exploration (OpenTargets Search: -CDK15,PFTK2).

## 8. Other Comments

At present, no clinical trials have been registered that specifically target CDK15, as searches in ClinicalTrials.gov returned no interventions with CDK15, PFTK2, or ALS2CR7 in the intervention or title fields (Clinical Trials Search: AREA[InterventionName]CDK15 OR AREA[InterventionName]PFTK2 OR AREA[OfficialTitle]Cyclin-dependent kinase 15). This absence indicates that CDK15 remains largely in the domain of preclinical research. Consequently, there are no widely recognized small-molecule inhibitors or other pharmacological agents specifically developed against CDK15. Nevertheless, given its antiapoptotic function and potential involvement in cancer cell survival, CDK15 represents an attractive target for future drug discovery initiatives. In addition, the emerging genetic association with depressive disorder reinforces the need to further explore CDK15’s role in neurological processes. Notably, the overall paucity of data regarding its precise substrates, regulatory mechanisms, and structure underscores the value of continued structural, biochemical, and functional studies to define its role more clearly. Future research leveraging high-resolution structural techniques and targeted inhibitor screens could potentially yield valuable insights into the development of specific CDK15 modulators (karimbayli2024insightsintothe pages 17-17, pluta2024cyclin‐dependentkinasesmasters pages 47-49).

## 9. References

1. Clinical Trials Search: AREA[InterventionName]CDK15 OR AREA[InterventionName]PFTK2 OR AREA[OfficialTitle]Cyclin-dependent kinase 15
2. OpenTargets Search: -CDK15,PFTK2
3. karimbayli2024insightsintothe pages 1-2
4. karimbayli2024insightsintothe pages 2-4
5. karimbayli2024insightsintothe pages 15-17
6. karimbayli2024insightsintothe pages 17-17
7. liao2016therolesand pages 12-13
8. ding2020therolesof pages 21-23
9. malumbres2014cyclindependentkinases pages 1-2
10. malumbres2014cyclindependentkinases pages 3-5
11. malumbres2014cyclindependentkinases pages 6-7
12. pluta2024cyclin‐dependentkinasesmasters pages 12-14
13. pluta2024cyclin‐dependentkinasesmasters pages 41-42
14. pluta2024cyclin‐dependentkinasesmasters pages 47-49
15. wood2018structuralinsightsinto pages 2-3
16. duster2021biochemicalcharacterizationof pages 23-28
17. łukasik2021cyclindependentkinases(cdk) pages 1-2

References

1. (OpenTargets Search: -CDK15,PFTK2): Open Targets Query (-CDK15,PFTK2, 1 results). Ochoa, D. et al. (2023). The next-generation Open Targets Platform: reimagined, redesigned, rebuilt. Nucleic Acids Research.
2. (karimbayli2024insightsintothe pages 1-2): Javad Karimbayli, Ilenia Pellarin, Barbara Belletti, and Gustavo Baldassarre. Insights into the structural and functional activities of forgotten kinases: pctaires cdks. Molecular Cancer, Jun 2024. URL: https://doi.org/10.1186/s12943-024-02043-6, doi:10.1186/s12943-024-02043-6. This article has 4 citations and is from a highest quality peer-reviewed journal.
3. (karimbayli2024insightsintothe pages 17-17): Javad Karimbayli, Ilenia Pellarin, Barbara Belletti, and Gustavo Baldassarre. Insights into the structural and functional activities of forgotten kinases: pctaires cdks. Molecular Cancer, Jun 2024. URL: https://doi.org/10.1186/s12943-024-02043-6, doi:10.1186/s12943-024-02043-6. This article has 4 citations and is from a highest quality peer-reviewed journal.
4. (karimbayli2024insightsintothe pages 2-4): Javad Karimbayli, Ilenia Pellarin, Barbara Belletti, and Gustavo Baldassarre. Insights into the structural and functional activities of forgotten kinases: pctaires cdks. Molecular Cancer, Jun 2024. URL: https://doi.org/10.1186/s12943-024-02043-6, doi:10.1186/s12943-024-02043-6. This article has 4 citations and is from a highest quality peer-reviewed journal.
5. (pluta2024cyclin‐dependentkinasesmasters pages 41-42): Aleksandra J. Pluta, Cécilia Studniarek, Shona Murphy, and Chris J. Norbury. Cyclin‐dependent kinases: masters of the eukaryotic universe. WIREs RNA, Sep 2024. URL: https://doi.org/10.1002/wrna.1816, doi:10.1002/wrna.1816. This article has 19 citations.
6. (wood2018structuralinsightsinto pages 2-3): 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.
7. (ding2020therolesof pages 21-23): L. Ding, Jiaqi Cao, Wen-Lien Lin, Hongjian Chen, Xianhui Xiong, Hongshun Ao, Min Yu, Jie Lin, and Qing-hua Cui. The roles of cyclin-dependent kinases in cell-cycle progression and therapeutic strategies in human breast cancer. International Journal of Molecular Sciences, 21:1960, Mar 2020. URL: https://doi.org/10.3390/ijms21061960, doi:10.3390/ijms21061960. This article has 609 citations and is from a peer-reviewed journal.
8. (karimbayli2024insightsintothe pages 15-17): Javad Karimbayli, Ilenia Pellarin, Barbara Belletti, and Gustavo Baldassarre. Insights into the structural and functional activities of forgotten kinases: pctaires cdks. Molecular Cancer, Jun 2024. URL: https://doi.org/10.1186/s12943-024-02043-6, doi:10.1186/s12943-024-02043-6. This article has 4 citations and is from a highest quality peer-reviewed journal.
9. (pluta2024cyclin‐dependentkinasesmasters pages 47-49): Aleksandra J. Pluta, Cécilia Studniarek, Shona Murphy, and Chris J. Norbury. Cyclin‐dependent kinases: masters of the eukaryotic universe. WIREs RNA, Sep 2024. URL: https://doi.org/10.1002/wrna.1816, doi:10.1002/wrna.1816. This article has 19 citations.
10. (duster2021biochemicalcharacterizationof pages 23-28): RS Düster. Biochemical characterization of the human cyclin-dependent kinases cdk7 and cdk10. Unknown journal, 2021.
11. (malumbres2014cyclindependentkinases pages 1-2): Marcos Malumbres. Cyclin-dependent kinases. Genome Biology, 15:122-122, Jun 2014. URL: https://doi.org/10.1186/gb4184, doi:10.1186/gb4184. This article has 1369 citations and is from a highest quality peer-reviewed journal.
12. (malumbres2014cyclindependentkinases pages 3-5): Marcos Malumbres. Cyclin-dependent kinases. Genome Biology, 15:122-122, Jun 2014. URL: https://doi.org/10.1186/gb4184, doi:10.1186/gb4184. This article has 1369 citations and is from a highest quality peer-reviewed journal.
13. (malumbres2014cyclindependentkinases pages 6-7): Marcos Malumbres. Cyclin-dependent kinases. Genome Biology, 15:122-122, Jun 2014. URL: https://doi.org/10.1186/gb4184, doi:10.1186/gb4184. This article has 1369 citations and is from a highest quality peer-reviewed journal.
14. (pluta2024cyclin‐dependentkinasesmasters pages 12-14): Aleksandra J. Pluta, Cécilia Studniarek, Shona Murphy, and Chris J. Norbury. Cyclin‐dependent kinases: masters of the eukaryotic universe. WIREs RNA, Sep 2024. URL: https://doi.org/10.1002/wrna.1816, doi:10.1002/wrna.1816. This article has 19 citations.
15. (łukasik2021cyclindependentkinases(cdk) pages 1-2): Paweł Łukasik, Michał Załuski, and Izabela Gutowska. Cyclin-dependent kinases (cdk) and their role in diseases development–review. International Journal of Molecular Sciences, 22:2935, Mar 2021. URL: https://doi.org/10.3390/ijms22062935, doi:10.3390/ijms22062935. This article has 198 citations and is from a peer-reviewed journal.
16. (liao2016therolesand pages 12-13): Yunfei Liao, Yong Feng, Jacson Shen, Francis J. Hornicek, and Zhenfeng Duan. The roles and therapeutic potential of cyclin-dependent kinases (cdks) in sarcoma. Cancer and Metastasis Reviews, 35:151-163, Dec 2016. URL: https://doi.org/10.1007/s10555-015-9601-1, doi:10.1007/s10555-015-9601-1. This article has 50 citations and is from a peer-reviewed journal.