1. Phylogeny  
   DCLK2, also known as DCAMKL2, DCDC3B, DCK2, or CaMK-like CREB regulatory kinase 2, belongs to the doublecortin-like kinase family within the broader CaMK group of serine/threonine kinases. It shares significant sequence and domain homology with other members of the family, including DCLK1 and doublecortin (DCX), and exhibits approximately 68% amino acid identity with DCLK1, placing it among evolutionarily conserved kinases that emerged early in the metazoan lineage (hu2024kinomewidesirnascreen pages 3-5, ohmae2006molecularidentificationand pages 4-5). Comparative phylogenetic analyses based on kinase domain conservation indicate that DCLK2 co-evolved with other CaMK-like kinases and is classified within a subgroup that distinguishes itself by a markedly reduced Ca²⁺/calmodulin affinity compared to classical CaMKs (venkat2023mechanisticandevolutionary pages 17-18). Its evolutionary conservation is supported by the presence of one-to-one orthologs across several vertebrate species, consistent with the core kinase families identified in early eukaryotic evolution (venkat2023mechanisticandevolutionary pages 4-5).
2. Reaction Catalyzed  
   DCLK2 catalyzes the transfer of phosphate from ATP to serine or threonine residues on target proteins. The chemical reaction can be summarized as: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (hu2024kinomewidesirnascreen pages 1-3).
3. Cofactor Requirements  
   The catalytic activity of DCLK2 is dependent on divalent cations, with magnesium (Mg²⁺) being required as a cofactor, as is typical for serine/threonine protein kinases (hu2024kinomewidesirnascreen pages 3-5).
4. Substrate Specificity  
   DCLK2 phosphorylates serine/threonine residues within protein substrates; in the context of clear cell renal cell carcinoma (ccRCC), it directly phosphorylates TANK-binding kinase 1 (TBK1) on Ser172, which is essential for TBK1 activation (hu2024kinomewidesirnascreen pages 10-11). Although a defined consensus motif for DCLK2 has not been fully elucidated, its substrate recognition appears to be isoform specific, as evidenced by distinct catalytic activities observed between isoforms such as DCLK2203 and DCLK2201 (hu2024kinomewidesirnascreen pages 10-11). Data from the wider serine/threonine kinase family suggest that substrate specificity may reflect preferences for amino acid residues proximal to the targeted serine or threonine, yet current reports on DCLK2 emphasize its role in phosphorylating TBK1 and, by similarity, possibly the CREB coactivator CRTC2/TORC2 (hu2024kinomewidesirnascreen pages 1-3, song2021thexlinkedintellectual pages 19-25).
5. Structure  
   DCLK2 is characterized by an N-terminal region that contains tandem doublecortin (DCX) domains responsible for microtubule binding and stabilization, followed by a C-terminal serine/threonine kinase domain. The DCX domains confer binding to microtubules, which is a hallmark of the DCX family of proteins, while the kinase domain exhibits conserved motifs typical of CaMK family kinases, including a glycine-rich loop, a catalytic lysine residue, and an activation loop (hu2024kinomewidesirnascreen pages 3-5, ohmae2006molecularidentificationand pages 4-5). Structural analyses and AlphaFold-derived models predict that the kinase domain of DCLK2 adopts an active-like conformation; key catalytic residues such as Lys423 are critical for activity, as mutation to a kinase-dead form (K423A) abrogates its ability to phosphorylate substrates such as TBK1 (hu2024kinomewidesirnascreen pages 10-11). A notable structural feature of DCLK2 is its isoform-specific regulatory variation; the predominant ccRCC isoform, DCLK2203, lacks an autoinhibitory C-terminal threonine (T693) that is present in other isoforms, thereby exhibiting increased kinase activity (hu2024kinomewidesirnascreen pages 10-11).
6. Regulation  
   DCLK2 is regulated at multiple levels. Isoform-specific alternative splicing generates variants with differing catalytic capacities, as exemplified by DCLK2203, which is endowed with enhanced kinase activity due to the absence of an autoinhibitory C-terminal threonine residue present in DCLK2201 (hu2024kinomewidesirnascreen pages 10-11). In addition, the expression levels of DCLK2 are modulated by the nonsense-mediated mRNA decay (NMD) pathway; downregulation of UPF1 in ccRCC correlates with elevated expression of DCLK2203 (hu2024kinomewidesirnascreen pages 10-11). Moreover, the catalytic activity of DCLK2 is essential for the phosphorylation of TBK1, and kinase-dead mutants fail to rescue cellular growth phenotypes associated with endogenous DCLK2 depletion, indicating strict catalytic dependence (hu2024kinomewidesirnascreen pages 10-11). Prior studies also suggest that regulatory mechanisms common to the CaMK family, such as phosphorylation and possible conformational autoinhibition by C-terminal domains, may be applicable to DCLK2, albeit with a significantly reduced dependence on Ca²⁺/calmodulin (hu2024kinomewidesirnascreen pages 3-5, venkat2023mechanisticandevolutionary pages 17-18).
7. Function  
   DCLK2 functions as a serine/threonine kinase with key roles in oncogenic signaling, particularly in clear cell renal cell carcinoma (ccRCC). It phosphorylates TBK1 on Ser172, an event that activates TBK1 and subsequently triggers downstream signaling pathways including the phosphorylation of p62 at Ser366, thereby promoting tumorigenesis (hu2024kinomewidesirnascreen pages 10-11, hu2024kinomewidesirnascreen pages 1-3). Expression of the predominant DCLK2203 isoform is observed in ccRCC, and functional assays demonstrate that depletion of DCLK2 impairs anchorage-independent growth and tumor formation in kidney cancer models (hu2024kinomewidesirnascreen pages 1-3, hu2024kinomewidesirnascreen pages 10-11). By similarity to other members of the DCX superfamily, DCLK2 may also participate in microtubule regulation; however, its documented oncogenic function appears primarily linked to the activation of TBK1 rather than classical microtubule modulation (hu2024kinomewidesirnascreen pages 3-5, ohmae2006molecularidentificationand pages 4-5).
8. Other Comments  
   Experimental inhibitors such as DCLK1-IN-1, originally developed for DCLK1, have exhibited inhibitory activity against DCLK2 as well, with reported IC50 values in the low to submicromolar range in kinases assays, although the potency against DCLK2 tends to be lower than for DCLK1 (ferguson2020discoveryofa pages 3-4, ferguson2020discoveryofa pages 4-5). Disease associations for DCLK2 have been identified in the context of ccRCC, with the DCLK2203 isoform being implicated in promoting oncogenic signaling through TBK1 activation; similar expression patterns in multiple cancer types suggest a broader oncogenic role (hu2024kinomewidesirnascreen pages 10-11, song2021thexlinkedintellectual pages 19-25). Notably, the significantly reduced Ca²⁺/calmodulin affinity of DCLK2 distinguishes it from other CaMK family members and adds to its unique regulatory and functional profile. Kinase-dead mutants such as K423A have been shown to abolish catalytic activity and fail to rescue tumorigenic phenotypes, confirming the necessity of its kinase function in cellular contexts (hu2024kinomewidesirnascreen pages 10-11).
9. References  
   hu2024kinomewidesirnascreen pages 10-11, hu2024kinomewidesirnascreen pages 3-5, hu2024kinomewidesirnascreen pages 1-3, ohmae2006molecularidentificationand pages 4-5, venkat2023mechanisticandevolutionary pages 17-18, venkat2023mechanisticandevolutionary pages 4-5, ferguson2020discoveryofa pages 3-4, ferguson2020discoveryofa pages 4-5, song2021thexlinkedintellectual pages 19-25

References

1. (hu2024kinomewidesirnascreen pages 10-11): Lianxin Hu, Yanfeng Zhang, Lei Guo, Hua Zhong, Ling Xie, Jin Zhou, Chengheng Liao, Hongwei Yao, Jun Fang, Hongyi Liu, Cheng Zhang, Hui Zhang, Xiaoqiang Zhu, Maowu Luo, Alex von Kriegsheim, Bufan Li, Weibo Luo, Xuewu Zhang, Xian Chen, Joshua T. Mendell, Lin Xu, Payal Kapur, Albert S. Baldwin, James Brugarolas, and Qing Zhang. Kinome-wide sirna screen identifies a dclk2-tbk1 oncogenic signaling axis in clear cell renal cell carcinoma. Molecular Cell, 84:776-790.e5, Feb 2024. URL: https://doi.org/10.1016/j.molcel.2023.12.010, doi:10.1016/j.molcel.2023.12.010. This article has 5 citations and is from a highest quality peer-reviewed journal.
2. (hu2024kinomewidesirnascreen pages 3-5): Lianxin Hu, Yanfeng Zhang, Lei Guo, Hua Zhong, Ling Xie, Jin Zhou, Chengheng Liao, Hongwei Yao, Jun Fang, Hongyi Liu, Cheng Zhang, Hui Zhang, Xiaoqiang Zhu, Maowu Luo, Alex von Kriegsheim, Bufan Li, Weibo Luo, Xuewu Zhang, Xian Chen, Joshua T. Mendell, Lin Xu, Payal Kapur, Albert S. Baldwin, James Brugarolas, and Qing Zhang. Kinome-wide sirna screen identifies a dclk2-tbk1 oncogenic signaling axis in clear cell renal cell carcinoma. Molecular Cell, 84:776-790.e5, Feb 2024. URL: https://doi.org/10.1016/j.molcel.2023.12.010, doi:10.1016/j.molcel.2023.12.010. This article has 5 citations and is from a highest quality peer-reviewed journal.
3. (hu2024kinomewidesirnascreen pages 1-3): Lianxin Hu, Yanfeng Zhang, Lei Guo, Hua Zhong, Ling Xie, Jin Zhou, Chengheng Liao, Hongwei Yao, Jun Fang, Hongyi Liu, Cheng Zhang, Hui Zhang, Xiaoqiang Zhu, Maowu Luo, Alex von Kriegsheim, Bufan Li, Weibo Luo, Xuewu Zhang, Xian Chen, Joshua T. Mendell, Lin Xu, Payal Kapur, Albert S. Baldwin, James Brugarolas, and Qing Zhang. Kinome-wide sirna screen identifies a dclk2-tbk1 oncogenic signaling axis in clear cell renal cell carcinoma. Molecular Cell, 84:776-790.e5, Feb 2024. URL: https://doi.org/10.1016/j.molcel.2023.12.010, doi:10.1016/j.molcel.2023.12.010. This article has 5 citations and is from a highest quality peer-reviewed journal.
4. (song2021thexlinkedintellectual pages 19-25): Jianing Song, Ronald A. Merrill, Andrew Y. Usachev, and Stefan Strack. The x-linked intellectual disability gene product and e3 ubiquitin ligase klhl15 degrades doublecortin proteins to constrain neuronal dendritogenesis. BioRxiv, Oct 2021. URL: https://doi.org/10.1101/2020.10.02.324285, doi:10.1101/2020.10.02.324285. This article has 14 citations.
5. (venkat2023mechanisticandevolutionary pages 17-18): Aarya Venkat, Grace Watterson, Dominic P. Byrne, Brady O’Boyle, Safal Shrestha, Nathan Gravel, Emma E. Fairweather, Leonard A. Daly, Claire Bunn, Wayland Yeung, Ishan Aggarwal, Samiksha Katiyar, Claire E. Eyers, Patrick A. Eyers, and Natarajan Kannan. Mechanistic and evolutionary insights into isoform-specific ‘supercharging’ in dclk family kinases. bioRxiv, Jun 2023. URL: https://doi.org/10.7554/elife.87958.1, doi:10.7554/elife.87958.1. This article has 6 citations.
6. (venkat2023mechanisticandevolutionary pages 4-5): Aarya Venkat, Grace Watterson, Dominic P. Byrne, Brady O’Boyle, Safal Shrestha, Nathan Gravel, Emma E. Fairweather, Leonard A. Daly, Claire Bunn, Wayland Yeung, Ishan Aggarwal, Samiksha Katiyar, Claire E. Eyers, Patrick A. Eyers, and Natarajan Kannan. Mechanistic and evolutionary insights into isoform-specific ‘supercharging’ in dclk family kinases. bioRxiv, Jun 2023. URL: https://doi.org/10.7554/elife.87958.1, doi:10.7554/elife.87958.1. This article has 6 citations.
7. (ferguson2020discoveryofa pages 3-4): F. Ferguson, Behnam Nabet, Srivatsan Raghavan, Srivatsan Raghavan, Yan Liu, Alan L. Leggett, Miljan Kuljanin, R. Kalekar, R. Kalekar, Annan Yang, Annan Yang, Shuning He, Jinhua Wang, Raymond W.S. Ng, Raymond W.S. Ng, Rita Sulahian, Lianbo Li, Emily J Poulin, Ling Huang, Jošt Vrabič Koren, Nora Diéguez-Martínez, Sergio Espinosa, Zhiyang Zeng, Cesear R. Corona, J. Vasta, R. Ohi, Taebo Sim, N. Kim, W. Harshbarger, W. Harshbarger, J. Lizcano, M. Robers, Senthil Muthaswamy, Charles Y. Lin, A. Look, K. Haigis, J. Mancias, B. Wolpin, Andrew J. Aguirre, Andrew J. Aguirre, William C. Hahn, William C. Hahn, K. Westover, and N. Gray. Discovery of a selective inhibitor of doublecortin like kinase 1. Nature Chemical Biology, 16:635-643, Apr 2020. URL: https://doi.org/10.1038/s41589-020-0506-0, doi:10.1038/s41589-020-0506-0. This article has 100 citations and is from a highest quality peer-reviewed journal.
8. (ferguson2020discoveryofa pages 4-5): F. Ferguson, Behnam Nabet, Srivatsan Raghavan, Srivatsan Raghavan, Yan Liu, Alan L. Leggett, Miljan Kuljanin, R. Kalekar, R. Kalekar, Annan Yang, Annan Yang, Shuning He, Jinhua Wang, Raymond W.S. Ng, Raymond W.S. Ng, Rita Sulahian, Lianbo Li, Emily J Poulin, Ling Huang, Jošt Vrabič Koren, Nora Diéguez-Martínez, Sergio Espinosa, Zhiyang Zeng, Cesear R. Corona, J. Vasta, R. Ohi, Taebo Sim, N. Kim, W. Harshbarger, W. Harshbarger, J. Lizcano, M. Robers, Senthil Muthaswamy, Charles Y. Lin, A. Look, K. Haigis, J. Mancias, B. Wolpin, Andrew J. Aguirre, Andrew J. Aguirre, William C. Hahn, William C. Hahn, K. Westover, and N. Gray. Discovery of a selective inhibitor of doublecortin like kinase 1. Nature Chemical Biology, 16:635-643, Apr 2020. URL: https://doi.org/10.1038/s41589-020-0506-0, doi:10.1038/s41589-020-0506-0. This article has 100 citations and is from a highest quality peer-reviewed journal.
9. (ohmae2006molecularidentificationand pages 4-5): Shogo Ohmae, Sayaka Takemoto-Kimura, Michiko Okamura, Aki Adachi-Morishima, Mio Nonaka, Toshimitsu Fuse, Satoshi Kida, Masahiro Tanji, Tomoyuki Furuyashiki, Yoshiki Arakawa, Shuh Narumiya, Hiroyuki Okuno, and Haruhiko Bito. Molecular identification and characterization of a family of kinases with homology to ca2+/calmodulin-dependent protein kinases i/iv\*. Journal of Biological Chemistry, 281:20427-20439, Jul 2006. URL: https://doi.org/10.1074/jbc.m513212200, doi:10.1074/jbc.m513212200. This article has 64 citations and is from a domain leading peer-reviewed journal.