1. Phylogeny:  
   Calcium/calmodulin-dependent protein kinase type II subunit beta (CAMK2B) is a member of the CaMKII family, a subfamily of serine/threonine kinases that is evolutionarily conserved across all metazoans and even extends its roots to unicellular relatives such as choanoflagellates, where the kinase domains share approximately 50% sequence identity with human CaMKII (bhattacharyya2020structuralinsightsinto pages 5-6).  
   The CaMKII family comprises four principal isoforms—α, β, γ, and δ—with CAMK2B corresponding to the beta subunit that exhibits a high degree of conservation in its catalytic domain (approximately 95% identity among isoforms) and moderate conservation in its oligomerization (hub) domain (approximately 80% identity), while showing notable divergence in the kinase-hub linker region (bhattacharyya2020structuralinsightsinto pages 1-3).  
   Gene duplication events during vertebrate evolution led to the emergence of CAMK2B along with its paralogous counterparts, which have subsequently acquired isoform-specific regulatory and functional traits that are maintained in diverse species including mammals and invertebrates (chia2018ahomozygouslossoffunction pages 1-2).  
   Phylogenetic analyses based on kinase domain sequences have placed CAMK2B within a core set of proteins involved in calcium signaling, demonstrating a clear evolutionary relationship with other Ca2+/calmodulin-dependent kinases and underscoring its ancient origin (ohmae2006molecularidentificationand pages 4-5).  
   Comparative evolutionary studies further indicate that the overall domain organization of CAMK2B—featuring a conserved catalytic core, a regulatory segment, an extended intrinsically disordered linker, and a hub domain—is inherited from a common ancestral CaMKII gene, and such structural modules have been preserved to ensure proper signal transduction in neuron‐rich tissues (venkat2023mechanisticandevolutionary pages 25-26).
2. Reaction Catalyzed:  
   CAMK2B catalyzes the phosphorylation of serine/threonine residues on substrate proteins by transferring the γ-phosphate group from ATP to specific hydroxyl groups in the substrates, following the reaction: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H+ (bhattacharyya2020structuralinsightsinto pages 1-3).
3. Cofactor Requirements:  
   The enzymatic activity of CAMK2B requires Mg2+ as a critical cofactor for ATP binding and phosphotransfer, ensuring proper catalytic function during phosphorylation (bhattacharyya2020structuralinsightsinto pages 1-3).  
   In addition, the activation of CAMK2B is tightly coupled to the binding of Ca2+ ions in complex with calmodulin, which serves as a regulatory switch to relieve autoinhibition (du2011decodingofcalcium pages 12-14).
4. Substrate Specificity:  
   CAMK2B is a serine/threonine-specific kinase, and its substrate specificity is dictated by the conformational state of its catalytic domain, which, in its inactive form, is occluded by an autoinhibitory regulatory segment that is displaced upon Ca2+/calmodulin binding (bhattacharyya2020structuralinsightsinto pages 1-3).  
   Once activated, the substrate docking groove becomes accessible, permitting the binding and phosphorylation of a broad range of substrates that typically contain serine or threonine residues embedded within sequences that favor interaction with basic and hydrophobic residues in the kinase active site (bhattacharyya2020structuralinsightsinto pages 15-16).  
   Prominent substrates include proteins involved in synaptic transmission, such as components of the AMPA receptor complex and various actin-associated proteins, which are crucial for synaptic plasticity and dendritic spine remodeling (chia2018ahomozygouslossoffunction pages 2-3).  
   The phosphorylation event itself is precise, with the enzyme recognizing a target motif that, although not fully defined by a single consensus sequence, requires proper orientation within the docking site formed by catalytic domain residues (bhattacharyya2020structuralinsightsinto pages 17-19).
5. Structure:  
   CAMK2B exhibits a modular architecture typical of CaMKII isoforms, beginning with an N-terminal kinase (catalytic) domain that harbors conserved structural features such as the glycine-rich loop for ATP binding, a catalytic lysine residue, and an activation loop that is subject to autophosphorylation (bhattacharyya2020structuralinsightsinto pages 1-3).  
   This catalytic domain is followed by a regulatory segment that contains both an autoinhibitory domain and a Ca2+/calmodulin-binding domain; in the absence of Ca2+, this segment obstructs the substrate-binding site, thereby maintaining the enzyme in an inactive conformation (bhattacharyya2020structuralinsightsinto pages 3-5).  
   Downstream of the regulatory segment lies an intrinsically disordered linker region, which in CAMK2B is significantly longer—approximately 200 amino acids—compared to other isoforms; this extended linker is associated with the protein’s unique actin-binding and bundling activity as well as its role in targeting the holoenzyme to specific subcellular locations (bhattacharyya2020structuralinsightsinto pages 5-6, bhattacharyya2020structuralinsightsinto pages 15-16).  
   The C-terminal region comprises the association or hub domain, which is essential for oligomerization into either dodecameric or tetradecameric holoenzymes that form a donut-shaped ring structure, a configuration that permits dynamic subunit exchange and coordinated regulation across the holoenzyme (bhattacharyya2020structuralinsightsinto pages 1-3, bhattacharyya2020structuralinsightsinto pages 6-8).  
   Key structural features include the hydrophobic spine that supports the active conformation, as well as the orientation of the C-helix, both of which are critical for maintaining catalytic competence and for the allosteric transitions that occur upon Ca2+/calmodulin binding (ohmae2006molecularidentificationand pages 10-11).
6. Regulation:  
   The regulatory mechanism of CAMK2B is multifaceted, beginning with an autoinhibitory state in which the regulatory segment occludes the catalytic domain to prevent unscheduled phosphorylation activity (bhattacharyya2020structuralinsightsinto pages 1-3).  
   Elevated intracellular Ca2+ levels lead to binding of calmodulin, which interacts with the Ca2+/calmodulin-binding domain and displaces the autoinhibitory segment, thereby activating the kinase (bhattacharyya2020structuralinsightsinto pages 15-16, du2011decodingofcalcium pages 12-14).  
   Following activation, CAMK2B undergoes autophosphorylation at a conserved threonine residue within the activation loop; this post-translational modification confers Ca2+/calmodulin-independent (autonomous) kinase activity, allowing the enzyme to remain active even after Ca2+ levels subside (bhattacharyya2020structuralinsightsinto pages 5-6, bhattacharyya2020structuralinsightsinto pages 17-19).  
   Subsequent phosphorylation events at additional regulatory sites, such as Thr305 and Thr306, act to inhibit further Ca2+/calmodulin binding and contribute to the termination of the active state (bhattacharyya2020structuralinsightsinto pages 15-16).  
   Moreover, conformational changes associated with activation facilitate subunit exchange within the holoenzyme, a process that amplifies the spread of kinase activity throughout the molecular complex (bhattacharyya2020structuralinsightsinto pages 16-17).
7. Function:  
   CAMK2B plays critical roles in both neuronal and muscle tissues.  
   In neurons, CAMK2B is predominantly expressed and is integral to the formation and remodeling of dendritic spines as well as synaptogenesis; it modulates synaptic plasticity by acting downstream of N-methyl-D-aspartate receptor (NMDAR) activity, thereby supporting long-term potentiation (LTP) and hippocampus-dependent learning (bhattacharyya2020structuralinsightsinto pages 1-3, chia2018ahomozygouslossoffunction pages 1-2).  
   Its kinase activity leads to the phosphorylation of substrate proteins involved in synaptic transmission, while its kinase-independent role is manifested through direct binding and bundling of actin filaments, a process essential for the reorganization of the actin cytoskeleton during synaptic remodeling (bhattacharyya2020structuralinsightsinto pages 15-16).  
   In developing hippocampal neurons, CAMK2B contributes to the arborization of the dendritic tree and supports dendritic remodeling in mature neurons, thereby influencing neuronal network formation and plasticity (chia2018ahomozygouslossoffunction pages 2-3).  
   Beyond its neuronal functions, CAMK2B is also implicated in the regulation of sarcoplasmic reticulum Ca2+ transport in skeletal muscle, suggesting a broader role in muscle physiology (bhattacharyya2020structuralinsightsinto pages 1-3).  
   The integration of these activities positions CAMK2B as a central mediator of calcium signal transduction, linking transient Ca2+ influx to both immediate biochemical responses and longer-term structural modifications at synapses (thiriet2013preambletocytoplasmic pages 7-11).
8. Other Comments:  
   CAMK2B is subject to pharmacological inhibition by compounds such as KN-62 and KN-93, which have been shown to inhibit Ca2+/calmodulin-dependent activation by competing with calmodulin binding; however, these inhibitors are not completely isoform-specific and affect other CaMK family members (hemmings1997proteinkinaseand pages 13-17).  
   Mutations and dysregulation of CAMK2B have been associated with various neurodevelopmental disorders, including intellectual disability and seizure phenotypes, highlighting its critical role in proper neuronal development and synaptic maintenance (chia2018ahomozygouslossoffunction pages 1-2, bhattacharyya2020structuralinsightsinto pages 17-19).  
   The uniquely extended kinase-hub linker region of CAMK2B also confers actin-bundling activity independent of its catalytic function, a property that distinguishes it from other CaMKII isoforms and is essential for targeting and stabilizing synaptic structures (bhattacharyya2020structuralinsightsinto pages 15-16).  
   Current research efforts are focused on the development of more selective inhibitors that target specific regulatory or allosteric sites within CAMK2B to minimize off-target effects, as well as on elucidating the precise roles of its kinase-independent functions in synaptic plasticity and muscle physiology (hemmings1997proteinkinaseand pages 10-13).
9. References:
10. Bhattacharyya, M., Karandur, D., & Kuriyan, J. Structural insights into the regulation of Ca2+/calmodulin-dependent protein kinase II (CaMKII). Cold Spring Harbor Perspectives in Biology, Oct 2020. doi:10.1101/cshperspect.a035147 (pages 1-3, 3-5, 5-6, 12-14, 15-16, 16-17, 17-19).
11. Chia, P. H., Lei Zhong, et al. A homozygous loss-of-function CAMK2A mutation causes growth delay, frequent seizures and severe intellectual disability. eLife, May 2018. doi:10.7554/elife.32451 (pages 1-2, 2-3).
12. Hemmings, H. C. Protein kinase and phosphatase inhibitors: applications in neuroscience. Regulatory Protein Modification, 1997. doi:10.1385/0-89603-415-1:121 (pages 10-13, 13-17).
13. Ohmae, S., Takemoto-Kimura, S., et al. Molecular identification and characterization of a family of kinases with homology to Ca2+/calmodulin-dependent protein kinases I/IV. Journal of Biological Chemistry, Jul 2006. doi:10.1074/jbc.m513212200 (pages 1-1, 4-5, 10-11, 5-6).
14. Tokumitsu, H. & Sakagami, H. Molecular mechanisms underlying Ca2+/calmodulin-dependent protein kinase kinase signal transduction. International Journal of Molecular Sciences, Sep 2022. doi:10.3390/ijms231911025 (pages 5-7).
15. Matynia, A., Kushner, S. A., & Silva, A. J. Genetic approaches to molecular and cellular cognition: a focus on LTP and learning and memory. Annual Review of Genetics, Dec 2002. doi:10.1146/annurev.genet.36.062802.091007 (pages 11-13).
16. Thiriet, M. Preamble to cytoplasmic protein kinases. In Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems, Jul 2013. doi:10.1007/978-1-4614-4370-4\_3 (pages 1-4, 7-11).
17. Du, L., Yang, T., Puthanveettil, S. V., & Poovaiah, B. W. Decoding of calcium signal through calmodulin: Calmodulin-binding proteins in plants. Signaling and Communication in Plants, Jan 2011. doi:10.1007/978-3-642-20829-4\_11 (pages 12-14, 45-47).
18. Venkat, A., Watterson, G., Byrne, D. P., O’Boyle, B., Shrestha, S., Gravel, N., Fairweather, E. E., Daly, L. A., Bunn, C., Yeung, W., Aggarwal, I., Katiyar, S., Eyers, C. E., Eyers, P. A., & Kannan, N. Mechanistic and evolutionary insights into isoform-specific ‘supercharging’ in DCLK family kinases. eLife, Oct 2023. doi:10.7554/elife.87958 (pages 25-26).

References

1. (bhattacharyya2020structuralinsightsinto pages 1-3): Moitrayee Bhattacharyya, Deepti Karandur, and J. Kuriyan. Structural insights into the regulation of ca2+/calmodulin-dependent protein kinase ii (camkii). Cold Spring Harbor perspectives in biology, Oct 2020. URL: https://doi.org/10.1101/cshperspect.a035147, doi:10.1101/cshperspect.a035147. This article has 90 citations and is from a peer-reviewed journal.
2. (bhattacharyya2020structuralinsightsinto pages 3-5): Moitrayee Bhattacharyya, Deepti Karandur, and J. Kuriyan. Structural insights into the regulation of ca2+/calmodulin-dependent protein kinase ii (camkii). Cold Spring Harbor perspectives in biology, Oct 2020. URL: https://doi.org/10.1101/cshperspect.a035147, doi:10.1101/cshperspect.a035147. This article has 90 citations and is from a peer-reviewed journal.
3. (bhattacharyya2020structuralinsightsinto pages 5-6): Moitrayee Bhattacharyya, Deepti Karandur, and J. Kuriyan. Structural insights into the regulation of ca2+/calmodulin-dependent protein kinase ii (camkii). Cold Spring Harbor perspectives in biology, Oct 2020. URL: https://doi.org/10.1101/cshperspect.a035147, doi:10.1101/cshperspect.a035147. This article has 90 citations and is from a peer-reviewed journal.
4. (bhattacharyya2020structuralinsightsinto pages 15-16): Moitrayee Bhattacharyya, Deepti Karandur, and J. Kuriyan. Structural insights into the regulation of ca2+/calmodulin-dependent protein kinase ii (camkii). Cold Spring Harbor perspectives in biology, Oct 2020. URL: https://doi.org/10.1101/cshperspect.a035147, doi:10.1101/cshperspect.a035147. This article has 90 citations and is from a peer-reviewed journal.
5. (bhattacharyya2020structuralinsightsinto pages 16-17): Moitrayee Bhattacharyya, Deepti Karandur, and J. Kuriyan. Structural insights into the regulation of ca2+/calmodulin-dependent protein kinase ii (camkii). Cold Spring Harbor perspectives in biology, Oct 2020. URL: https://doi.org/10.1101/cshperspect.a035147, doi:10.1101/cshperspect.a035147. This article has 90 citations and is from a peer-reviewed journal.
6. (bhattacharyya2020structuralinsightsinto pages 17-19): Moitrayee Bhattacharyya, Deepti Karandur, and J. Kuriyan. Structural insights into the regulation of ca2+/calmodulin-dependent protein kinase ii (camkii). Cold Spring Harbor perspectives in biology, Oct 2020. URL: https://doi.org/10.1101/cshperspect.a035147, doi:10.1101/cshperspect.a035147. This article has 90 citations and is from a peer-reviewed journal.
7. (chia2018ahomozygouslossoffunction pages 1-2): Poh Hui Chia, Franklin Lei Zhong, Shinsuke Niwa, Carine Bonnard, Kagistia Hana Utami, Ruizhu Zeng, Hane Lee, Ascia Eskin, Stanley F Nelson, William H Xie, Samah Al-Tawalbeh, Mohammad El-Khateeb, Mohammad Shboul, Mahmoud A Pouladi, Mohammed Al-Raqad, and Bruno Reversade. A homozygous loss-of-function camk2a mutation causes growth delay, frequent seizures and severe intellectual disability. eLife, May 2018. URL: https://doi.org/10.7554/elife.32451, doi:10.7554/elife.32451. This article has 75 citations and is from a domain leading peer-reviewed journal.
8. (chia2018ahomozygouslossoffunction pages 2-3): Poh Hui Chia, Franklin Lei Zhong, Shinsuke Niwa, Carine Bonnard, Kagistia Hana Utami, Ruizhu Zeng, Hane Lee, Ascia Eskin, Stanley F Nelson, William H Xie, Samah Al-Tawalbeh, Mohammad El-Khateeb, Mohammad Shboul, Mahmoud A Pouladi, Mohammed Al-Raqad, and Bruno Reversade. A homozygous loss-of-function camk2a mutation causes growth delay, frequent seizures and severe intellectual disability. eLife, May 2018. URL: https://doi.org/10.7554/elife.32451, doi:10.7554/elife.32451. This article has 75 citations and is from a domain leading peer-reviewed journal.
9. (hemmings1997proteinkinaseand pages 10-13): Hugh C. Hemmings. Protein kinase and phosphatase inhibitors: applications in neuroscience. Regulatory Protein Modification, pages 121-218, 1997. URL: https://doi.org/10.1385/0-89603-415-1:121, doi:10.1385/0-89603-415-1:121. This article has 18 citations.
10. (hemmings1997proteinkinaseand pages 13-17): Hugh C. Hemmings. Protein kinase and phosphatase inhibitors: applications in neuroscience. Regulatory Protein Modification, pages 121-218, 1997. URL: https://doi.org/10.1385/0-89603-415-1:121, doi:10.1385/0-89603-415-1:121. This article has 18 citations.
11. (ohmae2006molecularidentificationand pages 10-11): Shogo Ohmae, S. Takemoto-Kimura, M. Okamura, Aki Adachi-Morishima, Mio Nonaka, Toshimitsu Fuse, S. Kida, Masahiro Tanji, T. Furuyashiki, Y. Arakawa, S. Narumiya, H. Okuno, and H. 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.
12. (ohmae2006molecularidentificationand pages 4-5): Shogo Ohmae, S. Takemoto-Kimura, M. Okamura, Aki Adachi-Morishima, Mio Nonaka, Toshimitsu Fuse, S. Kida, Masahiro Tanji, T. Furuyashiki, Y. Arakawa, S. Narumiya, H. Okuno, and H. 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.
13. (bhattacharyya2020structuralinsightsinto pages 6-8): Moitrayee Bhattacharyya, Deepti Karandur, and J. Kuriyan. Structural insights into the regulation of ca2+/calmodulin-dependent protein kinase ii (camkii). Cold Spring Harbor perspectives in biology, Oct 2020. URL: https://doi.org/10.1101/cshperspect.a035147, doi:10.1101/cshperspect.a035147. This article has 90 citations and is from a peer-reviewed journal.
14. (du2011decodingofcalcium pages 12-14): Liqun Du, Tianbao Yang, Sathyanarayanan V. Puthanveettil, and B. W. Poovaiah. Decoding of calcium signal through calmodulin: calmodulin-binding proteins in plants. Signaling and Communication in Plants, pages 177-233, Jan 2011. URL: https://doi.org/10.1007/978-3-642-20829-4\_11, doi:10.1007/978-3-642-20829-4\_11. This article has 35 citations.
15. (thiriet2013preambletocytoplasmic pages 7-11): M Thiriet M Thiriet. Preamble to cytoplasmic protein kinases. Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems, pages 109-135, Jul 2013. URL: https://doi.org/10.1007/978-1-4614-4370-4\_3, doi:10.1007/978-1-4614-4370-4\_3. This article has 2 citations.
16. (venkat2023mechanisticandevolutionary pages 25-26): 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. eLife, Oct 2023. URL: https://doi.org/10.7554/elife.87958, doi:10.7554/elife.87958. This article has 6 citations and is from a domain leading peer-reviewed journal.