1. Phylogeny  
   STK17B, also known as DRAK2, is a member of the death‐associated protein kinase (DAPK) family, a group of serine/threonine kinases that regulate apoptotic cell death and related stress responses (zheng2022newinsightsinto pages 2-4).  
   Within this family, STK17B is classified together with DAPK1, DAPK2, DAPK3, and DRAK1, and it is evolutionarily conserved across vertebrate species, with orthologs identified in diverse mammalian lineages (kogel2001thedapkinase pages 2-4).  
   Phylogenetic analyses indicate that while DAPK1, DAPK2, and DAPK3 share higher sequence homology with each other, DRAK2 is more distantly related and shares approximately 50% sequence identity in its catalytic domain with DAPK1, a divergence that is characteristic of the DAPK subfamily (zheng2022newinsightsinto pages 2-4, temmerman2013structuralandfunctional pages 5-6).  
   STK17B is further grouped within the DMT kinase branch of the calcium/calmodulin‐(CaM) regulated kinase (CAMK) superfamily, although, unlike some of its counterparts, it lacks a canonical CaM‐binding regulatory region, which distinguishes its regulatory properties from other kinases in the CAMK core (temmerman2013structuralandfunctional pages 5-6, zheng2022newinsightsinto pages 2-4).  
   The evolutionary history of STK17B reflects an early divergence from the common ancestor of eukaryotic kinases, and its conservation in lymphoid tissues suggests that its specialized functions in apoptosis and immune regulation have been maintained throughout vertebrate evolution (inbal2000deathassociatedproteinkinaserelated pages 1-2).  
   Thus, by phylogenetic criteria, STK17B occupies a distinct niche among death‐associated kinases, setting it apart functionally and structurally from other more CaM‐dependent members of the CAMK family (kogel2001thedapkinase pages 2-4).
2. Reaction Catalyzed  
   STK17B catalyzes the transfer of a phosphate group from ATP to the hydroxyl group present on serine or threonine residues within substrate proteins (gao2014discoveryofdual pages 1-7).  
   The reaction follows the classical mechanism of serine/threonine phosphorylation whereby ATP and a protein substrate interact at the active site of the enzyme, resulting in the conversion of ATP to ADP and the addition of a phosphate group to the target amino acid residue, with the concomitant release of a proton (gao2014discoveryofdual pages 1-7).  
   By similarity to other members of the DAPK family, STK17B has been shown to phosphorylate regulatory substrates such as myosin light chains and p70S6 kinase, thereby modulating aspects of cytoskeletal dynamics and cell survival signaling (gao2014discoveryofdual pages 1-7).
3. Cofactor Requirements  
   Like most serine/threonine kinases, the catalytic activity of STK17B requires a divalent metal ion, with Mg²⁺ serving as the essential cofactor necessary for ATP binding and proper phosphoryl transfer (zheng2022newinsightsinto pages 2-4).  
   This magnesium dependence is a common feature among kinases in the CAMK and DAPK families and is consistent with the catalytic mechanisms observed in structurally related enzymes (zheng2022newinsightsinto pages 2-4).  
   No evidence has been reported that STK17B requires alternative metal cofactors such as Mn²⁺, and its activity appears to be strictly modulated by the presence of Mg²⁺ under physiological conditions (zheng2022newinsightsinto pages 2-4).
4. Substrate Specificity  
   STK17B exhibits substrate specificity characteristic of serine/threonine kinases, with a preference for phosphorylating hydroxyl groups on serine and threonine residues within target proteins (gao2014discoveryofdual pages 1-7).  
   Experimental observations have demonstrated that STK17B phosphorylates substrates such as myosin regulatory light chain and p70S6 kinase, which are integral to the regulation of cytoskeletal structure and signal transduction pathways involved in apoptosis (gao2014discoveryofdual pages 1-7).  
   Although a definitive consensus sequence for substrate recognition by STK17B has not been conclusively established, its kinase domain shares considerable structural similarity with other DAPK family members known to target proteins involved in apoptotic signaling cascades (zheng2022newinsightsinto pages 2-4).  
   Several studies have noted that the phosphorylation reaction mediated by STK17B can alter substrate conformation and function, thereby influencing downstream cellular processes such as immune cell activation and programmed cell death (gao2014discoveryofdual pages 1-7).
5. Structure  
   STK17B is a protein of 372 amino acids that consists of a central N-terminal catalytic kinase domain and a C-terminal region that appears to play roles in regulatory protein–protein interactions and subcellular localization (zheng2022newinsightsinto pages 2-4).  
   The catalytic domain of STK17B displays all of the hallmark features of serine/threonine kinases, including a conserved ATP-binding pocket, a catalytic loop containing essential residues, a DFG (Asp–Phe–Gly) motif critical for coordinating divalent metal ions, and an αC helix that contributes to the proper orientation of the active site (temmerman2013structuralandfunctional pages 5-6).  
   Unlike DAPK1 and DAPK2, STK17B lacks a calmodulin-binding autoregulatory domain, which is consistent with experimental observations indicating that its activity is not directly regulated by Ca²⁺/calmodulin binding (zheng2022newinsightsinto pages 2-4, temmerman2013structuralandfunctional pages 5-6).  
   The overall three‐dimensional structure of STK17B can be described as a bilobal architecture in which the smaller N-terminal lobe is predominantly composed of β‐sheets and the larger C-terminal lobe is mainly α‐helical, a common structural arrangement observed among serine/threonine kinases (temmerman2013structuralandfunctional pages 5-6).  
   Key catalytic residues, including the lysine that facilitates ATP binding, are conserved and have been mapped to the active site, ensuring the enzyme’s ability to coordinate ATP and promote efficient phosphoryl transfer (inbal2000deathassociatedproteinkinaserelated pages 1-2).  
   The activation loop of STK17B, which contains multiple serine residues such as Ser12, is subject to autophosphorylation; however, unlike many kinases in which phosphorylation of the activation loop is strictly required for catalysis, mutation studies in STK17B suggest that these modifications primarily influence substrate docking and subcellular positioning rather than the core catalytic process (friedrich2007modulationofdrak2 pages 1-2).  
   Additional structural elements, including potential nuclear localization signals, have been identified in regions outside the catalytic domain, and these sequences may be responsible for the dual cytoplasmic and nuclear localization of the enzyme observed in various cell types (zheng2022newinsightsinto pages 7-8, thiriet2013cytoplasmicproteinserinethreonine pages 82-86).  
   Comparative structural analyses with other members of the DAPK family reveal that while the catalytic domains share approximately 50% sequence identity with DAPK1, the divergence in their C-terminal regions underlies differences in subcellular localization, regulatory protein binding, and possibly substrate specificity (gao2014discoveryofdual pages 1-7, temmerman2013structuralandfunctional pages 5-6).  
   Crystallographic data and AlphaFold-based structural models support a high degree of conservation in the core kinase fold of STK17B, while also highlighting unique surface features – such as exposed hydrophobic patches and distinct charge distributions – that may serve as docking sites for interacting partners or allosteric regulators (zheng2022newinsightsinto pages 2-4, temmerman2013structuralandfunctional pages 6-7).  
   Such structural insights not only confirm STK17B’s role as a bona fide serine/threonine kinase but also provide a molecular framework for understanding how specific inhibitors might interact with its active site and allosteric regions to modulate its function in a cellular context (gao2014discoveryofdual pages 1-7).
6. Regulation  
   STK17B is regulated primarily through post‐translational modifications, with autophosphorylation playing a major role in modulating its catalytic activity and substrate interactions (friedrich2007modulationofdrak2 pages 1-2).  
   Autophosphorylation at specific serine residues such as Ser12 has been implicated in fine‐tuning the kinase’s enzymatic activity and may also influence its subcellular localization, although such modifications do not drastically alter the intrinsic catalytic function (friedrich2007modulationofdrak2 pages 1-2).  
   In addition, regulatory proteins such as the calcium‐binding protein CHP have been shown to bind STK17B and inhibit its activity in a calcium‐dependent manner, suggesting that intermolecular interactions can serve as negative regulatory mechanisms (kuwahara2003theapoptosisinducingprotein pages 5-5).  
   Moreover, signaling downstream of the T cell receptor can induce changes in STK17B’s autophosphorylation status, thereby modulating the activation threshold of T lymphocytes and contributing to the overall regulation of immune responses (scheuplein2024evaluationofstk17b pages 12-13).  
   Additional layers of regulation may be provided by interactions with 14-3-3 proteins, which have been reported to influence the dimerization state and protect key phosphosites, further refining the enzyme’s functional output in response to cellular cues (zheng2022newinsightsinto pages 12-12).  
   Collectively, these regulatory mechanisms – including autophosphorylation, inhibitory protein interactions, and receptor-mediated signaling cascades – ensure that STK17B activity is precisely controlled within the context of stress responses and apoptosis (harris2015drak2doesnot pages 14-14).
7. Function  
   STK17B functions as a positive regulator of apoptosis through its catalytic activity and plays a significant role in modulating immune cell signaling (gao2014discoveryofdual pages 1-7).  
   It is expressed at low levels in most tissues but is highly enriched in lymphoid cells, particularly T and B lymphocytes, where its expression pattern underscores its involvement in adaptive immune responses (scheuplein2024evaluationofstk17b pages 1-2, zheng2022newinsightsinto pages 8-10).  
   In T cells, STK17B acts to modulate the activation threshold of the T cell receptor, and genetic deletion or inhibition of DRAK2 has been associated with resistance to autoimmune conditions such as experimental autoimmune encephalomyelitis and type 1 diabetes, indicating its role in fine-tuning immune responses (gao2014discoveryofdual pages 1-7, scheuplein2024evaluationofstk17b pages 13-13).  
   Beyond its immunological functions, STK17B is implicated in the phosphorylation of key substrates – for example, myosin light chain and p70S6 kinase – which can affect cellular processes ranging from cytoskeletal dynamics and cell contraction to the regulation of protein synthesis and survival pathways (gao2014discoveryofdual pages 1-7).  
   Furthermore, the enzyme’s pro‐apoptotic activity contributes to the elimination of damaged or aberrantly activated cells, thereby serving as a safeguard against uncontrolled cell proliferation and tumorigenesis (harris2015drak2doesnot pages 14-14).  
   In pancreatic islet β-cells, cytokine‐induced upregulation of STK17B has been linked to enhanced apoptosis, suggesting that it may also play a role in the pathogenesis of diabetes by modulating cell survival under inflammatory conditions (zheng2022newinsightsinto pages 7-8).  
   The integration of these diverse functional roles in both the immune system and non-lymphoid tissues highlights STK17B as a multifunctional kinase that operates at the crossroads of apoptotic regulation, cellular stress responses, and immune modulation (gao2014discoveryofdual pages 1-7, zheng2022newinsightsinto pages 7-8).
8. Other Comments  
   Recent medicinal chemistry efforts have identified a series of potent inhibitors for STK17B, including novel thieno[2,3‑b]pyridine derivatives that exhibit nanomolar binding affinity and functional enzymatic inhibition, albeit with challenges in achieving selectivity over the closely related DRAK1 isoform (gao2014discoveryofdual pages 1-7).  
   Additional inhibitor classes, such as indirubin derivatives and compounds like SC82510, have been reported to modulate DRAK2 activity in various experimental models, providing promising starting points for the development of selective chemical probes aimed at elucidating DRAK2 biology in both autoimmune diseases and transplant rejection settings (zheng2022newinsightsinto pages 7-8).  
   Disease associations with alterations in STK17B activity are extensive; for instance, aberrant DRAK2 function has been linked to T-cell hypersensitivity, autoimmune disease pathogenesis, and adverse outcomes in islet transplantation, indicating that dysregulation of its apoptotic signaling pathways can have significant pathological consequences (gao2014discoveryofdual pages 1-7, scheuplein2024evaluationofstk17b pages 13-13).  
   Furthermore, ongoing research continues to explore the involvement of STK17B in cancer biology, where its role in apoptosis and immune regulation may render it a promising target for cancer immunotherapy, despite some studies indicating that its contributions in tumor surveillance may be context dependent (harris2015drak2doesnot pages 14-14, kim2019deathassociatedproteinkinase pages 12-14).  
   Given these multifaceted roles, STK17B remains a focus of intense investigation, and the identification of selective inhibitors is expected to facilitate further mechanistic studies and stimulate translational research into the therapeutic modulation of apoptotic and immune responses in various diseases (tur2017restorationofdap pages 7-9).
9. References
10. gao2014discoveryofdual pages 1-7
11. scheuplein2024evaluationofstk17b pages 1-2
12. zheng2022newinsightsinto pages 2-4
13. elbadawy2018novelfunctionsof pages 10-12
14. friedrich2007modulationofdrak2 pages 1-2
15. harris2015drak2doesnot pages 14-14
16. kim2019deathassociatedproteinkinase pages 12-14
17. kogel2001thedapkinase pages 2-4
18. kuwahara2003theapoptosisinducingprotein pages 5-5
19. temmerman2013structuralandfunctional pages 5-6
20. inbal2000deathassociatedproteinkinaserelated pages 1-2
21. scheidtmann2007dlkzipkinasea pages 1-2
22. tur2017restorationofdap pages 7-9

References

1. (gao2014discoveryofdual pages 1-7): Ling-Jie Gao, Sona Kovackova, Michal Šála, Anna Teresa Ramadori, Steven De Jonghe, and Piet Herdewijn. Discovery of dual death-associated protein related apoptosis inducing protein kinase 1 and 2 inhibitors by a scaffold hopping approach. Journal of Medicinal Chemistry, 57:7624-7643, Sep 2014. URL: https://doi.org/10.1021/jm5007929, doi:10.1021/jm5007929. This article has 45 citations and is from a highest quality peer-reviewed journal.
2. (scheuplein2024evaluationofstk17b pages 13-13): Felix Scheuplein, Florian Renner, John E. Campbell, Robert Campbell, Chris De Savi, Jan Eckmann, Holger Fischer, Jie Ge, Luke Green, Peter Jakob, Joseph L. Kim, Caitlin Kinkema, Katie McGinn, Ricardo Medina, Annemarie Müller, Nisha Perez, Emanuele Perola, Yoav Timsit, Tary Traore, Ulrike Hopfer, Stefka Tyanova, Manuel Tzouros, Ruduan Wang, Richard Woessner, Marion Dorsch, and James R. Bischoff. Evaluation of stk17b as a cancer immunotherapy target utilizing highly potent and selective small molecule inhibitors. Frontiers in Immunology, Oct 2024. URL: https://doi.org/10.3389/fimmu.2024.1411395, doi:10.3389/fimmu.2024.1411395. This article has 1 citations and is from a peer-reviewed journal.
3. (zheng2022newinsightsinto pages 2-4): Youwei Zheng, Xinchao Li, Lirun Kuang, and Yong Wang. New insights into the characteristics of drak2 and its role in apoptosis: from molecular mechanisms to clinically applied potential. Frontiers in Pharmacology, Oct 2022. URL: https://doi.org/10.3389/fphar.2022.1014508, doi:10.3389/fphar.2022.1014508. This article has 6 citations and is from a peer-reviewed journal.
4. (zheng2022newinsightsinto pages 7-8): Youwei Zheng, Xinchao Li, Lirun Kuang, and Yong Wang. New insights into the characteristics of drak2 and its role in apoptosis: from molecular mechanisms to clinically applied potential. Frontiers in Pharmacology, Oct 2022. URL: https://doi.org/10.3389/fphar.2022.1014508, doi:10.3389/fphar.2022.1014508. This article has 6 citations and is from a peer-reviewed journal.
5. (zheng2022newinsightsinto pages 8-10): Youwei Zheng, Xinchao Li, Lirun Kuang, and Yong Wang. New insights into the characteristics of drak2 and its role in apoptosis: from molecular mechanisms to clinically applied potential. Frontiers in Pharmacology, Oct 2022. URL: https://doi.org/10.3389/fphar.2022.1014508, doi:10.3389/fphar.2022.1014508. This article has 6 citations and is from a peer-reviewed journal.
6. (elbadawy2018novelfunctionsof pages 10-12): Mohamed Elbadawy, Tatsuya Usui, Hideyuki Yamawaki, and Kazuaki Sasaki. Novel functions of death-associated protein kinases through mitogen-activated protein kinase-related signals. International Journal of Molecular Sciences, 19:3031, Oct 2018. URL: https://doi.org/10.3390/ijms19103031, doi:10.3390/ijms19103031. This article has 61 citations and is from a peer-reviewed journal.
7. (friedrich2007modulationofdrak2 pages 1-2): Monica L. Friedrich, Meng Cui, Jeniffer B. Hernandez, Brian M. Weist, Hilde-Marie Andersen, Xiaowu Zhang, Lan Huang, and Craig M. Walsh. Modulation of drak2 autophosphorylation by antigen receptor signaling in primary lymphocytes. Journal of Biological Chemistry, 282:4573-4584, Feb 2007. URL: https://doi.org/10.1074/jbc.m606675200, doi:10.1074/jbc.m606675200. This article has 30 citations and is from a domain leading peer-reviewed journal.
8. (harris2015drak2doesnot pages 14-14): Tarsha L. Harris and Maureen A. McGargill. Drak2 does not regulate tgf-β signaling in t cells. PLOS ONE, 10:e0123650, May 2015. URL: https://doi.org/10.1371/journal.pone.0123650, doi:10.1371/journal.pone.0123650. This article has 11 citations and is from a peer-reviewed journal.
9. (kim2019deathassociatedproteinkinase pages 12-14): Nami Kim, Dongmei Chen, Xiao Zhen Zhou, and Tae Ho Lee. Death-associated protein kinase 1 phosphorylation in neuronal cell death and neurodegenerative disease. International Journal of Molecular Sciences, 20:3131, Jun 2019. URL: https://doi.org/10.3390/ijms20133131, doi:10.3390/ijms20133131. This article has 77 citations and is from a peer-reviewed journal.
10. (kogel2001thedapkinase pages 2-4): Donat Kögel, Jochen H.M. Prehn, and Karl Heinz Scheidtmann. The dap kinase family of pro‐apoptotic proteins: novel players in the apoptotic game. BioEssays, Apr 2001. URL: https://doi.org/10.1002/bies.1050, doi:10.1002/bies.1050. This article has 137 citations and is from a peer-reviewed journal.
11. (kuwahara2003theapoptosisinducingprotein pages 5-5): H. Kuwahara, Jun-ichi Kamei, N. Nakamura, M. Matsumoto, H. Inoue, and H. Kanazawa. The apoptosis-inducing protein kinase drak2 is inhibited in a calcium-dependent manner by the calcium-binding protein chp. Journal of Biochemistry, 134:245-250, Aug 2003. URL: https://doi.org/10.1093/jb/mvg137, doi:10.1093/jb/mvg137. This article has 42 citations and is from a peer-reviewed journal.
12. (scheuplein2024evaluationofstk17b pages 1-2): Felix Scheuplein, Florian Renner, John E. Campbell, Robert Campbell, Chris De Savi, Jan Eckmann, Holger Fischer, Jie Ge, Luke Green, Peter Jakob, Joseph L. Kim, Caitlin Kinkema, Katie McGinn, Ricardo Medina, Annemarie Müller, Nisha Perez, Emanuele Perola, Yoav Timsit, Tary Traore, Ulrike Hopfer, Stefka Tyanova, Manuel Tzouros, Ruduan Wang, Richard Woessner, Marion Dorsch, and James R. Bischoff. Evaluation of stk17b as a cancer immunotherapy target utilizing highly potent and selective small molecule inhibitors. Frontiers in Immunology, Oct 2024. URL: https://doi.org/10.3389/fimmu.2024.1411395, doi:10.3389/fimmu.2024.1411395. This article has 1 citations and is from a peer-reviewed journal.
13. (scheuplein2024evaluationofstk17b pages 12-13): Felix Scheuplein, Florian Renner, John E. Campbell, Robert Campbell, Chris De Savi, Jan Eckmann, Holger Fischer, Jie Ge, Luke Green, Peter Jakob, Joseph L. Kim, Caitlin Kinkema, Katie McGinn, Ricardo Medina, Annemarie Müller, Nisha Perez, Emanuele Perola, Yoav Timsit, Tary Traore, Ulrike Hopfer, Stefka Tyanova, Manuel Tzouros, Ruduan Wang, Richard Woessner, Marion Dorsch, and James R. Bischoff. Evaluation of stk17b as a cancer immunotherapy target utilizing highly potent and selective small molecule inhibitors. Frontiers in Immunology, Oct 2024. URL: https://doi.org/10.3389/fimmu.2024.1411395, doi:10.3389/fimmu.2024.1411395. This article has 1 citations and is from a peer-reviewed journal.
14. (temmerman2013structuralandfunctional pages 5-6): Koen Temmerman, Bertrand Simon, and Matthias Wilmanns. Structural and functional diversity in the activity and regulation of dapk‐related protein kinases. The FEBS Journal, Nov 2013. URL: https://doi.org/10.1111/febs.12384, doi:10.1111/febs.12384. This article has 42 citations.
15. (temmerman2013structuralandfunctional pages 6-7): Koen Temmerman, Bertrand Simon, and Matthias Wilmanns. Structural and functional diversity in the activity and regulation of dapk‐related protein kinases. The FEBS Journal, Nov 2013. URL: https://doi.org/10.1111/febs.12384, doi:10.1111/febs.12384. This article has 42 citations.
16. (thiriet2013cytoplasmicproteinserinethreonine pages 82-86): M Thiriet M Thiriet. Cytoplasmic protein serine/threonine kinases. Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems, pages 175-310, Jul 2013. URL: https://doi.org/10.1007/978-1-4614-4370-4\_5, doi:10.1007/978-1-4614-4370-4\_5. This article has 11 citations.
17. (zheng2022newinsightsinto pages 12-12): Youwei Zheng, Xinchao Li, Lirun Kuang, and Yong Wang. New insights into the characteristics of drak2 and its role in apoptosis: from molecular mechanisms to clinically applied potential. Frontiers in Pharmacology, Oct 2022. URL: https://doi.org/10.3389/fphar.2022.1014508, doi:10.3389/fphar.2022.1014508. This article has 6 citations and is from a peer-reviewed journal.
18. (inbal2000deathassociatedproteinkinaserelated pages 1-2): Boaz Inbal, Gidi Shani, Ofer Cohen, Joseph L. Kissil, and Adi Kimchi. Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis. Molecular and Cellular Biology, 20:1044-1054, Feb 2000. URL: https://doi.org/10.1128/mcb.20.3.1044-1054.2000, doi:10.1128/mcb.20.3.1044-1054.2000. This article has 201 citations and is from a domain leading peer-reviewed journal.
19. (scheidtmann2007dlkzipkinasea pages 1-2): Karl Heinz Scheidtmann. Dlk/zip kinase, a novel ser/thr‐specific protein kinase with multiple functions. Signal Transduction, 7:248-259, Jun 2007. URL: https://doi.org/10.1002/sita.200600112, doi:10.1002/sita.200600112. This article has 9 citations and is from a peer-reviewed journal.
20. (tur2017restorationofdap pages 7-9): M. Tur, A. K. Daramola, S. Gattenlöhner, M. Herling, S. Chetty, and S. Barth. Restoration of dap kinase tumor suppressor function: a therapeutic strategy to selectively induce apoptosis in cancer cells using immunokinase fusion proteins. Biomedicines, Oct 2017. URL: https://doi.org/10.3390/biomedicines5040059, doi:10.3390/biomedicines5040059. This article has 17 citations and is from a peer-reviewed journal.