1. Phylogeny  
   STK10, also known as lymphocyte‐oriented kinase (LOK), is a serine/threonine protein kinase that belongs to the STE20‐like kinase family. Within this family, STK10 is classified in the germinal center kinase (GCK) subgroup and exhibits high sequence homology with other STE20 family members such as SLK. Orthologs of STK10 have been identified in human, mouse, and rat, which supports its evolutionary conservation among mammalian species. Comparative phylogenetic analyses place STK10 in a cluster of kinases that are derived from the ancient complement of eukaryotic protein kinases, demonstrating conserved kinase domain architecture observed across species (serafim2021discoveryofa pages 15-18, spiridonov2005identificationandcharacterization pages 1-2).
2. Reaction Catalyzed  
   STK10 catalyzes the phosphorylation reaction in which a phosphate group is transferred from ATP to the hydroxyl group of serine or threonine residues on substrate proteins. The overall chemical reaction can be represented as:  
     ATP + [protein]–(L-serine/L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺  
   This catalytic process is common among serine/threonine kinases and underlies the role of STK10 in regulating phosphorylation‐dependent signaling events by modifying key regulatory proteins (Information section).
3. Cofactor Requirements  
   Like other serine/threonine kinases, the catalytic activity of STK10 is dependent on the binding of ATP in the presence of divalent cations. In particular, Mg²⁺ is required as a cofactor to facilitate the proper coordination of ATP in the active site, thereby allowing efficient phosphotransfer to the substrate protein (Information section).
4. Substrate Specificity  
   STK10 phosphorylates serine/threonine residues on protein substrates with a marked specificity for particular sequence motifs. Experimental studies, including those summarized in a kinome substrate specificity atlas, indicate that STK10 exhibits a consensus substrate preference in which a serine or threonine residue is immediately followed by a proline residue (S/T-P motif). This proline-directed kinase specificity aligns with observations for many kinases within the CMGC group and is consistent with the substrate motifs recognized in high-throughput peptide phosphorylation assays (cesaro2020prevalenceandsignificance pages 17-18, johnson2023anatlasof pages 18-20). In addition to the S/T-P motif preference, STK10 phosphorylates substrates with critical roles in cytoskeletal regulation, such as ERM proteins (e.g., moesin), and it has been shown to mediate the phosphorylation of PLK1 under in vitro conditions. These substrate interactions are determined by sequence-dependent binding features that include contributions from residues flanking the phosphorylation site, as described in systematic kinase profiling studies (serafim2021discoveryofa pages 43-46).
5. Structure  
   STK10 is composed of an N-terminal catalytic domain and a C-terminal non-catalytic region that is predicted to form a coiled-coil structure. The N-terminal kinase domain shows the typical bilobal architecture characteristic of protein kinases. The smaller N-terminal lobe contains a glycine-rich loop that is involved in ATP binding, while the larger C-terminal lobe harbors the conserved catalytic loop, the activation segment with the DFG motif, and elements that contribute to substrate binding, such as the hinge region. High-resolution crystal structures of STK10 complexed with small-molecule inhibitors have revealed that the ATP binding site is defined by a network of hydrogen bonds with the kinase hinge and a hydrophobic binding pocket that can accommodate ligands with diverse chemical scaffolds. Notably, structural studies have shown that the kinase domain of STK10 exhibits considerable conformational flexibility; for example, the position of the αC-helix and the DFG motif can vary between active (DFG-in) and inactive (DFG-out) conformations. Inhibitor-bound complexes have further identified key catalytic and regulatory features, including the assembly of catalytic (C) and regulatory (R) spines and the conformational dynamics of the glycine-rich loop, which together modulate ligand binding and enzymatic activity (serafim2021discoveryofa pages 11-15, serafim2021discoveryofa pages 15-18, asquith2020designandanalysis pages 18-22).
6. Regulation  
   Regulation of STK10 activity involves post-translational modifications and protein-protein interactions. The kinase is known to undergo autophosphorylation, a modification that is common among serine/threonine kinases and that may contribute to its full catalytic activation. In vitro biochemical characterizations have demonstrated that purified full-length STK10 is heavily autophosphorylated, which is indicative of an active regulatory mechanism within the enzyme itself (serafim2021discoveryofa pages 1-6, serafim2021discoveryofa pages 43-46). Although specific phosphorylation sites on STK10 have been mapped in some studies, the precise regulatory effects of such modifications on STK10 activity remain to be fully elucidated. Furthermore, the presence of a C-terminal coiled-coil domain suggests that STK10 may engage in homodimerization or interact with scaffolding proteins, potentially modulating its subcellular localization and activity. While related kinases in the STE20 family are known to undergo caspase-mediated cleavage during apoptotic signaling, the specific enzymes responsible for similar regulatory events in STK10 have not been conclusively identified (serafim2021discoveryofa pages 43-46, thiriet2013cytoplasmicproteinserinethreonine pages 11-14).
7. Function  
   STK10 plays a critical role in the regulation of lymphocyte migration through its capacity to phosphorylate proteins that modulate cytoskeletal dynamics. One of the primary substrates of STK10 is the moesin (MSN) protein, which belongs to the ERM (ezrin-radixin-moesin) family; phosphorylation of ERM proteins by STK10 facilitates the linkage between the plasma membrane and the actin cytoskeleton. In addition to its function in cytoskeletal remodeling, STK10 has been implicated in cell cycle regulation through its ability to phosphorylate polo-like kinase 1 (PLK1) in vitro, although further in vivo evidence is required to establish this role definitively. Expression studies indicate that STK10 is predominantly expressed in lymphoid tissues such as the thymus, spleen, and bone marrow, which is consistent with its involvement in regulating lymphocyte behavior. Functional studies in cancer cell models have demonstrated context-dependent roles for STK10; for instance, targeted knockout experiments in cervical cancer cells have shown that depletion of STK10 leads to altered cellular adhesion, migration, and invasion, while investigations in prostate cancer models have reported modulation of apoptosis, cell proliferation, and cell cycle progression following alteration of STK10 activity (Information section, zhang2020knockoutofstk10 pages 9-10, zhang2021stk10knockoutinhibits pages 5-6).
8. Other Comments  
   A number of small-molecule inhibitors targeting STK10 have been developed, often as dual inhibitors with activity against the closely related kinase SLK. In particular, compounds based on a maleimide scaffold have been reported to exhibit potent inhibitory activity (with low nanomolar potency in biochemical assays) and have been utilized as chemical tools to probe STK10-mediated signaling pathways. In addition to these experimental inhibitors, the modulation of STK10 activity has been explored in the context of cancer, where changes in its expression or activity are associated with alterations in cell migration and proliferation. In cervical cancer cells, for example, knockout of STK10 has been linked to an increase in migratory and invasive properties, whereas in prostate cancer models, STK10 depletion has been associated with enhanced cell proliferation and tumor growth in xenograft studies. Moreover, STK10 functions as a negative regulator of MAP3K1/MEKK1 signaling, and its kinase activity is implicated in maintaining proper lymphocyte migration. These functional insights suggest that STK10 is a potential target for therapeutic intervention in disorders related to immune cell dysfunction and tumor progression (serafim2021discoveryofa pages 15-18, zhang2020knockoutofstk10 pages 9-10, zhang2021stk10knockoutinhibits pages 5-6).
9. References
10. Serafim, R. A. M., Sorrell, F. J., Berger, B.-T., Collins, R. J., Vasconcelos, S. N. S., Massirer, K. B., Knapp, S., Bennett, J., Fedorov, O., Patel, H., Zuercher, W. J., & Elkins, J. M. (2021). Discovery of a potent dual SLK/STK10 inhibitor based on a maleimide scaffold. Journal of Medicinal Chemistry, 64:13259-13278 (pages 1-6, 11-15, 15-18, 22-25, 43-46, 46-48).
11. Asquith, C. R. M., Laitinen, T., Bennett, J. M., Wells, C. I., Elkins, J. M., Zuercher, W. J., Tizzard, G. J., & Poso, A. (2020). Design and analysis of the 4‐anilinoquin(az)oline kinase inhibition profiles of GAK/SLK/STK10 using quantitative structure‐activity relationships. ChemMedChem, 15:26-49 (pages 1-3, 18-22).
12. Cesaro, L., & Pinna, L. A. (2020). Prevalence and significance of the commonest phosphorylated motifs in the human proteome: a global analysis. Cellular and Molecular Life Sciences, 77:5281-5298 (pages 16-17, 17-18).
13. Johnson, J. L., Yaron, T. M., Huntsman, E. M., Kerelsky, A., Song, J., Regev, A., Lin, T.-Y., Liberatore, K., Cizin, D. M., Cohen, B. M., Vasan, N., Ma, Y., Krismer, K., Torres Robles, J., van de Kooij, B., van Vlimmeren, A. E., Andrée-Busch, N., Käufer, N. F., Dorovkov, M. V., Ryazanov, A. G., Takagi, Y., Kastenhuber, E. R., Goncalves, M. D., Hopkins, B. D., Elemento, O., Taatjes, D. J., Maucuer, A., Yamashita, A., Degterev, A., Uduman, M., Lu, J., Landry, S. D., Zhang, B., Cossentino, I., Linding, R., Blenis, J., Hornbeck, P. V., Turk, B. E., & Yaffe, M. B. (2023). An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613:759-766 (pages 18-20).
14. Spiridonov, N. A., Wong, L., Zerfas, P. M., Starost, M. F., Pack, S. D., Paweletz, C. P., & Johnson, G. R. (2005). Identification and characterization of SSTK, a serine/threonine protein kinase essential for male fertility. Molecular and Cellular Biology, 25:4250-4261 (pages 1-2, 4-5).
15. Chen, C., Ha, B. H., Thévenin, A. F., Lou, H. J., Zhang, R., Yip, K. Y., Peterson, J. R., Gerstein, M., Kim, P. M., Filippakopoulos, P., Knapp, S., Boggon, T. J., & Turk, B. E. (2014). Identification of a major determinant for serine-threonine kinase phosphoacceptor specificity. Molecular Cell, 53:140-147 (page 8-8).
16. Goldsmith, E. J., Akella, R., Min, X., Zhou, T., & Humphreys, J. M. (2007). Substrate and docking interactions in serine/threonine protein kinases. Chemical Reviews, 107:5065-5081 (pages 1-2, 3-4, 5-6).
17. O’Boyle, B., Yeung, W., Lu, J. D., Katiyar, S., Yaron-Barir, T. M., Johnson, J. L., Cantley, L. C., & Kannan, N. (2025). An atlas of bacterial serine-threonine kinases reveals functional diversity and key distinctions from eukaryotic kinases. Science Signaling, 18:eadt8686 (pages 35-39).
18. Zhang, L., Lu, S.-Y., Guo, R., Ma, J.-X., Tang, L.-Y., Shen, Y., Shen, C., Lu, L.-M., Wang, Z.-G., Liu, J., & Zhang, H.-X. (2020). Knockout of STK10 promotes the migration and invasion of cervical cancer cells. Translational Cancer Research, 9:7079-7090 (pages 9-10).
19. Zhang, L., Lu, S.-Y., Guo, R., Ma, J.-X., Tang, L.-Y., Wang, J.-J., Shen, C.-L., Lu, L.-M., Liu, J., Wang, Z.-G., & Zhang, H.-X. (2021). STK10 knockout inhibits cell migration and promotes cell proliferation via modulating the activity of ERM and p38 MAPK in prostate cancer cells. Experimental and Therapeutic Medicine, 22:851 (pages 5-6).

References

1. (cesaro2020prevalenceandsignificance pages 17-18): Luca Cesaro and Lorenzo A. Pinna. Prevalence and significance of the commonest phosphorylated motifs in the human proteome: a global analysis. Cellular and Molecular Life Sciences, 77:5281-5298, Feb 2020. URL: https://doi.org/10.1007/s00018-020-03474-2, doi:10.1007/s00018-020-03474-2. This article has 21 citations and is from a domain leading peer-reviewed journal.
2. (serafim2021discoveryofa pages 1-6): Ricardo A. M. Serafim, Fiona J. Sorrell, Benedict-Tilman Berger, Ross J. Collins, Stanley N. S. Vasconcelos, Katlin B. Massirer, Stefan Knapp, James Bennett, Oleg Fedorov, Hitesh Patel, William J. Zuercher, and Jonathan M. Elkins. Discovery of a potent dual slk/stk10 inhibitor based on a maleimide scaffold. Journal of Medicinal Chemistry, 64:13259-13278, Aug 2021. URL: https://doi.org/10.1021/acs.jmedchem.0c01579, doi:10.1021/acs.jmedchem.0c01579. This article has 13 citations and is from a highest quality peer-reviewed journal.
3. (serafim2021discoveryofa pages 11-15): Ricardo A. M. Serafim, Fiona J. Sorrell, Benedict-Tilman Berger, Ross J. Collins, Stanley N. S. Vasconcelos, Katlin B. Massirer, Stefan Knapp, James Bennett, Oleg Fedorov, Hitesh Patel, William J. Zuercher, and Jonathan M. Elkins. Discovery of a potent dual slk/stk10 inhibitor based on a maleimide scaffold. Journal of Medicinal Chemistry, 64:13259-13278, Aug 2021. URL: https://doi.org/10.1021/acs.jmedchem.0c01579, doi:10.1021/acs.jmedchem.0c01579. This article has 13 citations and is from a highest quality peer-reviewed journal.
4. (serafim2021discoveryofa pages 15-18): Ricardo A. M. Serafim, Fiona J. Sorrell, Benedict-Tilman Berger, Ross J. Collins, Stanley N. S. Vasconcelos, Katlin B. Massirer, Stefan Knapp, James Bennett, Oleg Fedorov, Hitesh Patel, William J. Zuercher, and Jonathan M. Elkins. Discovery of a potent dual slk/stk10 inhibitor based on a maleimide scaffold. Journal of Medicinal Chemistry, 64:13259-13278, Aug 2021. URL: https://doi.org/10.1021/acs.jmedchem.0c01579, doi:10.1021/acs.jmedchem.0c01579. This article has 13 citations and is from a highest quality peer-reviewed journal.
5. (asquith2020designandanalysis pages 18-22): Christopher R. M. Asquith, Tuomo Laitinen, James M. Bennett, Carrow I. Wells, Jonathan M. Elkins, William J. Zuercher, Graham J. Tizzard, and Antti Poso. Design and analysis of the 4‐anilinoquin(az)oline kinase inhibition profiles of gak/slk/stk10 using quantitative structure‐activity relationships. ChemMedChem, 15:26-49, Nov 2020. URL: https://doi.org/10.1002/cmdc.201900521, doi:10.1002/cmdc.201900521. This article has 24 citations and is from a peer-reviewed journal.
6. (johnson2023anatlasof pages 18-20): Jared L. Johnson, Tomer M. Yaron, Emily M. Huntsman, Alexander Kerelsky, Junho Song, Amit Regev, Ting-Yu Lin, Katarina Liberatore, Daniel M. Cizin, Benjamin M. Cohen, Neil Vasan, Yilun Ma, Konstantin Krismer, Jaylissa Torres Robles, Bert van de Kooij, Anne E. van Vlimmeren, Nicole Andrée-Busch, Norbert F. Käufer, Maxim V. Dorovkov, Alexey G. Ryazanov, Yuichiro Takagi, Edward R. Kastenhuber, Marcus D. Goncalves, Benjamin D. Hopkins, Olivier Elemento, Dylan J. Taatjes, Alexandre Maucuer, Akio Yamashita, Alexei Degterev, Mohamed Uduman, Jingyi Lu, Sean D. Landry, Bin Zhang, Ian Cossentino, Rune Linding, John Blenis, Peter V. Hornbeck, Benjamin E. Turk, Michael B. Yaffe, and Lewis C. Cantley. An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613:759-766, Jan 2023. URL: https://doi.org/10.1038/s41586-022-05575-3, doi:10.1038/s41586-022-05575-3. This article has 436 citations and is from a highest quality peer-reviewed journal.
7. (serafim2021discoveryofa pages 43-46): Ricardo A. M. Serafim, Fiona J. Sorrell, Benedict-Tilman Berger, Ross J. Collins, Stanley N. S. Vasconcelos, Katlin B. Massirer, Stefan Knapp, James Bennett, Oleg Fedorov, Hitesh Patel, William J. Zuercher, and Jonathan M. Elkins. Discovery of a potent dual slk/stk10 inhibitor based on a maleimide scaffold. Journal of Medicinal Chemistry, 64:13259-13278, Aug 2021. URL: https://doi.org/10.1021/acs.jmedchem.0c01579, doi:10.1021/acs.jmedchem.0c01579. This article has 13 citations and is from a highest quality peer-reviewed journal.
8. (spiridonov2005identificationandcharacterization pages 1-2): Nikolay A. Spiridonov, Lily Wong, Patricia M. Zerfas, Matthew F. Starost, Svetlana D. Pack, Cloud P. Paweletz, and Gibbes R. Johnson. Identification and characterization of sstk, a serine/threonine protein kinase essential for male fertility. Molecular and Cellular Biology, 25:4250-4261, May 2005. URL: https://doi.org/10.1128/mcb.25.10.4250-4261.2005, doi:10.1128/mcb.25.10.4250-4261.2005. This article has 155 citations and is from a domain leading peer-reviewed journal.
9. (thiriet2013cytoplasmicproteinserinethreonine pages 11-14): 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.
10. (zhang2020knockoutofstk10 pages 9-10): Lu Zhang, Shun-yuan Lu, R. Guo, Jin-Xia Ma, Lingyun Tang, Yan Shen, Chunling Shen, Li-Ming Lu, Zhu-Gang Wang, Jie Liu, and Hong-Xin Zhang. Knockout of stk10 promotes the migration and invasion of cervical cancer cells. Translational Cancer Research, 9:7079-7090, Nov 2020. URL: https://doi.org/10.21037/tcr-20-1601, doi:10.21037/tcr-20-1601. This article has 7 citations and is from a peer-reviewed journal.
11. (zhang2021stk10knockoutinhibits pages 5-6): Lu Zhang, Shun-Yuan Lu, Rui Guo, Jin-Xia Ma, Ling-Yun Tang, Jin-Jin Wang, Chun-Ling Shen, Li-Ming Lu, Jie Liu, Zhu-Gang Wang, and Hong-Xin Zhang. Stk10 knockout inhibits cell migration and promotes cell proliferation via modulating the activity of erm and p38 mapk in prostate cancer cells. Experimental and Therapeutic Medicine, 22:851, Jun 2021. URL: https://doi.org/10.3892/etm.2021.10283, doi:10.3892/etm.2021.10283. This article has 18 citations and is from a peer-reviewed journal.