1. Phylogeny  
   STK25, also known as YSK1 or SOK1, is classified as a member of the germinal center kinase III (GCKIII) subfamily within the larger grouping of the STE20 family of serine/threonine kinases. Its evolutionary lineage places it in close relation to kinases such as MST3 and MST4, and comprehensive kinome analyses—such as the substrate‐specificity atlas developed by Johnson et al.—cluster STK25 within the motif group that includes MST4, YSK1, MST3, as well as members of the TAO kinase family (johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 4-5). Orthologs of STK25 have been identified throughout the metazoan lineage, underscoring its conservation across species from invertebrates to mammals. This conservation reflects the fundamental roles that STE20 kinases play in diverse signaling networks, thereby situating STK25 as part of an evolutionarily ancient regulatory module that can be traced back to the common ancestors of eukaryotes (li2023cellularimpactsof pages 4-6).
2. Reaction Catalyzed  
   STK25 catalyzes the transfer of a phosphate group from ATP to the hydroxyl group of serine or threonine residues in substrate proteins. In biochemical terms, the reaction can be represented as:  
     ATP + [protein]‑(L‑serine or L‑threonine) → ADP + [protein]‑(L‑serine/threonine‑phosphate) + H⁺  
   This phosphorylation reaction is fundamental to its function as a serine/threonine kinase and is comparable to the reactions catalyzed by other members of the STE20 kinase family (li2023cellularimpactsof pages 4-6).
3. Cofactor Requirements  
   The catalytic activity of STK25 is dependent on typical kinase cofactor requirements. As with most serine/threonine kinases, STK25 utilizes ATP as a phosphate donor, and its activity is supported by divalent metal ions such as Mg²⁺, which are essential for proper substrate binding and phosphoryl transfer. Although detailed cofactor binding studies specific to STK25 are not extensively outlined in the available peer‐reviewed literature, its classification as a conventional serine/threonine kinase implies the standard cofactor requirement of Mg²⁺—a feature that is consistent with other kinases in its family (qiu2023molecularmechanismsinvolved pages 1-3).
4. Substrate Specificity  
   The substrate specificity of STK25 is determined by the precise amino acid sequence surrounding the targeted serine or threonine residue. In the comprehensive atlas of substrate specificities for the human serine/threonine kinome, STK25 was assigned to the YSK1/MST4 cluster, indicating that its substrate recognition properties are similar to those of related GCKIII kinases (johnson2023anatlasof pages 6-7). Functionally, STK25 has been implicated in phosphorylating a range of substrates that participate in the regulation of cell migration, adhesion, and polarity. For example, in cellular contexts where modulation of the cytoskeleton is critical, STK25 has been shown to target proteins involved in the control of actin dynamics and Golgi organization (li2023cellularimpactsof pages 25-26). Although a definitive consensus substrate motif for STK25 remains to be fully characterized in peer‐reviewed analyses, the available data suggest that the local peptide environment—comprising basic or hydrophobic residues—contributes significantly to substrate selection, in line with observations reported for similar STE20 kinases (johnson2023anatlasof pages 2-3).
5. Structure  
   The structural organization of STK25 is characterized by a conserved N-terminal serine/threonine kinase domain followed by a C-terminal regulatory region. The N-terminal domain is responsible for its catalytic activity and contains key functional elements including the ATP-binding motif, the activation loop—which is targeted by autophosphorylation events—and structurally conserved residues that form the hydrophobic spine and contribute to stabilization of the active conformation (li2023cellularimpactsof pages 4-6, li2023cellularimpactsof pages 6-7). In addition, the C-terminal region of STK25 appears to harbor regulatory motifs, such as putative coiled-coil domains, that mediate its dimerization and facilitate interactions with components of the STRIPAK complex. These protein–protein interaction domains are essential for the recruitment of STK25 into multiprotein signaling complexes and thereby determine its subcellular localization, particularly its targeting to Golgi membranes—a localization critical for its role in regulating protein transport events and cell polarity (li2023cellularimpactsof pages 3-4, johnson2023anatlasof pages 4-5). Structural predictions from homology models and comparative analyses with closely related kinases indicate that the core kinase domain maintains the typical bilobal architecture seen in protein kinases, with a smaller N-lobe and a larger C-lobe, and with a flexible activation loop that is modulated by phosphorylation-dependent conformational changes.
6. Regulation  
   Regulation of STK25 is achieved through both post-translational modifications and association with specific regulatory protein complexes. One key regulatory mechanism involves autophosphorylation within its activation loop, which is a common feature among serine/threonine kinases and is necessary for full activation of STK25 (li2023cellularimpactsof pages 4-6). Additionally, STK25 is an integral component of the striatin-interacting phosphatase and kinase (STRIPAK) complex. Within this multiprotein assembly, STK25 interacts with scaffold proteins such as striatins and regulatory molecules like CCM3, which bridge its association with protein phosphatase 2A (PP2A). The PP2A subunit is involved in dephosphorylating kinases within the complex, thereby providing a counterbalancing mechanism for the phosphorylation events driven by STK25 (li2023cellularimpactsof pages 22-23, li2023cellularimpactsof pages 23-25). Moreover, the dynamic assembly of STRIPAK complexes and the concomitant modulation of kinase and phosphatase activities illustrate an important layer of allosteric and conformational regulation that underlies STK25’s activity in response to environmental stress and signaling cues (zhao2023newinsightsinto pages 22-24).
7. Function  
   STK25 functions as an oxidant stress-activated serine/threonine kinase that plays several roles in cellular physiology. Its activity is linked to the cellular response to environmental oxidative stress, which leads to modulation of various downstream signaling pathways responsible for cell adhesion, polarity, and migration. As a component of the STRIPAK complex, STK25 is involved in regulating protein dephosphorylation and phosphorylation events across multiple pathways, including the Hippo, MAPK, nuclear receptor, and cytoskeletal remodeling cascades (li2023cellularimpactsof pages 4-6, li2023cellularimpactsof pages 23-25). In particular, STK25’s localization to the Golgi apparatus allows it to act in the regulation of protein transport events that are critical for maintaining cell morphology and directed motility. Furthermore, by influencing substrates that control cytoskeletal dynamics, STK25 exerts regulatory control over cell cycle progression, differentiation, apoptosis, metabolism, and immune responses. Several studies have linked the functional outputs of STK25 to processes such as epithelial–mesenchymal transition (EMT) and cellular migration, processes that are vital for both normal development and disease states such as tumor progression (li2023cellularimpactsof pages 25-26, ma2023newinsightsinto pages 23-24). The ability of STK25 to integrate stress signals and modulate key regulatory pathways emphasizes its central role in maintaining cellular homeostasis under conditions of both physiological and pathological stress.
8. Other Comments  
   STK25 has attracted attention as a potential target for therapeutic intervention given its involvement in multiple signaling pathways associated with oncogenesis, metabolic disorders, and vascular abnormalities. In several studies, aberrant regulation of STK25 has been linked to cancer progression; this is thought to be mediated through its role in modulating the Hippo pathway and, consequently, cell proliferation and apoptosis (li2023cellularimpactsof pages 23-25, ma2023newinsightsinto pages 23-24). In addition, its function in controlling protein transport and cytoskeletal dynamics suggests that inhibitors designed to modulate STK25 activity could have therapeutic implications in the treatment of diseases marked by altered cell adhesion and migration. Although specific small molecule inhibitors of STK25 remain under investigation, efforts to target components of the STRIPAK complex have provided experimental leads for potential chemical modulators. Overall, the integration of STK25 within the dynamic STRIPAK assembly and its central role in relaying environmental and oxidant stress signals underscore its significance in cellular signal transduction and highlight its relevance in multiple disease contexts (li2023cellularimpactsof pages 11-12, gundogdu2019mob(mpsone pages 21-23).
9. References  
   [1] Li, T. A., Martin, T. A., Lane, J., & Jiang, W. G. “Cellular impacts of striatins and the STRIPAK complex and their roles in the development and metastasis in clinical cancers.” Cancers, Dec 2023, pages 3-4, 4-6, 9-11, 22-23, 23-25, 25-26, 11-12.  
   [2] Johnson, J. L., Yaron, T. M., Huntsman, E. M., Kerelsky, A., Song, J., Regev, A., … & Cantley, L. C. “An atlas of substrate specificities for the human serine/threonine kinome.” Nature, Jan 2023, pages 1-2, 2-3, 4-5, 5-6, 6-6, 6-7, 10-11.  
   [3] Qiu, J., Xiong, J., Jiang, L., Wang, X., Zhang, K., & Yu, H. “Molecular mechanisms involved in regulating protein activity and biological function of MST3.” Cell Division, May 2023, pages 1-3, 3-7, 7-8, 9-10, 10-11.  
   [4] Zhao, Y., Sheldon, M., Sun, Y., & Ma, L. “New insights into YAP/TAZ-TEAD-mediated gene regulation and biological processes in cancer.” Cancers, Nov 2023, pages 22-24.  
   [5] Ma, L. “New insights into YAP/TAZ-TEAD-mediated gene regulation and biological processes in cancer.” Cancers, 2023, pages 23-24.  
   [6] Gundogdu, R., & Hergovich, A. “Mob (Mps one binder) proteins in the Hippo pathway and cancer.” Cells, Jun 2019, pages 21-23.

References

1. (li2023cellularimpactsof pages 4-6): A. Li, Tracy A. Martin, J. Lane, and Wen G Jiang. Cellular impacts of striatins and the stripak complex and their roles in the development and metastasis in clinical cancers (review). Cancers, Dec 2023. URL: https://doi.org/10.3390/cancers16010076, doi:10.3390/cancers16010076. This article has 7 citations and is from a peer-reviewed journal.
2. (johnson2023anatlasof pages 1-2): 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.
3. (johnson2023anatlasof pages 2-3): 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.
4. (johnson2023anatlasof pages 6-7): 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.
5. (li2023cellularimpactsof pages 22-23): A. Li, Tracy A. Martin, J. Lane, and Wen G Jiang. Cellular impacts of striatins and the stripak complex and their roles in the development and metastasis in clinical cancers (review). Cancers, Dec 2023. URL: https://doi.org/10.3390/cancers16010076, doi:10.3390/cancers16010076. This article has 7 citations and is from a peer-reviewed journal.
6. (li2023cellularimpactsof pages 23-25): A. Li, Tracy A. Martin, J. Lane, and Wen G Jiang. Cellular impacts of striatins and the stripak complex and their roles in the development and metastasis in clinical cancers (review). Cancers, Dec 2023. URL: https://doi.org/10.3390/cancers16010076, doi:10.3390/cancers16010076. This article has 7 citations and is from a peer-reviewed journal.
7. (li2023cellularimpactsof pages 25-26): A. Li, Tracy A. Martin, J. Lane, and Wen G Jiang. Cellular impacts of striatins and the stripak complex and their roles in the development and metastasis in clinical cancers (review). Cancers, Dec 2023. URL: https://doi.org/10.3390/cancers16010076, doi:10.3390/cancers16010076. This article has 7 citations and is from a peer-reviewed journal.
8. (li2023cellularimpactsof pages 6-7): A. Li, Tracy A. Martin, J. Lane, and Wen G Jiang. Cellular impacts of striatins and the stripak complex and their roles in the development and metastasis in clinical cancers (review). Cancers, Dec 2023. URL: https://doi.org/10.3390/cancers16010076, doi:10.3390/cancers16010076. This article has 7 citations and is from a peer-reviewed journal.
9. (qiu2023molecularmechanismsinvolved pages 1-3): Jing Qiu, Junzhi Xiong, Lu Jiang, Xinmin Wang, Kebin Zhang, and Hua Yu. Molecular mechanisms involved in regulating protein activity and biological function of mst3. Cell Division, May 2023. URL: https://doi.org/10.1186/s13008-023-00090-x, doi:10.1186/s13008-023-00090-x. This article has 6 citations and is from a peer-reviewed journal.
10. (johnson2023anatlasof pages 4-5): 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.
11. (zhao2023newinsightsinto pages 22-24): Yang Zhao, Marisela Sheldon, Yutong Sun, and Li Ma. New insights into yap/taz-tead-mediated gene regulation and biological processes in cancer. Cancers, 15:5497, Nov 2023. URL: https://doi.org/10.3390/cancers15235497, doi:10.3390/cancers15235497. This article has 24 citations and is from a peer-reviewed journal.
12. (gundogdu2019mob(mpsone pages 21-23): Ramazan Gundogdu and Alexander Hergovich. Mob (mps one binder) proteins in the hippo pathway and cancer. Cells, 8:569, Jun 2019. URL: https://doi.org/10.3390/cells8060569, doi:10.3390/cells8060569. This article has 50 citations and is from a peer-reviewed journal.
13. (li2023cellularimpactsof pages 11-12): A. Li, Tracy A. Martin, J. Lane, and Wen G Jiang. Cellular impacts of striatins and the stripak complex and their roles in the development and metastasis in clinical cancers (review). Cancers, Dec 2023. URL: https://doi.org/10.3390/cancers16010076, doi:10.3390/cancers16010076. This article has 7 citations and is from a peer-reviewed journal.
14. (li2023cellularimpactsof pages 3-4): A. Li, Tracy A. Martin, J. Lane, and Wen G Jiang. Cellular impacts of striatins and the stripak complex and their roles in the development and metastasis in clinical cancers (review). Cancers, Dec 2023. URL: https://doi.org/10.3390/cancers16010076, doi:10.3390/cancers16010076. This article has 7 citations and is from a peer-reviewed journal.
15. (ma2023newinsightsinto pages 23-24): New Insights into YAP/TAZ-TEAD-Mediated Gene Regulation and Biological Processes in Cancer. Cancers 2023, 15, 5497