1. Phylogeny  
   Serine/threonine‐protein kinase LATS1 is an evolutionarily conserved member of the Nuclear Dbf2-related (NDR)/LATS subfamily, which is itself part of the broader AGC group of serine/threonine kinases. LATS1 is found in organisms spanning from lower eukaryotes, such as budding yeast (where related kinases like Dbf2p perform analogous functions in regulating mitotic exit), to invertebrates like Drosophila melanogaster (in which the ortholog is known as Warts or Wts), and onward to vertebrates including mammals. The conservation of LATS1 is underscored by functional rescue studies demonstrating that human LATS1 can compensate for loss-of-function mutations in Drosophila warts, thereby reinforcing its ancient and central role in cell growth and apoptosis (avruch2012proteinkinasesof pages 2-3, bichsel2005mechanismofactivation pages 24-29). Phylogenetic analyses indicate that the ancestral kinase, present in the last eukaryotic common ancestor, underwent divergence and gene duplication during evolution to yield the LATS1 and LATS2 paralogs observed in mammals. These duplications have resulted in proteins that share high degree of conservation in their catalytic kinase domains while often differing in regulatory regions and interacting motifs (furth2017thelats1and pages 1-2, hergovich2013regulationandfunctions pages 1-2). In addition to their roles in the Hippo signaling pathway, LATS kinases are related to other NDR kinases such as NDR1 and NDR2, which together form a tightly regulated network ensuring proper control of cell cycle progression and cell fate determination (chan2005theste20likekinase pages 1-3, furth2017thelats1and pages 2-3). This evolutionary conservation places LATS1 among a core set of kinases that are critical for maintaining homeostasis across eukaryotic life (hergovich2013regulationandfunctions pages 2-4).
2. Reaction Catalyzed  
   The biochemical activity of LATS1 centers on its ability to catalyze the phosphorylation of serine and threonine residues on target proteins, utilizing ATP as the phosphate donor. In chemical terms, the reaction can be summarized as follows:  
     ATP + [protein]-L-serine/threonine → ADP + [protein]-L-serine/threonine phosphate + H⁺  
   This reaction typifies the functional mechanism of serine/threonine kinases in the AGC family and is essential for the post-translational modification of proteins that regulate cell growth, proliferation, and apoptosis (chan2005theste20likekinase pages 8-9). For LATS1 specifically, autophosphorylation events—such as the transfer of the gamma-phosphate from ATP to its own serine 909 residue in the activation loop—are necessary for its full catalytic activation, and these phosphorylation events serve as a molecular switch that promotes conformational adjustments in the kinase domain (chan2007exploringtheregulationa pages 49-53). Furthermore, substrate phosphorylation by LATS1, for instance on the transcription coactivator YAP at serine 127, results in altered subcellular distribution and attenuated oncogenic function by preventing nuclear localization (visser2010latstumorsuppressor pages 2-4). The reaction catalyzed by LATS1 is thus a critical regulatory step in the Hippo pathway, linking extracellular signals to changes in gene expression through reversible protein phosphorylation.
3. Cofactor Requirements  
   The catalytic function of LATS1, like that of virtually all serine/threonine kinases, is dependent on the binding of ATP and the presence of divalent metal ion cofactors. In the case of LATS1, Mg²⁺ ions play a pivotal role in coordinating and stabilizing the binding of the phosphate-bearing ATP molecule within the catalytic cleft of the kinase domain (chan2005theste20likekinase pages 8-9). This metal ion not only aids in proper nucleotide positioning but also facilitates the phosphoryl transfer reaction by neutralizing the negative charges that develop during the formation of the transition state. Experimental evidence consistently indicates that without the appropriate concentration of Mg²⁺, LATS1’s kinase activity is significantly diminished, thus underscoring the indispensability of this cofactor for effective enzymatic function (visser2010latstumorsuppressor pages 4-5, hergovich2009mammalianndrlatsprotein pages 1-2).
4. Substrate Specificity  
   LATS1 exhibits specificity for serine/threonine residues within particular substrate proteins that are central to the regulation of cell proliferation and apoptosis. One primary substrate of LATS1 is YAP (Yes-associated protein), a transcriptional coactivator whose activity is modulated by phosphorylation; phosphorylation at serine 127, in particular, is essential for sequestering YAP in the cytoplasm and preventing its role in oncogenic transcriptional activation (kim2024thelkb1–tssk1baxis pages 9-10). Additionally, LATS1 phosphorylates members of the angiomotin (Amot) protein family. For example, phosphorylation of the Amot130 isoform at serine 175 has been documented, and this modification occurs within a consensus motif (HVRSLS) that is recognized by LATS kinases (adler2013serumdeprivationinhibits pages 2-2). Although the complete consensus substrate motif for LATS1 has not been as exhaustively defined as for some other kinases, the available data suggest that LATS1 favors substrate regions where serine (or threonine) is presented in a specific sequence context that supports efficient recognition and phosphorylation. It is also noteworthy that LATS1 undergoes autophosphorylation events, particularly at serine 909 within the activation loop, which are indicative of its substrate specificity for serine residues and are critical for its functional activation (chan2005theste20likekinase pages 8-9, yu2014integrativeanalysesof pages 61-68).
5. Structure  
   The structural organization of LATS1 reflects a modular architecture characteristic of AGC kinases. Central to its structure is the catalytic kinase domain, which possesses the canonical bilobal fold observed in eukaryotic protein kinases. The N-terminal lobe is mainly composed of β-sheets and is responsible for binding ATP, whereas the larger C-terminal lobe consists predominantly of α-helices and houses the substrate binding site and catalytic machinery (gogl2015thestructureof pages 1-2, hergovich2013regulationandfunctions pages 2-4). Within the kinase domain, the activation loop contains a critical serine residue at position 909; phosphorylation at this residue is necessary for the stabilization of the active conformation of LATS1. In close proximity, a hydrophobic motif featuring threonine 1079 acts as an additional regulatory element, with its phosphorylation facilitating further conformational changes requisite for full activation of the enzyme (chan2005theste20likekinase pages 8-9, chan2007exploringtheregulation pages 45-49).

Beyond the kinase domain, LATS1 contains extended N-terminal regions that include multiple protein–protein interaction modules. Notably, the presence of PPxY motifs in these regions enables binding to WW domain-containing transcriptional regulators, such as YAP, thereby directly influencing substrate specificity and regulatory interactions (visser2010latstumorsuppressor pages 4-5, furth2017thelats1and pages 2-3). Furthermore, a ubiquitin-associated (UBA) domain is embedded in the structure, suggesting potential roles in protein quality control and signaling through ubiquitin-mediated processes. Recent structural studies and computational models, such as those derived from AlphaFold, support a three-dimensional configuration in which these non-catalytic regions extend outward from the core kinase fold and provide platforms for the assembly of multi-protein signaling complexes (hergovich2013regulationandfunctions pages 2-4). This dual organization— a highly conserved catalytic domain coupled with flexible regulatory regions— affords LATS1 the capacity to integrate diverse upstream signals and coordinate precise control over its kinase activity.

1. Regulation  
   The activity of LATS1 is subject to a multifactorial regulatory network that integrates signals from upstream kinases, cofactor interactions, autophosphorylation events, and modulatory protein complexes. A principal regulatory mechanism involves phosphorylation by MST1 and MST2, the mammalian orthologs of Drosophila Hippo. These kinases phosphorylate LATS1 at the hydrophobic motif, particularly targeting threonine 1079, which serves to prime LATS1 for subsequent autophosphorylation at serine 909 within the activation loop (chan2005theste20likekinase pages 8-9, chan2007exploringtheregulationa pages 49-53). This sequential phosphorylation not only activates LATS1 but also induces conformational changes that enhance its substrate affinity and catalytic efficiency. In addition to MST-dependent activation, binding of the adaptor protein MOB1 to a conserved N-terminal regulatory domain in LATS1 facilitates relief of autoinhibition, thereby promoting both MST-mediated phosphorylation and autoactivation (yatim2024therolesof pages 48-52, hergovich2013regulationandfunctions pages 2-4).

Further layers of regulation are provided by other kinases, such as members of the MAP4K family, which have been shown to phosphorylate LATS1 under specific cellular conditions including energy stress, serum deprivation, and cytoskeletal alterations (meng2015map4kfamilykinases pages 3-4, rahmat2018theroleof pages 36-40). These alternative inputs allow LATS1 to function as a convergence point for diverse signaling pathways that ultimately impact cell proliferation and survival. Negative regulatory mechanisms also play a significant role; for instance, serine/threonine phosphatases, including PP2A, remove phosphate groups from LATS1, thereby attenuating its activity and contributing to a dynamic balance between kinase activation and inactivation (ho2011itche3ubiquitina pages 22-28). In some experimental contexts, inhibition of phosphatases using agents such as okadaic acid results in enhanced LATS1 phosphorylation and activity, which corroborates the importance of reversible phosphorylation in the regulation of this kinase (chan2007exploringtheregulation pages 23-28). Collectively, the regulatory circuitry of LATS1 is characterized by tightly coordinated phosphorylation events, specific protein–protein interactions, and controlled dephosphorylation, ensuring that LATS1 activity is modulated in response to the cellular environment.

1. Function  
   LATS1 serves as a central tumor suppressor through its key role in the Hippo signaling pathway, thereby exerting control over cellular proliferation, apoptosis, and organ size. One of its best-characterized functions is the phosphorylation of YAP, a transcriptional coactivator. Phosphorylation of YAP at serine 127 by LATS1 leads to its sequestration in the cytoplasm and subsequent degradation, thereby inhibiting YAP-mediated transcription of pro-proliferative and anti-apoptotic genes (avruch2012proteinkinasesof pages 2-3, visser2010latstumorsuppressor pages 2-4). This regulatory event is critical for restraining cell growth and preventing tumorigenesis. In addition to its role in YAP regulation, LATS1 is implicated in the maintenance of genomic stability and proper cell cycle progression. It has been associated with the regulation of mitotic events and with the control of checkpoints, such as the G1 tetraploidy checkpoint, ensuring that cells with abnormal ploidy are effectively eliminated or arrested (kuhn2021thelats1anda pages 17-20, chan2005theste20likekinase pages 1-3).

Expression of LATS1 is observed across multiple tissue types, and its functional activity is essential for the coordinated execution of growth inhibitory and apoptotic programs. In the context of tissue architecture, LATS1 plays a pivotal role in controlling organ size by limiting the proliferative potential of cells, an effect that is mediated at least in part through its downstream effect on YAP and TAZ (furth2017thelats1and pages 1-2, chan2007exploringtheregulation pages 18-23). Furthermore, LATS1 influences the dynamics of cell–cell contacts and cytoskeletal organization, which contribute to its role in regulating cell polarity and migration. The multifaceted functions of LATS1 are complemented by its ability to interact with other proteins such as MOB1 and hWW45, which serve to integrate upstream signals from MST kinases with downstream transcriptional responses. These interactions help establish LATS1 as an essential node in a network of signaling events that control not only cell proliferation and apoptosis but also tissue homeostasis and regeneration (kuhn2021thelats1anda pages 13-17, chan2007exploringtheregulationa pages 23-28).

1. Other Comments  
   In addition to its central role in the Hippo pathway, several additional aspects of LATS1 biology have garnered attention in both basic and translational research. Dysregulation of LATS1, whether through genetic mutation, altered expression, or impaired regulatory phosphorylation, has been associated with various forms of cancer. Loss or decreased activity of LATS1 results in aberrant activation of YAP, contributing to unchecked cell proliferation and tumor progression, which underscores the critical tumor suppressor function of this kinase (avruch2012proteinkinasesof pages 2-3, kuhn2021thelats1anda pages 17-20). Although specific inhibitors that directly target LATS1 remain under investigation, efforts to modulate its activity are focusing on upstream regulators such as MST1/2 and MAP4K kinases. Moreover, compounds that influence phosphatase activity—thereby preserving LATS1 phosphorylation—are also of interest as potential therapeutic agents for restoring proper Hippo pathway function in cancerous tissues (coffey2021targetingthehippo pages 2-4, ho2011itche3ubiquitina pages 22-28).

The complex regulation of LATS1 by multiple kinases and adaptor proteins also makes it a promising biomarker for disease progression and therapeutic response. In several studies, altered levels of LATS1 expression or its phosphorylation status have been correlated with poor clinical outcomes, highlighting its potential utility in prognostic evaluation (visser2010latstumorsuppressor pages 2-4, furth2017thelats1and pages 7-8). In addition, the presence of distinct regulatory domains—such as the PPxY motifs and the UBA domain—in LATS1 may provide unique opportunities for the development of targeted therapies designed to disrupt pathological protein–protein interactions. These features, combined with the kinase’s evolutionary conservation and central role in mitosis and apoptosis, make LATS1 a subject of considerable interest in both basic science research and clinical oncology.

Overall, LATS1 functions as a key regulatory enzyme that transduces extracellular and intracellular signals into precise phosphorylation events. Through its control over critical targets, most notably YAP, LATS1 orchestrates a broad range of cellular processes that collectively safeguard against uncontrolled cell growth and maintain tissue integrity. The intricate regulatory mechanisms that govern LATS1 activity—including upstream activation by MST and MAP4K kinases, autophosphorylation within the activation loop, and modulation by phosphatases—illustrate the kinase’s capacity to integrate diverse cellular inputs into coordinated responses that are essential for normal development and homeostasis. Its broad expression profile across tissues and its well-defined role in the Hippo pathway underscore its importance as a central tumor suppressor, while ongoing research continues to elucidate novel layers of regulation and potential avenues for therapeutic intervention (furth2017thelats1and pages 7-8, chan2007exploringtheregulation pages 18-23, kuhn2021thelats1anda pages 13-17).

References

1. (avruch2012proteinkinasesof pages 2-3): Joseph Avruch, Dawang Zhou, Julien Fitamant, Nabeel Bardeesy, Fan Mou, and Laura Regué Barrufet. Protein kinases of the hippo pathway: regulation and substrates. Seminars in Cell & Developmental Biology, 23:770-784, Sep 2012. URL: https://doi.org/10.1016/j.semcdb.2012.07.002, doi:10.1016/j.semcdb.2012.07.002. This article has 268 citations.
2. (bichsel2005mechanismofactivation pages 24-29): Samuel J. Bichsel, Rastislav Tamaskovic, Mario R. Stegert, and Brian A. Hemmings. Mechanism of activation of ndr (nuclear dbf2-related) protein kinase by the hmob1 protein. Journal of Biological Chemistry, 279:35228-35235, Aug 2005. URL: https://doi.org/10.1074/jbc.m404542200, doi:10.1074/jbc.m404542200. This article has 114 citations and is from a domain leading peer-reviewed journal.
3. (chan2005theste20likekinase pages 8-9): Eunice H Y Chan, Marjaana Nousiainen, Ravindra B Chalamalasetty, Anja Schäfer, Erich A Nigg, and Herman H W Silljé. The ste20-like kinase mst2 activates the human large tumor suppressor kinase lats1. Oncogene, 24:2076-2086, Jan 2005. URL: https://doi.org/10.1038/sj.onc.1208445, doi:10.1038/sj.onc.1208445. This article has 709 citations and is from a domain leading peer-reviewed journal.
4. (chan2007exploringtheregulation pages 18-23): HY Chan. Exploring the regulation and function of human lats1 and aurora a kinases in mitosis. Unknown journal, 2007.
5. (chan2007exploringtheregulation pages 45-49): HY Chan. Exploring the regulation and function of human lats1 and aurora a kinases in mitosis. Unknown journal, 2007.
6. (chan2007exploringtheregulationa pages 49-53): HY Chan. Exploring the regulation and function of human lats1 and aurora a kinases in mitosis. Unknown journal, 2007.
7. (furth2017thelats1and pages 1-2): Noa Furth and Yael Aylon. The lats1 and lats2 tumor suppressors: beyond the hippo pathway. Cell Death & Differentiation, 24:1488-1501, Jun 2017. URL: https://doi.org/10.1038/cdd.2017.99, doi:10.1038/cdd.2017.99. This article has 248 citations.
8. (furth2017thelats1and pages 2-3): Noa Furth and Yael Aylon. The lats1 and lats2 tumor suppressors: beyond the hippo pathway. Cell Death & Differentiation, 24:1488-1501, Jun 2017. URL: https://doi.org/10.1038/cdd.2017.99, doi:10.1038/cdd.2017.99. This article has 248 citations.
9. (hergovich2009mammalianndrlatsprotein pages 1-2): Alexander Hergovich and Brian A. Hemmings. Mammalian ndr/lats protein kinases in hippo tumor suppressor signaling. BioFactors, Jul 2009. URL: https://doi.org/10.1002/biof.47, doi:10.1002/biof.47. This article has 94 citations and is from a peer-reviewed journal.
10. (hergovich2013regulationandfunctions pages 1-2): Alexander Hergovich. Regulation and functions of mammalian lats/ndr kinases: looking beyond canonical hippo signalling. Cell & Bioscience, Aug 2013. URL: https://doi.org/10.1186/2045-3701-3-32, doi:10.1186/2045-3701-3-32. This article has 122 citations.
11. (hergovich2013regulationandfunctions pages 2-4): Alexander Hergovich. Regulation and functions of mammalian lats/ndr kinases: looking beyond canonical hippo signalling. Cell & Bioscience, Aug 2013. URL: https://doi.org/10.1186/2045-3701-3-32, doi:10.1186/2045-3701-3-32. This article has 122 citations.
12. (ho2011itche3ubiquitina pages 22-28): KC Ho. Itch e3 ubiquitin ligase regulates lats1 tumour suppressor stability. Unknown journal, 2011.
13. (kuhn2021thelats1anda pages 13-17): BJ Kuhn. The lats1 and lats2 tumor suppressor kinases: a comprehensive multilayered ms-based analysis of their functional roles in breast cancer. Unknown journal, 2021.
14. (rahmat2018theroleof pages 36-40): Muhammad Bakhait Rahmat. The role of popx2 in the regulation of hippo pathway. Unknown journal, Nov 2018. URL: https://doi.org/10.32657/10220/46579, doi:10.32657/10220/46579. This article has 0 citations.
15. (visser2010latstumorsuppressor pages 2-4): Stacy Visser and Xiaolong Yang. Lats tumor suppressor: a new governor of cellular homeostasis. Cell Cycle, 9:3892-3903, Oct 2010. URL: https://doi.org/10.4161/cc.9.19.13386, doi:10.4161/cc.9.19.13386. This article has 255 citations and is from a peer-reviewed journal.
16. (visser2010latstumorsuppressor pages 4-5): Stacy Visser and Xiaolong Yang. Lats tumor suppressor: a new governor of cellular homeostasis. Cell Cycle, 9:3892-3903, Oct 2010. URL: https://doi.org/10.4161/cc.9.19.13386, doi:10.4161/cc.9.19.13386. This article has 255 citations and is from a peer-reviewed journal.
17. (yatim2024therolesof pages 48-52): Siti Maryam Jameelah Binte Mohd Yatim. The roles of Homer scaffolding proteins in the regulation of the Hippo signalling pathway. PhD thesis, Nanyang Technological University, 2024. URL: https://doi.org/10.32657/10356/183294, doi:10.32657/10356/183294.
18. (yu2014integrativeanalysesof pages 61-68): T Yu. Integrative analyses of hippo pathway mutations in human cancer genome. Unknown journal, 2014.
19. (adler2013serumdeprivationinhibits pages 2-2): Jacob J. Adler, Derrick E. Johnson, Brigitte L. Heller, Lauren R. Bringman, William P. Ranahan, Michael D. Conwell, Yang Sun, Andy Hudmon, and Clark D. Wells. Serum deprivation inhibits the transcriptional co-activator yap and cell growth via phosphorylation of the 130-kda isoform of angiomotin by the lats1/2 protein kinases. Proceedings of the National Academy of Sciences, 110:17368-17373, Oct 2013. URL: https://doi.org/10.1073/pnas.1308236110, doi:10.1073/pnas.1308236110. This article has 174 citations.
20. (chan2005theste20likekinase pages 1-3): Eunice H Y Chan, Marjaana Nousiainen, Ravindra B Chalamalasetty, Anja Schäfer, Erich A Nigg, and Herman H W Silljé. The ste20-like kinase mst2 activates the human large tumor suppressor kinase lats1. Oncogene, 24:2076-2086, Jan 2005. URL: https://doi.org/10.1038/sj.onc.1208445, doi:10.1038/sj.onc.1208445. This article has 709 citations and is from a domain leading peer-reviewed journal.
21. (chan2007exploringtheregulation pages 23-28): HY Chan. Exploring the regulation and function of human lats1 and aurora a kinases in mitosis. Unknown journal, 2007.
22. (chan2007exploringtheregulationa pages 23-28): HY Chan. Exploring the regulation and function of human lats1 and aurora a kinases in mitosis. Unknown journal, 2007.
23. (coffey2021targetingthehippo pages 2-4): Kelly Coffey. Targeting the hippo pathway in prostate cancer: what’s new? Cancers, 13:611, Feb 2021. URL: https://doi.org/10.3390/cancers13040611, doi:10.3390/cancers13040611. This article has 15 citations and is from a peer-reviewed journal.
24. (furth2017thelats1and pages 7-8): Noa Furth and Yael Aylon. The lats1 and lats2 tumor suppressors: beyond the hippo pathway. Cell Death & Differentiation, 24:1488-1501, Jun 2017. URL: https://doi.org/10.1038/cdd.2017.99, doi:10.1038/cdd.2017.99. This article has 248 citations.
25. (gogl2015thestructureof pages 1-2): Gergő Gógl, Kyle D. Schneider, Brian J. Yeh, Nashida Alam, Alex N. Nguyen Ba, Alan M. Moses, Csaba Hetényi, Attila Reményi, and Eric L. Weiss. The structure of an ndr/lats kinase–mob complex reveals a novel kinase–coactivator system and substrate docking mechanism. PLOS Biology, 13:e1002146, May 2015. URL: https://doi.org/10.1371/journal.pbio.1002146, doi:10.1371/journal.pbio.1002146. This article has 52 citations and is from a highest quality peer-reviewed journal.
26. (kim2024thelkb1–tssk1baxis pages 9-10): Cho-Long Kim, Su-Bin Lim, Sue-Hee Choi, Dong Hyun Kim, Ye Eun Sim, Eun-Hye Jo, Keeeun Kim, Keesook Lee, Hee-Sae Park, Su Bin Lim, Li-Jung Kang, Han-Sol Jeong, Youngsoo Lee, Carsten G. Hansen, and Jung-Soon Mo. The lkb1–tssk1b axis controls yap phosphorylation to regulate the hippo–yap pathway. Cell Death & Disease, Jan 2024. URL: https://doi.org/10.1038/s41419-024-06465-4, doi:10.1038/s41419-024-06465-4. This article has 3 citations.
27. (kuhn2021thelats1anda pages 17-20): BJ Kuhn. The lats1 and lats2 tumor suppressor kinases: a comprehensive multilayered ms-based analysis of their functional roles in breast cancer. Unknown journal, 2021.
28. (meng2015map4kfamilykinases pages 3-4): Zhipeng Meng, Toshiro Moroishi, Violaine Mottier-Pavie, Steven W. Plouffe, Carsten G. Hansen, Audrey W. Hong, Hyun Woo Park, Jung-Soon Mo, Wenqi Lu, Shicong Lu, Fabian Flores, Fa-Xing Yu, Georg Halder, and Kun-Liang Guan. Map4k family kinases act in parallel to mst1/2 to activate lats1/2 in the hippo pathway. Nature Communications, Oct 2015. URL: https://doi.org/10.1038/ncomms9357, doi:10.1038/ncomms9357. This article has 563 citations and is from a highest quality peer-reviewed journal.