## Phylogeny

LATS2 is a serine/threonine kinase that belongs to the AGC kinase family (furth2017thelats1and pages 1-2, furth2017thelats1and pages 10-11, yu2015mutationanalysisof pages 3-5). Most sources classify it within the Dbf2-related or Nuclear Dbf-2-related (NDR) kinase subfamily, along with LATS1 and NDR1/2, based on the kinome classification by Manning et al. (furth2017thelats1and pages 1-2, furth2017thelats1and pages 2-3, furth2017thelats1and pages 3-4, huntoon2010heatshockprotein pages 1-2, yu2015mutationanalysisof pages 3-5). However, some sources place it in the STE group, specifically the STE20 family (furth2017thelats1and pages 3-3, johnson2023anatlasof pages 4-4, johnson2023anatlasof pages 7-7). The kinase family is conserved in mammals and has a Drosophila ortholog named Warts (he2016newinsightsinto pages 1-2).

## Reaction Catalyzed

The kinase catalyzes the ATP-dependent phosphorylation of protein substrates on serine or threonine residues (furth2017thelats1and pages 1-2, furth2017thelats1and pages 3-3, toloczko2017deubiquitinatingenzymeusp9x pages 29-31). ATP + a [protein]-L-serine = ADP + a [protein]-L-serine phosphate (furth2017thelats1and pages 1-2, furth2017thelats1and pages 3-3). ATP + a [protein]-L-threonine = ADP + a [protein]-L-threonine phosphate (furth2017thelats1and pages 1-2, furth2017thelats1and pages 3-3).

## Cofactor Requirements

LATS2 catalytic activity is dependent on divalent cations, with Mg2+ being the physiologically relevant cofactor required to coordinate ATP binding (furth2017thelats1and pages 1-2, furth2017thelats1and pages 2-3, hoa2016thecharacterisationof pages 1-2).

## Substrate Specificity

LATS2 phosphorylates serine or threonine residues within specific consensus motifs (furth2017thelats1and pages 1-2). One identified consensus motif is HxRxxS/T (furth2017thelats1and pages 9-10). The substrate motif is also characterized by a hydrophobic residue at the +1 position, consistent with findings from Johnson et al. (furth2017thelats1and pages 3-3). In addition to phosphorylation site motifs, LATS2 recognizes substrates such as YAP and TAZ through interaction with PPxY motifs present on the target proteins (furth2017thelats1and pages 2-3, yu2015mutationanalysisof pages 3-5).

## Structure

LATS2 contains a C-terminal kinase domain and an N-terminal regulatory region (furth2017thelats1and pages 2-3, hoa2016thecharacterisationof pages 1-2). The N-terminus contains a proline-rich domain, a PAPA repeat, an evolutionarily conserved ubiquitin-associated (UBA) domain, one PPxY motif, and LATS conserved domains LCD1 and LCD2 (furth2017thelats1and pages 2-3, furth2017thelats1and pages 3-3, yu2015mutationanalysisof pages 2-3, yu2015mutationanalysisof pages 3-5). LCD1 contains a Conserved N-terminal Motif (CNM; aa 71-88) (yu2015mutationanalysisof pages 2-3). The serine/threonine kinase catalytic domain (aa ~705-1010) contains conserved motifs for ATP binding and catalysis, such as the GxGxxGxV loop, DxKxxN, and DFG motif (furth2017thelats1and pages 3-4, yu2015mutationanalysisof pages 3-5). Key regulatory features within the kinase domain include an activation loop and a hydrophobic motif (furth2017thelats1and pages 1-2, furth2017thelats1and pages 3-4). An insert between subdomains VII and VIII of the kinase domain may exert autoinhibitory control (yu2015mutationanalysisof pages 3-5). According to the AlphaFold model (UniProt Q9NRM7), LATS2 has a bilobed kinase domain with an active site cleft (furth2017thelats1and pages 1-2). The model confirms a spatial architecture with the conserved kinase domain at the C-terminus, while the N-terminal regulatory motifs are positioned separately from the catalytic core (furth2017thelats1and pages 2-3).

## Regulation

LATS2 activity is regulated by post-translational modifications and protein-protein interactions (furth2017thelats1and pages 3-3). Phosphorylation Activation of LATS2 requires phosphorylation by upstream kinases (furth2017thelats1and pages 1-2). The MST1/2 kinases phosphorylate and activate LATS2 at key residues within the hydrophobic motif (e.g., T1079, T1041) and the activation loop (e.g., S909, S872), a process facilitated by the MOB1 regulatory partner (furth2017thelats1and pages 1-2, furth2017thelats1and pages 2-3, he2016newinsightsinto pages 1-2, hoa2016thecharacterisationof pages 1-2, yu2015mutationanalysisof pages 3-5). LATS2 can also be activated by other kinases, including MAP4Ks and PKA (furth2017thelats1and pages 2-3). During mitosis, Aurora A phosphorylates LATS2 at S380, and it is also a substrate for Aurora B and CDC2 (at S613) (furth2017thelats1and pages 10-11, yu2015mutationanalysisof pages 2-3). In response to DNA damage, LATS2 is phosphorylated by CHK1/2 at sites including S408 and S446 (furth2017thelats1and pages 2-3, yu2015mutationanalysisof pages 2-3). The phosphatase PP2A may counteract LATS2 phosphorylation (furth2017thelats1and pages 2-3). Ubiquitination LATS2 stability is modulated by ubiquitination. It is targeted for degradation by E3 ubiquitin ligases including Itch, WWP1, NEDD4, and SIAH2 (furth2017thelats1and pages 3-3, furth2017thelats1and pages 3-4). The CRL4-DCAF1 E3 ligase complex oligoubiquitinates LATS2, causing inactivation without degradation (furth2017thelats1and pages 3-4). The deubiquitinating enzyme USP9X counteracts this by stabilizing LATS2 protein levels (toloczko2017deubiquitinatingenzymeusp9x pages 29-31, toloczko2017deubiquitinatingenzymeusp9x pages 22-24). Protein Interactions MOB1 is an essential regulatory partner that binds to LATS2 to facilitate its activation by MST1/2 (furth2017thelats1and pages 1-2, furth2017thelats1and pages 12-12). LATS2 stability is dependent on the chaperone HSP90, making it an HSP90 client protein (huntoon2010heatshockprotein pages 5-7). The scaffold protein KIBRA can also stabilize LATS2 (furth2017thelats1and pages 3-4).

## Function

LATS2 is a core component of the Hippo signaling pathway and acts as a tumor suppressor by regulating cell proliferation, apoptosis, and organ size (furth2017thelats1and pages 1-2, huntoon2010heatshockprotein pages 1-2). It is expressed in various tissues, with high levels in the gastrointestinal tract and brain (furth2017thelats1and pages 9-10). It localizes to the cytoplasm, nucleus, plasma membrane, and centrosomes (furth2017thelats1and pages 6-7). Upstream kinases include MST1/2, Aurora A/B, CHK1/2, MAP4Ks, and PKA (furth2017thelats1and pages 2-3, furth2017thelats1and pages 10-11, yu2015mutationanalysisof pages 2-3). Its primary downstream substrates are the transcriptional coactivators YAP1 and TAZ (furth2017thelats1and pages 1-2). Upon activation, LATS2 phosphorylates YAP1 and TAZ, which inhibits their translocation into the nucleus, leading to their cytoplasmic retention via 14-3-3 protein binding or their proteasomal degradation (he2016newinsightsinto pages 1-2, he2016newinsightsinto pages 4-6). This suppression of YAP/TAZ nuclear activity inhibits oncogenic transcriptional programs (furth2017thelats1and pages 1-2). Beyond the Hippo pathway, LATS2 regulates the cell cycle by inhibiting Cyclin E/CDK2 to restrain the G1/S transition and interacts with CDC25B and CDC26 during mitosis (furth2017thelats1and pages 7-8). It also promotes apoptosis by downregulating BCL-xL and BCL2 (furth2017thelats1and pages 7-8). Nuclear LATS2 enhances p53 activity, suppresses β-catenin signaling, and represses steroid hormone receptor activity (furth2017thelats1and pages 6-7, furth2017thelats1and pages 7-8).

## Other Comments

Deregulation of LATS2 is implicated in multiple cancers, including breast, lung, hepatic, pancreatic, and head and neck cancers, as well as malignant pleural mesothelioma (MPM) (furth2017thelats1and pages 12-12, tranchant2017cooccurringmutationsof pages 12-16). Downregulation via promoter hypermethylation or miRNA repression correlates with aggressive tumor phenotypes (furth2017thelats1and pages 12-12). Somatic mutations are found in several cancers, with higher frequencies in uterine corpus endometrial carcinoma (5.2%) and stomach adenocarcinoma (4.1%) (yu2015mutationanalysisof pages 1-2). Mutations are concentrated in the kinase domain and impair its tumor suppressor function (yu2015mutationanalysisof pages 1-2). Specific cancer-associated mutations that result in loss of function include p.R958H in MPM, G909R, and C953\* (tranchant2017cooccurringmutationsof pages 12-16, yu2015mutationanalysisof pages 3-5). The P72L mutation impairs interaction with Merlin/NF2, which is required for activation (yu2015mutationanalysisof pages 2-3). Genetic deletion of Lats2 is embryonically lethal in mice (furth2017thelats1and pages 1-2).

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