## Phylogeny

LATS2 is a serine/threonine protein kinase of the AGC super-family. Most sources place it in the NDR/Dbf2-related subfamily together with LATS1 and NDR1/2 (Furth & Aylon, 2017; Yu et al., 2015). A minority of classifications assign it to the STE20 group (Johnson et al., 2023). The family is conserved throughout mammals and has the Drosophila orthologue Warts (He et al., 2016).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Furth & Aylon, 2017).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Furth & Aylon, 2017; Hoa et al., 2016).

## Substrate Specificity

LATS2 phosphorylates Ser/Thr residues within the HxRxxS/T consensus, with a hydrophobic residue often found at the +1 position (Furth & Aylon, 2017; Johnson et al., 2023). Recognition of major physiological substrates YAP and TAZ is assisted by binding to their PPxY motifs (Furth & Aylon, 2017; Yu et al., 2015).

## Structure

The protein comprises an N-terminal regulatory region and a C-terminal bilobed kinase domain (~aa 705–1010). Regulatory segments include a proline-rich stretch, PAPA repeat, UBA domain, a single PPxY motif, and two LATS-conserved domains (LCD1 containing the conserved N-terminal motif, and LCD2) (Furth & Aylon, 2017; Yu et al., 2015). The kinase core contains canonical motifs (GxGxxGxV loop, DxKxxN, DFG), an activation loop and a hydrophobic motif; an insert between sub-domains VII and VIII may mediate autoinhibition (Yu et al., 2015). AlphaFold modelling (UniProt Q9NRM7) confirms the separated regulatory N-terminus and compact catalytic C-terminus (Furth & Aylon, 2017).

## Regulation

• Phosphorylation – Activated mainly by MST1/2 in a MOB1-dependent manner at hydrophobic-motif (T1079/T1041) and activation-loop (S909/S872) sites. Additional activating inputs come from MAP4Ks, PKA, and mitotic kinases Aurora A (S380) and Aurora B/CDC2 (S613). DNA damage triggers CHK1/2-mediated phosphorylation (S408/S446). PP2A can oppose these phosphorylations (Furth & Aylon, 2017; He et al., 2016; Hoa et al., 2016).  
• Ubiquitination – Itch, WWP1, NEDD4, and SIAH2 promote proteasomal degradation; CRL4-DCAF1 polyubiquitinates and inactivates LATS2 without degrading it. USP9X removes ubiquitin chains and stabilises the kinase (Furth & Aylon, 2017; Toloczko et al., 2017).  
• Protein interactions – MOB1 binds and promotes activation; HSP90 acts as a chaperone; KIBRA stabilises the kinase (Furth & Aylon, 2017; Huntoon et al., 2010).

## Function

Central tumour-suppressive kinase of the Hippo pathway. Activated LATS2 phosphorylates YAP1 and TAZ, leading to their cytoplasmic retention via 14-3-3 binding or proteasomal degradation, thereby limiting pro-oncogenic transcription (Furth & Aylon, 2017; He et al., 2016). Additional roles include:  
• Cell-cycle control – inhibition of Cyclin E/CDK2 and interaction with CDC25B/CDC26 to restrain G1/S and regulate mitosis (Furth & Aylon, 2017).  
• Apoptosis – suppression of BCL-xL and BCL2 (Furth & Aylon, 2017).  
• Nuclear functions – enhancement of p53 activity, repression of β-catenin signalling and steroid hormone receptor activity (Furth & Aylon, 2017).  
Expression is broad with elevated levels in gastrointestinal tract and brain, and the protein localises to cytoplasm, nucleus, plasma membrane and centrosomes (Furth & Aylon, 2017). Upstream kinases include MST1/2, Aurora A/B, CHK1/2, MAP4Ks and PKA; principal downstream substrates are YAP1 and TAZ (Furth & Aylon, 2017).

## Other Comments

LATS2 down-regulation (promoter hypermethylation, miRNA repression) or loss-of-function mutations are frequent in multiple cancers such as breast, lung, liver, pancreas, head-and-neck and malignant pleural mesothelioma (Furth & Aylon, 2017; Tranchant et al., 2017). Somatic mutations cluster in the kinase domain (e.g., p.R958H, G909R, C953\*) and diminish tumour-suppressor activity; P72L disrupts interaction with Merlin/NF2 (Yu et al., 2015). Complete Lats2 deletion is embryonically lethal in mice (Furth & Aylon, 2017).

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