Serine/threonine-protein kinase LATS1 – Comprehensive Nomenclature and Functional Profile

## Phylogeny

• AGC kinase group, NDR/LATS subfamily; ~85 % catalytic-domain identity with LATS2 (furth2017thelats1and pages 2-3).  
• Orthologs: Mus musculus Lats1, Rattus norvegicus Lats1, Xenopus laevis lats1, Danio rerio lats1, Drosophila melanogaster Warts, Caenorhabditis elegans Wts-1, Saccharomyces cerevisiae Dbf2/Dbf20 (furth2017thelats1and pages 1-2, visser2010latstumorsuppressor pages 1-2).  
• Human LATS1 rescues Drosophila Warts loss, confirming functional conservation (hergovich2013regulationandfunctions pages 1-2).

## Reaction Catalyzed

ATP + [protein] ⇌ ADP + [protein]-O-phospho-Ser/Thr (hao2008tumorsuppressorlats1 pages 1-1).

## Cofactor Requirements

No explicit divalent-cation requirement is reported in the available literature (furth2017thelats1and pages 2-3).

## Substrate Specificity

• Prefers H-X-(R/H/K)-X-X-S/T motif; His-5 is critical for YAP/TAZ phosphorylation (hao2008tumorsuppressorlats1 pages 11-12).  
• Also phosphorylates basic R/K-X-X-S/T motifs (hergovich2013regulationandfunctions pages 5-6).  
• Shows serine preference at the phospho-acceptor site (hao2008tumorsuppressorlats1 pages 11-12).

## Structure

Domain organisation  
– UBA domain (furth2017thelats1and pages 2-3).  
– Proline-rich P-stretch (visser2010latstumorsuppressor pages 2-4).  
– Dual PPxY motifs (furth2017thelats1and pages 2-3).  
– MOB-binding NTR domain, residues 621-703 (kim2016structuralbasisfor pages 8-10).  
– Kinase domain 705-1010 with VII–VIII insert (visser2010latstumorsuppressor pages 2-4).  
– Hydrophobic motifs 845-857 and 905-915 plus NFD/Thr1079 (furth2017thelats1and pages 3-4, chan2005theste20likekinase pages 1-3).

3D information  
• MOB1–LATS1 NTR complexes, PDB 5BRK/5BKK, show bi-helical NTR engaging MOB1 (kim2016structuralbasisfor pages 8-10).  
• AlphaFold model AF-O95835-F1 captures full AGC fold (kim2016structuralbasisfor pages 14-15).  
• Long activation segment analogous to NDR1 auto-inhibition (xiong2018structuralbasisfor pages 1-3).  
• Regulatory spine includes Ser909 (A-loop) and Thr1079 (HM) aligned by the C-helix (chan2005theste20likekinase pages 1-3).

## Regulation

Phosphorylation  
– MST1/2 prime Ser909 and Thr1079 (hergovich2013regulationandfunctions pages 2-4, furth2017thelats1and pages 2-3).  
– MOB1 binding triggers auto-phosphorylation at Ser674 and Ser1049 (furth2017thelats1and pages 2-3).  
– CDK1/CDC2 phosphorylates Thr490 and Ser613 in mitosis (furth2017thelats1and pages 3-4).  
– NUAK1 targets Ser464, decreasing stability (furth2017thelats1and pages 3-4).  
– MAP4Ks, PKA, CHK1/2 and ATR provide alternative inputs (furth2017thelats1and pages 2-3).  
– PP2A removes Ser909/Thr1079 phosphates (furth2017thelats1and pages 2-3).

Ubiquitination  
– NEDD4, ITCH and WWP1 poly-ubiquitinate Lys383, Lys527, Lys633, Lys968 (furth2017thelats1and pages 3-4).

Protein-protein control  
– Phospho-MOB1 binding to NTR is indispensable for activation (hergovich2009mammalianndrlatsprotein pages 1-2).  
– KIBRA and DCAF1 modulate activation and stability (furth2017thelats1and pages 3-3).

## Function

Expression/localisation  
– Highest expression in ovary; broad ectodermal distribution (visser2010latstumorsuppressor pages 4-5).  
– Centrosomal during interphase, spindle-associated in mitosis; cytoplasmic and nuclear pools observed (furth2017thelats1and pages 2-3, visser2010latstumorsuppressor pages 4-5).

Upstream regulators  
– MST1/2-SAV1, MOB1A/B (chan2005theste20likekinase pages 1-3, hergovich2013regulationandfunctions pages 2-4).  
– MAP4Ks, PKA, CHK1/2, ATR (furth2017thelats1and pages 2-3, meng2015map4kfamilykinases pages 3-4).  
– Merlin/NF2 for membrane recruitment (hergovich2013regulationandfunctions pages 1-2).

Downstream substrates  
– YAP1 and WWTR1/TAZ (hao2008tumorsuppressorlats1 pages 12-13, hergovich2013regulationandfunctions pages 5-6).  
– Aurora B (furth2017thelats1and pages 7-8).  
– MYPT1 Ser445 (hergovich2013regulationandfunctions pages 5-6).  
– RAF1 Ser259 (furth2017thelats1and pages 7-8).  
– Regulates Cyclin E/CDK2 and tetraploidy checkpoint (furth2017thelats1and pages 7-8).

Pathway  
Core effector kinase of the Hippo cascade governing organ size, apoptosis and contact inhibition (furth2017thelats1and pages 2-3, hergovich2013regulationandfunctions pages 1-2).

## Inhibitors

TRULI, an ATP-competitive inhibitor of LATS kinases, has been described in cellular studies (furth2017thelats1and pages 1-2).

## Other Comments

• LOH at 6q24-q25 in breast, liver and lung cancers (visser2010latstumorsuppressor pages 2-4).  
• Somatic mutation rate ~1.1 %; enriched in stomach, endometrial and bladder tumours (yu2015mutationanalysisof pages 1-2).  
• Function-impairing mutations I81M, R82Q, T255N, S336G, R744Q, N1038H cluster in critical domains (yu2015mutationanalysisof pages 2-3, yu2015mutationanalysisof pages 3-5).  
• Promoter hypermethylation and E3-mediated degradation contribute to down-regulation in cancer (furth2017thelats1and pages 3-4).

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