## Phylogeny

Member of the AGC kinase group, NDR/LATS sub-family; the catalytic domain shares ~85 % identity with LATS2 (Furth & Aylon, 2017). Orthologues span metazoans and fungi, including Mus musculus Lats1, Drosophila melanogaster Warts and Saccharomyces cerevisiae Dbf2/Dbf20 (Furth & Aylon, 2017; Visser & Yang, 2010). Human LATS1 functionally rescues Drosophila Warts loss, underscoring deep evolutionary conservation (Hergovich, 2013).

## Reaction Catalyzed

ATP + [protein] ⇌ ADP + [protein]-O-phospho-Ser/Thr (Hao et al., 2008).

## Cofactor Requirements

No divalent-cation requirement has been reported (Furth & Aylon, 2017).

## Substrate Specificity

Prefers an H-X-(R/H/K)-X-X-S/T consensus; the His at −5 is critical for efficient YAP/TAZ phosphorylation. Also accepts basic R/K-X-X-S/T motifs and displays an overall serine bias at the phospho-acceptor position (Hao et al., 2008; Hergovich, 2013).

## Structure

N-terminal UBA domain, proline-rich P-stretch, dual PPxY motifs, MOB-binding NTR (residues 621–703), kinase domain (705–1010) with a VII–VIII insert, and C-terminal hydrophobic motifs (845-857, 905-915) plus an NFD segment containing Thr1079 (Furth & Aylon, 2017; Visser & Yang, 2010). Crystal structures of MOB1-bound NTR (PDB 5BRK, 5BKK) reveal a bi-helical interface (Kim et al., 2016). An AlphaFold model depicts the full AGC fold; a long activation segment resembles the auto-inhibited NDR1 conformation (Xiong et al., 2018). The regulatory spine aligns Ser909 (activation loop) with Thr1079 (hydrophobic motif) (Chan et al., 2005).

## Regulation

Phosphorylation: MST1/2 prime Ser909 and Thr1079; MAP4Ks, PKA, CHK1/2 and ATR provide additional inputs (Furth & Aylon, 2017; Hergovich, 2013). MOB1 binding promotes auto-phosphorylation at Ser674 and Ser1049 (Furth & Aylon, 2017). CDK1 phosphorylates Thr490 and Ser613 in mitosis; NUAK1 phosphorylates Ser464, lowering stability (Furth & Aylon, 2017). PP2A de-phosphorylates Ser909/Thr1079 (Furth & Aylon, 2017).  
Ubiquitination: NEDD4, ITCH and WWP1 poly-ubiquitinate Lys383, Lys527, Lys633 and Lys968 (Furth & Aylon, 2017).  
Protein interactions: Phospho-MOB1 binding to the NTR is indispensable for activation; KIBRA and DCAF1 further modulate activity and turnover (Hergovich & Hemmings, 2009; Furth & Aylon, 2017).

## Function

Expression/localisation: Highest expression in ovary; broadly distributed in ectoderm-derived tissues (Visser & Yang, 2010). Localises to centrosomes during interphase, spindle microtubules in mitosis, and exists in both cytoplasmic and nuclear pools (Furth & Aylon, 2017).  
Upstream regulators: MST1/2-SAV1 complexes, MOB1A/B, MAP4Ks, PKA, CHK1/2, ATR and Merlin/NF2 (Chan et al., 2005; Meng et al., 2015; Hergovich, 2013).  
Downstream substrates: YAP1, WWTR1/TAZ, Aurora B, MYPT1 Ser445, RAF1 Ser259 and regulators of the Cyclin E/CDK2 tetraploidy checkpoint (Hao et al., 2008; Furth & Aylon, 2017; Hergovich, 2013).  
Pathway: Core effector kinase of the Hippo cascade controlling organ size, apoptosis and contact inhibition (Furth & Aylon, 2017; Hergovich, 2013).

## Inhibitors

TRULI is reported as an ATP-competitive inhibitor of LATS kinases in cell-based studies (Furth & Aylon, 2017).

## Other Comments

Loss of heterozygosity at 6q24-q25 is frequent in breast, liver and lung cancers (Visser & Yang, 2010). Somatic mutation rate is ~1.1 %, with recurrent functional mutations (I81M, R82Q, T255N, S336G, R744Q, N1038H) clustering in key domains (Yu et al., 2015). Promoter hypermethylation and enhanced ubiquitin-mediated degradation also dampen LATS1 levels in tumours (Furth & Aylon, 2017).

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