## Phylogeny

– Member of the STE20 kinase group, Germinal Center Kinase-II (GCK-II) subfamily (galan2016mst1mst2proteinkinases pages 1-3).  
– Closest human paralog: STK3/MST2, ≈75 % overall identity (fitamant2013mst12andother pages 33-36).  
– Orthologs: Mus musculus Stk4, Drosophila melanogaster Hippo (Hpo), Caenorhabditis elegans cst-1, Saccharomyces cerevisiae Ste20 (ling2008biosignalingofmammalian pages 1-2, avruch2012proteinkinasesof pages 2-3).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (record2010structuralcomparisonof pages 4-6).

## Cofactor Requirements

Requires Mg²⁺ for catalysis; Mn²⁺, Zn²⁺ or Co²⁺ can substitute in vitro (delpire2009themammalianfamily pages 8-9, record2010structuralcomparisonof pages 3-4).

## Substrate Specificity

Consensus motif: Φ-X-T-Φ-K/R-K/R (Φ = hydrophobic or aromatic), preferring threonine at the phospho-acceptor and basic residues at +2/+3 (miller2019comprehensiveprofilingof pages 3-5, miller2019comprehensiveprofilingof pages 28-29).  
Experimentally verified sites:  
– MOB1A/B Thr35, Thr12 (avruch2012proteinkinasesof pages 2-3).  
– LATS1 Thr1079, LATS2 Thr1041 (galan2016mst1mst2proteinkinases pages 9-11).  
– FOXO3 Ser207 (delpire2009themammalianfamily pages 7-9).  
– Histone H2B Ser14 (ling2008biosignalingofmammalian pages 8-9).  
– Ezrin Thr567 (record2010structuralcomparisonof pages 10-11).

## Structure

Domain organisation: N-terminal kinase domain (aa 30-281) containing Lys59 (ATP anchor), HRD catalytic triad and DFG motif; central autoinhibitory linker with caspase sites Asp326 and Asp349; C-terminal SARAH coiled-coil (aa 432-480) mediating homo-/heterodimerisation (unknownauthors2014integrativeanalysesof pages 68-73, fitamant2013mst12andother pages 33-36).  
Crystal structure PDB 3COM shows an active conformation with Lys59-Glu73 salt bridge and diphosphorylated Thr177/Thr183 activation loop (record2010structuralcomparisonof pages 4-6).  
Face-to-face dimers exchange activation loops for trans-autophosphorylation (record2010structuralcomparisonof pages 6-8).  
AlphaFold model PDB 5B7B confirms the canonical bilobal fold and SARAH placement (galan2016mst1mst2proteinkinases pages 13-14).

## Regulation

Post-translational modifications  
– Autophosphorylation at Thr183 activates the kinase (unknownauthors2017regulationofhippo pages 26-29).  
– TAO kinases phosphorylate the activation loop to augment activity (galan2016mst1mst2proteinkinases pages 9-11).  
– PP2A-STRIPAK complex and PTPN14 bind/dephosphorylate MST1 to inhibit signalling (galan2016mst1mst2proteinkinases pages 9-11, eden2024mst4anovel pages 17-18).  
– Oxidation-induced SARAH dimerisation enhances activity under oxidative stress (galan2016mst1mst2proteinkinases pages 9-11).  
– Akt phosphorylation at Thr120 and JNK phosphorylation at Ser82 attenuate activity (unknownauthors2014integrativeanalysesof pages 68-73).  
– Abl/Src phosphorylation at Tyr433 modulates stability and neuronal apoptosis (galan2016mst1mst2proteinkinases pages 9-11).  
– Caspase-3 cleavage at Asp326/Asp349 produces a 34 kDa fragment that translocates to the nucleus and is constitutively active (delpire2009themammalianfamily pages 7-9).  
Protein-protein interactions  
– SARAH-mediated association with SAV1 promotes dimerisation and activation; RASSF isoforms or STRIPAK limit activation (fitamant2013mst12andother pages 33-36, galan2016mst1mst2proteinkinases pages 3-4).

## Function

Expression: ubiquitous, highest in lymphoid tissues, heart, kidney and placenta (avruch2012proteinkinasesof pages 2-3, record2010structuralcomparisonof pages 3-4).  
Upstream inputs: Rap1-RAPL pathway, oxidative stress, TAO kinases, Akt, c-Abl/Src (ling2008biosignalingofmammalian pages 8-9, galan2016mst1mst2proteinkinases pages 9-11).  
Downstream cascade: phosphorylates MOB1A/B and activates LATS1/2 and NDR1/2; these kinases phosphorylate YAP/TAZ to restrict proliferation and promote apoptosis (avruch2012proteinkinasesof pages 2-3, hamilton2013hippopathwayand pages 33-36).  
Additional substrates: FOXO3 (nuclear translocation), histone H2B (chromatin condensation), Ezrin (cell polarity) (delpire2009themammalianfamily pages 7-9, record2010structuralcomparisonof pages 10-11).  
Physiological roles: organ size control, stress-induced apoptosis, maintenance of naïve T-cell homeostasis, suppression of cardiac hypertrophy (avruch2012proteinkinasesof pages 2-3, ling2008biosignalingofmammalian pages 8-9).

## Inhibitors

– XMU-MP-1: selective MST1/2 inhibitor, IC₅₀ ≈ 71 nM (galan2016mst1mst2proteinkinases pages 13-14).  
– Broad-spectrum ATP-competitive ligands such as staurosporine and quinazoline derivatives bind the active site in crystal complexes (record2010structuralcomparisonof pages 4-6, record2010structuralcomparisonof pages 8-10).

## Other Comments

Biallelic loss-of-function mutations cause autosomal-recessive combined immunodeficiency with profound naïve T-cell lymphopenia (galan2016mst1mst2proteinkinases pages 13-14, avruch2012proteinkinasesof pages 2-3).  
Somatic cancer mutations concentrate in the kinase domain; K59R abolishes ATP binding, V184M and R181Q impair Thr183 autophosphorylation, D326N/D349N confer caspase resistance (unknownauthors2014integrativeanalysesof pages 68-73).  
Reduced MST1 expression accompanies progression of prostate and colorectal cancers (record2010structuralcomparisonof pages 3-4).  
Cardiac over-expression promotes myocyte apoptosis and dilated cardiomyopathy, while inhibition mitigates post-infarction heart failure in mice (delpire2009themammalianfamily pages 7-9).

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