## Phylogeny

Serine/threonine kinase belonging to the STE20 group, Germinal-Center-Kinase II subfamily; most similar human paralogue is STK3/MST2 (~75 % identity) (Fitamant et al., 2013). Orthologues occur from yeast (Ste20) to flies (Hippo) and worms (cst-1) to mouse Stk4, highlighting broad conservation (Ling et al., 2008; Avruch et al., 2012).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇄ ADP + protein-O-phospho-Ser/Thr (Record et al., 2010).

## Cofactor Requirements

Requires Mg²⁺; Mn²⁺, Zn²⁺ or Co²⁺ can replace Mg²⁺ in vitro (Delpire, 2009; Record et al., 2010).

## Substrate Specificity

Prefers the consensus Φ-X-T-Φ-K/R-K/R (Φ = hydrophobic/aromatic) with threonine as the phospho-acceptor and basic residues at +2/+3 (Miller et al., 2019). Verified phosphosites include MOB1A/B Thr35 / Thr12, LATS1 Thr1079, LATS2 Thr1041, FOXO3 Ser207, Histone H2B Ser14, and Ezrin Thr567 (Avruch et al., 2012; Galan & Avruch, 2016; Delpire, 2009; Ling et al., 2008; Record et al., 2010).

## Structure

Contains an N-terminal kinase domain (aa 30–281) with Lys59 ATP anchor, HRD catalytic triad and DFG motif; a central autoinhibitory linker with caspase sites Asp326/Asp349; and a C-terminal SARAH coiled-coil (aa 432–480) for dimerisation (Fitamant et al., 2013; Galan & Avruch, 2016). Crystal structure 3COM shows an active conformation with a Lys59-Glu73 salt bridge and diphosphorylated Thr177/Thr183 activation loop; face-to-face dimers exchange activation loops for trans-autophosphorylation (Record et al., 2010). An AlphaFold model (5B7B) confirms the canonical bilobal fold and SARAH placement (Galan & Avruch, 2016).

## Regulation

• Autophosphorylation of Thr183 is activating (Unknown Authors, 2017).  
• TAO kinases phosphorylate the activation loop to enhance activity (Galan & Avruch, 2016).  
• PP2A-STRIPAK complex and PTPN14 dephosphorylate/ inhibit the kinase (Galan & Avruch, 2016; Eden et al., 2024).  
• Oxidative stress-induced SARAH dimerisation boosts activity (Galan & Avruch, 2016).  
• Akt (Thr120) and JNK (Ser82) phosphorylation reduce activity (Fitamant et al., 2013).  
• Abl/Src phosphorylation on Tyr433 influences stability and neuronal apoptosis (Galan & Avruch, 2016).  
• Caspase-3 cleavage at Asp326/Asp349 generates a constitutively active 34 kDa nuclear fragment (Delpire, 2009).  
• SARAH-mediated binding to SAV1 promotes activation, whereas RASSF isoforms or STRIPAK restrict it (Fitamant et al., 2013; Galan & Avruch, 2016).

## Function

Ubiquitously expressed, highest in lymphoid tissue, heart, kidney and placenta (Avruch et al., 2012; Record et al., 2010). Upstream inputs include Rap1-RAPL, oxidative stress, TAO kinases, Akt and c-Abl/Src (Ling et al., 2008; Galan & Avruch, 2016). The kinase phosphorylates MOB1A/B, thereby activating LATS1/2 and NDR1/2; these downstream kinases phosphorylate YAP/TAZ to curb proliferation and promote apoptosis (Avruch et al., 2012; Hamilton & O’Neill, 2013). Additional substrates—FOXO3, Histone H2B and Ezrin—link the enzyme to nuclear translocation, chromatin condensation and cell polarity (Delpire, 2009; Record et al., 2010). Physiological roles encompass organ-size control, stress-induced apoptosis, maintenance of naïve T-cell homeostasis and suppression of cardiac hypertrophy (Avruch et al., 2012; Ling et al., 2008).

## Inhibitors

• XMU-MP-1: selective inhibitor, IC₅₀ ≈ 71 nM (Galan & Avruch, 2016).  
• Broad ATP-competitive ligands (e.g., staurosporine, quinazoline derivatives) bind the active site in crystal complexes (Record et al., 2010).

## Other Comments

Biallelic loss-of-function variants cause autosomal-recessive combined immunodeficiency with severe naïve T-cell lymphopenia (Galan & Avruch, 2016; Avruch et al., 2012). Somatic cancer mutations cluster in the kinase domain (K59R, V184M, R181Q) or confer caspase resistance (D326N/D349N) (Unknown Authors, 2014). Reduced expression is linked to prostate and colorectal cancer progression (Record et al., 2010). Cardiac over-expression drives myocyte apoptosis and dilated cardiomyopathy, whereas inhibition is cardioprotective post-infarction (Delpire, 2009).

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