## Phylogeny

STK26 (MST4) is placed in the germinal-center kinase III (GCK-III) subgroup of the STE20 serine/threonine kinase superfamily (miller2019comprehensiveprofilingof pages 28-29).  
It forms a paralogous clade with MST3 (STK24) and STK25/SOK1 (miller2019comprehensiveprofilingof pages 28-29).  
Orthologs are reported in Mus musculus, Danio rerio and Drosophila melanogaster, demonstrating broad metazoan conservation (yin2012multiplefunctionsof pages 9-9).  
More distant homologues exist in filamentous fungi such as Sordaria macrospora and Neurospora crassa, retaining the activation-loop threonine (frey2015thestripakcomplex pages 105-106).  
Yeast kinases Orb3/Nak1 and Kic1 occupy the same evolutionary branch that governs polarized growth and cytokinesis (thompson2015mstkinasesin pages 1-3).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-phospho-Ser/Thr (record2010structuralcomparisonof pages 1-3).

## Cofactor Requirements

Catalytic activity depends on divalent cations; Mg²⁺ or Mn²⁺ efficiently support phosphorylation (yin2012multiplefunctionsof pages 9-9).

## Substrate Specificity

Johnson 2023 mapped a consensus phosphorylation motif for MST4, although the precise sequence is not provided in the excerpt (yin2012multiplefunctionsof pages 9-9).  
Validated cellular substrates include ATG4B Ser383, ERM proteins, GM130 and MOB4, indicating tolerance for serine or threonine within varied sequence contexts (unknownauthors2023mst3andmst4 pages 22-26).  
TRAF6 is an additional substrate, phosphorylated on Thr463/468 during innate immune responses (getu2023themammaliansterile pages 3-4).

## Structure

The protein contains an N-terminal kinase domain (residues 1–251) featuring the ATP-binding Lys53 and the catalytic HRD motif within a canonical bilobal fold (unknownauthors2023mst3andmst4 pages 22-26).  
The activation loop harbours Thr190, whose phosphorylation is essential for activity (record2010structuralcomparisonof pages 1-3).  
A C-terminal regulatory tail binds PDCD10 (CCM3) and GM130, enabling dimerization and subcellular targeting (unknownauthors2023mst3andmst4 pages 22-26).  
A crystal structure of the inactive kinase domain bound to a quinazoline inhibitor (PDB 3GGF) reveals a conserved hydrophobic spine and an unphosphorylated activation loop (record2010structuralcomparisonof pages 1-3).  
AlphaFold modelling reproduces the overall architecture and predicts a MO25 interaction surface that shields Thr190 from phosphatases (unknownauthors2023mst3andmst4 pages 22-26).

## Regulation

Autophosphorylation on Thr190 activates MST4 (yin2012multiplefunctionsof pages 9-9).  
PP2A contained within striatin-based STRIPAK complexes dephosphorylates Thr190 and suppresses kinase activity (unknownauthors2023mst3andmst4 pages 22-26).  
Allosteric binding of MO25/CAB39 stabilises the active conformation by protecting Thr190 from dephosphorylation (unknownauthors2023mst3andmst4 pages 22-26).  
GM130 anchors MST4 at the Golgi, promoting autophosphorylation, whereas CCM3 recruits the kinase into STRIPAK assemblies (frey2015thestripakcomplex pages 28-31).  
MST4 is resistant to caspase cleavage, distinguishing its apoptotic regulation from MST1/2 (wang2011stk24promotesmyogenic pages 28-32).

## Function

RNA-seq and GTEx datasets show ubiquitous expression with highest levels in placenta, thymus and immune tissues (getu2023themammaliansterile pages 3-4).  
Golgi localisation is mediated by GM130, with redistribution during polarized migration (unknownauthors2023mst3andmst4 pages 22-26).  
Epidermal growth factor receptor stimulation enhances MST4 activity in prostate tumour cells (shi2016stripakcomplexesin pages 1-2).  
STK26 and STK24 jointly limit RHO-driven Golgi reorientation during directed migration (unknownauthors2023mst3andmst4 pages 22-26).  
Phosphorylation of ATG4B Ser383 by MST4 increases autophagic flux (unknownauthors2023mst3andmst4 pages 22-26).  
ERM protein phosphorylation links MST4 to actin cytoskeleton remodelling (unknownauthors2023mst3andmst4 pages 22-26).  
MST4 phosphorylates AMPKα1 in vitro, connecting it to energy-sensing pathways (liu2022biochemicalpurificationuncovers pages 9-9).  
Within STRIPAK, MST4 phosphorylates MOB4, integrating Hippo pathway signalling (unknownauthors2023mst3andmst4 pages 22-26).

## Inhibitors

A quinazoline scaffold has been co-crystallised in the ATP pocket of MST4, but no selective inhibitors have been validated in cellular systems (record2010structuralcomparisonof pages 1-3).

## Other Comments

Over-expression of MST4 correlates with hepatocarcinogenesis and other cancers, promoting proliferation, migration and therapy resistance (getu2023themammaliansterile pages 15-18).  
Neratinib induces autophagic degradation of MST4, offering a potential therapeutic angle (getu2023themammaliansterile pages 15-18).  
Somatic STK26 mutations have been catalogued, though their functional impact remains undefined (miller2019comprehensiveprofilingof pages 28-29).

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