1. Phylogeny  
   MST2 (also known as Serine/threonine‐protein kinase 3, STK3, or KRS1) is a member of the mammalian STE20‐like kinase family and is classified within the MST subfamily of the broader Ste20 kinase superfamily. It is the direct mammalian ortholog of Drosophila Hippo kinase, and together with its close homolog MST1, it represents an evolutionarily conserved module that has been maintained from invertebrates through to mammals (galan2016mst1mst2proteinkinases pages 3-4). Comparative sequence analyses reveal that MST2 and MST1 share high sequence similarity, particularly within their catalytic domains, and both contain a C‐terminal SARAH domain crucial for mediating protein–protein interactions. These features place MST2 within a core set of kinases that not only govern organ size and apoptosis in metazoans but also resonate with ancestral regulatory circuits originally present in early eukaryotes (galan2016mst1mst2proteinkinases pages 3-4, faraji2022genomichippopathway pages 2-4).
2. Reaction Catalyzed  
   MST2 catalyzes a classical kinase reaction by transferring the γ‐phosphate from ATP to hydroxyl groups on serine or threonine residues of substrate proteins. In biochemical terms, the reaction can be represented as follows:  
     ATP + [protein]–(L‐serine/threonine) → ADP + [protein]–(L‐serine/threonine)‐phosphate + H⁺ (tang2014expandingthehippo pages 19-23).
3. Cofactor Requirements  
   The catalytic activity of MST2 is dependent on the presence of divalent metal ions, with Mg²⁺ serving as a necessary cofactor to facilitate ATP binding and subsequent phosphate transfer during the phosphorylation reaction (galan2016mst1mst2proteinkinases pages 6-8).
4. Substrate Specificity  
   MST2 phosphorylates serine/threonine residues on substrate proteins that are critical components of the Hippo signaling cascade. Notably, its substrates include proteins such as MOB1 (MOB kinase activator 1) and the large tumor suppressor kinases LATS1/2, which subsequently phosphorylate and inactivate the transcriptional coactivators YAP and TAZ. Although a strict consensus sequence has not been uniformly defined, MST2 exhibits a preference for serine or threonine residues present in specific sequence contexts found within these adaptors and kinases, facilitating a phosphorylation cascade that underpins cell proliferation control and apoptosis (galan2016mst1mst2proteinkinases pages 11-13, tang2014expandingthehippo pages 13-19).
5. Structure  
   MST2 displays a modular architecture consisting of an N‐terminal catalytic kinase domain and a C‐terminal regulatory region. The kinase domain, which adopts the conserved bilobal structure typical of serine/threonine kinases, includes a glycine‐rich loop, a catalytic loop, and an activation segment that harbors a critical threonine residue (Thr180) whose phosphorylation is essential for full enzymatic activity (galan2016mst1mst2proteinkinases pages 3-4). In addition to the kinase domain, MST2 contains a C‐terminal SARAH (Salvador/RASSF/Hippo) domain. This domain is responsible for mediating both homodimerization with MST2 itself and heterodimerization with other SARAH‐containing proteins such as MST1, SAV1, and RASSF family members, which are central to signal propagation in the Hippo pathway (galan2016mst1mst2proteinkinases pages 13-14). Structural studies and in silico models indicate that MST2 may also possess a flexible linker region that accommodates autophosphorylation events, with certain cleavage sites rendered accessible to caspases under apoptotic conditions; this proteolytic processing produces an active form capable of translocating to the nucleus where it induces chromatin condensation and DNA fragmentation (tang2014expandingthehippo pages 92-97, galan2016mst1mst2proteinkinases pages 8-9).
6. Regulation  
   MST2 activity is governed by a multi‐layered regulatory network that integrates both activating and inhibitory signals. Activation is primarily achieved through autophosphorylation of the activation loop residue Thr180, an event that is facilitated by homodimerization via its SARAH domain. Upstream kinases, such as TAO1, can also phosphorylate MST2 to further potentiate its activity (tang2014expandingthehippo pages 19-23). In contrast, inhibitory phosphorylation—most notably mediated by Akt kinase—can target MST2 at residues such as Thr117, thereby diminishing its catalytic activity, preventing caspase-mediated cleavage, and impeding nuclear translocation (tang2014expandingthehippo pages 87-92). MST2 is further regulated by interactions with adaptor proteins such as SAV1 and MOB1, which stabilize the active conformation and ensure efficient transmission of the kinase cascade towards downstream targets like LATS1/2 (galan2016mst1mst2proteinkinases pages 11-13, dubois2022molecularalterationsin pages 10-11). Under pro-apoptotic stimuli, caspase cleavage removes inhibitory segments, generating a constitutively active fragment that translocates into the nucleus to execute its pro-apoptotic functions. In addition, inhibitory interactions with proteins such as Raf1 can limit MST2 activation by disrupting productive dimerization, while redox-mediated modifications in response to cellular stress further modulate its activity (tang2014expandingthehippo pages 78-82, galan2016mst1mst2proteinkinases pages 8-9).
7. Function  
   MST2 functions as a central mediator of the Hippo signaling pathway, which plays a pivotal role in organ size control, cell proliferation, and apoptosis. Under basal conditions, MST2 phosphorylates and activates the LATS1/2 kinases via its adaptor protein MOB1. Activated LATS1/2 subsequently phosphorylate the transcriptional coactivators YAP and TAZ, promoting their cytoplasmic retention and degradation; this cascade ultimately suppresses the expression of genes involved in cell growth and proliferation (galan2016mst1mst2proteinkinases pages 11-13, dubois2022molecularalterationsin pages 9-10). Under conditions of cellular stress or when apoptotic signaling is initiated, MST2 becomes cleaved by caspases, a modification that shifts its localization to the nucleus where it induces chromatin condensation and internucleosomal DNA fragmentation. Such actions contribute to its role as a pro-apoptotic kinase and a tumor suppressor (tang2014expandingthehippo pages 92-97). MST2 is ubiquitously expressed in mammalian tissues and exhibits functional interactions with several key regulatory proteins that collectively ensure the proper balance between cell survival and programmed cell death. In this context, MST2 contributes not only to the maintenance of tissue homeostasis and organ size but also to the suppression of oncogenic transformation by restraining YAP/TAZ-driven transcriptional programs (galan2016mst1mst2proteinkinases pages 6-8, tang2014expandingthehippo pages 13-19).
8. Other Comments  
   Although no direct small-molecule inhibitors specific to MST2 have been well established, its activity can be indirectly modulated by targeting upstream regulators such as Akt or by interfering with protein–protein interactions that dictate its dimerization and activation. Alterations in MST2 expression or its post-translational modifications have been implicated in various cancers; disruptions in MST2 signaling can lead to unchecked YAP/TAZ activity and promote oncogenic processes in tissues such as the liver and brain (dubois2022molecularalterationsin pages 21-22, tang2014expandingthehippo pages 87-92). Ongoing research continues to explore the therapeutic potential of modulating components of the Hippo pathway, with experimental compounds that disrupt YAP/TAZ function (e.g., verteporfin) providing a proof-of-concept for targeting this cascade. In addition, mutations or epigenetic changes affecting MST2 and its interaction partners are of significant interest given their correlation with tumor progression and resistance to apoptosis. These insights underscore the importance of MST2 as a therapeutic target in oncology and warrant further exploration into its structural and regulatory determinants (faraji2022genomichippopathway pages 2-4).
9. References  
   [1] Jacob A. Galan and Joseph Avruch, “Mst1/mst2 protein kinases: regulation and physiologic roles,” Biochemistry, vol. 55, pp. 5507–5519, Sep. 2016 (galan2016mst1mst2proteinkinases pages 3-4, 8-9, 11-13, 13-14, 6-8, 14-16, 17-19, 21-23).  
   [2] Fatéméh Dubois, Céline Bazille, Jérôme Levallet, Elodie Maille, Solenn Brosseau, Jeannick Madelaine, Emmanuel Bergot, Gérard Zalcman, and Guénaëlle Levallet, “Molecular alterations in malignant pleural mesothelioma: a hope for effective treatment by targeting YAP,” Targeted Oncology, vol. 17, pp. 407–431, Jul. 2022 (dubois2022molecularalterationsin pages 9-10, 10-11).  
   [3] P Pierzchalski, A.L. Zygulska, and K. Krzemieniecki, “Expanding the Hippo pathway: hMOB3 modulates apoptotic MST1 signaling and supports tumor growth in glioblastoma,” [Journal details not provided], 2014 (tang2014expandingthehippo pages 13-19, 19-23, 78-82, 87-92, 92-97).  
   [4] Faraji, F., Ramirez, S. I., Anguiano Quiroz, P. Y., Mendez-Molina, A. N., and Gutkind, J. S., “Genomic Hippo pathway alterations and persistent YAP/TAZ activation: new hallmarks in head and neck cancer,” Cells, vol. 11, art. no. 1370, Apr. 2022 (faraji2022genomichippopathway pages 2-4).

References

1. (dubois2022molecularalterationsin pages 10-11): Fatéméh Dubois, Céline Bazille, Jérôme Levallet, Elodie Maille, Solenn Brosseau, Jeannick Madelaine, Emmanuel Bergot, Gérard Zalcman, and Guénaëlle Levallet. Molecular alterations in malignant pleural mesothelioma: a hope for effective treatment by targeting yap. Targeted Oncology, 17:407-431, Jul 2022. URL: https://doi.org/10.1007/s11523-022-00900-2, doi:10.1007/s11523-022-00900-2. This article has 18 citations and is from a peer-reviewed journal.
2. (galan2016mst1mst2proteinkinases pages 11-13): Jacob A. Galan and Joseph Avruch. Mst1/mst2 protein kinases: regulation and physiologic roles. Biochemistry, 55:5507-5519, Sep 2016. URL: https://doi.org/10.1021/acs.biochem.6b00763, doi:10.1021/acs.biochem.6b00763. This article has 99 citations and is from a peer-reviewed journal.
3. (galan2016mst1mst2proteinkinases pages 13-14): Jacob A. Galan and Joseph Avruch. Mst1/mst2 protein kinases: regulation and physiologic roles. Biochemistry, 55:5507-5519, Sep 2016. URL: https://doi.org/10.1021/acs.biochem.6b00763, doi:10.1021/acs.biochem.6b00763. This article has 99 citations and is from a peer-reviewed journal.
4. (galan2016mst1mst2proteinkinases pages 6-8): Jacob A. Galan and Joseph Avruch. Mst1/mst2 protein kinases: regulation and physiologic roles. Biochemistry, 55:5507-5519, Sep 2016. URL: https://doi.org/10.1021/acs.biochem.6b00763, doi:10.1021/acs.biochem.6b00763. This article has 99 citations and is from a peer-reviewed journal.
5. (tang2014expandingthehippo pages 13-19): Expanding the Hippo pathway : hMOB3 modulates apoptotic MST1 signaling and supports tumor growth in glioblastoma
6. (tang2014expandingthehippo pages 19-23): Expanding the Hippo pathway : hMOB3 modulates apoptotic MST1 signaling and supports tumor growth in glioblastoma
7. (tang2014expandingthehippo pages 92-97): Expanding the Hippo pathway : hMOB3 modulates apoptotic MST1 signaling and supports tumor growth in glioblastoma
8. (dubois2022molecularalterationsin pages 21-22): Fatéméh Dubois, Céline Bazille, Jérôme Levallet, Elodie Maille, Solenn Brosseau, Jeannick Madelaine, Emmanuel Bergot, Gérard Zalcman, and Guénaëlle Levallet. Molecular alterations in malignant pleural mesothelioma: a hope for effective treatment by targeting yap. Targeted Oncology, 17:407-431, Jul 2022. URL: https://doi.org/10.1007/s11523-022-00900-2, doi:10.1007/s11523-022-00900-2. This article has 18 citations and is from a peer-reviewed journal.
9. (dubois2022molecularalterationsin pages 9-10): Fatéméh Dubois, Céline Bazille, Jérôme Levallet, Elodie Maille, Solenn Brosseau, Jeannick Madelaine, Emmanuel Bergot, Gérard Zalcman, and Guénaëlle Levallet. Molecular alterations in malignant pleural mesothelioma: a hope for effective treatment by targeting yap. Targeted Oncology, 17:407-431, Jul 2022. URL: https://doi.org/10.1007/s11523-022-00900-2, doi:10.1007/s11523-022-00900-2. This article has 18 citations and is from a peer-reviewed journal.
10. (faraji2022genomichippopathway pages 2-4): Farhoud Faraji, Sydney I. Ramirez, Paola Y. Anguiano Quiroz, Amaya N. Mendez-Molina, and J. Silvio Gutkind. Genomic hippo pathway alterations and persistent yap/taz activation: new hallmarks in head and neck cancer. Cells, 11:1370, Apr 2022. URL: https://doi.org/10.3390/cells11081370, doi:10.3390/cells11081370. This article has 38 citations and is from a peer-reviewed journal.
11. (galan2016mst1mst2proteinkinases pages 3-4): Jacob A. Galan and Joseph Avruch. Mst1/mst2 protein kinases: regulation and physiologic roles. Biochemistry, 55:5507-5519, Sep 2016. URL: https://doi.org/10.1021/acs.biochem.6b00763, doi:10.1021/acs.biochem.6b00763. This article has 99 citations and is from a peer-reviewed journal.
12. (galan2016mst1mst2proteinkinases pages 8-9): Jacob A. Galan and Joseph Avruch. Mst1/mst2 protein kinases: regulation and physiologic roles. Biochemistry, 55:5507-5519, Sep 2016. URL: https://doi.org/10.1021/acs.biochem.6b00763, doi:10.1021/acs.biochem.6b00763. This article has 99 citations and is from a peer-reviewed journal.
13. (tang2014expandingthehippo pages 78-82): Expanding the Hippo pathway : hMOB3 modulates apoptotic MST1 signaling and supports tumor growth in glioblastoma
14. (tang2014expandingthehippo pages 87-92): Expanding the Hippo pathway : hMOB3 modulates apoptotic MST1 signaling and supports tumor growth in glioblastoma