## Phylogeny

MOS is a serine/threonine protein kinase that functions as a MAP kinase kinase kinase (MAPKKK) within the MAPK signaling pathway (avilov2023phosphoproteomicsidentifiestargets pages 1-3, dupre2011mosinthe pages 2-3, singh1997mosandthe pages 1-2). MOS is functionally equivalent to the proto-oncogene Raf-1 and is also described as belonging to a kinase family related to SRC kinases (dupre2011mosinthe pages 2-3, dupre2011mosinthe pages 1-2). Some sources classify MOS within the STE group and the STE7 family of MAPKKKs based on its function and homology to other kinases in this group (dupre2011mosinthe pages 2-3, yang1996inhibitionofvmos pages 10-10). However, another source states that the STE7 family contains MAPKKs, not MAPKKKs, and therefore MOS would not be classified in this group (chen1997thecaseinkinase pages 1-1). Hierarchical clustering based on substrate motif selectivity places MOS within a cluster that includes MAP3K and Alpha/MLK kinases (johnson2023anatlasof pages 4-5). Orthologs are conserved in vertebrates, including *Xenopus*, mice, and starfish, as well as in some invertebrates, but the gene is lost or non-essential in species such as *Drosophila* and *C. elegans* (avilov2023phosphoproteomicsidentifiestargets pages 1-3, dupre2011mosinthe pages 2-3).

## Reaction Catalyzed

MOS catalyzes the transfer of a phosphate group from ATP to a serine or threonine residue on a protein substrate (dupre2011mosinthe pages 1-2, shibuya1993mosinducesthe pages 1-2, singh1992themosproto‐oncogene pages 1-2). The reaction is ATP + [a protein] = ADP + [a phosphoprotein] (robertson1996identificationofan pages 2-2).

## Cofactor Requirements

The kinase activity of MOS is dependent on divalent cations (avilov2023phosphoproteomicsidentifiestargets pages 1-3, avilov2023phosphoproteomicsidentifiestargets pages 3-4). Assays have used Mn²⁺ or Mg²⁺ (robertson1996identificationofan pages 2-2, shibuya1993mosinducesthe pages 2-3). In vitro activity has also been shown to require dithiothreitol (robertson1996identificationofan pages 7-7).

## Substrate Specificity

MOS is a serine/threonine kinase that directly phosphorylates and activates MKK/MEK1 at residues Ser-218 and Ser-222 (chen1995ser3isimportant pages 1-2, chen1997thecaseinkinase pages 1-1, dupre2011mosinthe pages 2-3). There is conflicting information regarding the profiling of MOS substrate specificity in a comprehensive kinome atlas; some sources state that MOS was not mentioned or profiled, and no consensus motif or Position-Specific Scoring Matrix (PSSM) was determined (johnson2023anatlasof pages 6-7, johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 3-4). In contrast, another source indicates MOS was included in the dataset and appears in a motif clustering figure, though the explicit consensus motif or PSSM is not provided in the excerpt (johnson2023anatlasof pages 4-5). Other identified substrates include proteins involved in translation and spindle organization, such as Cyclin B and CPEB, as well as vimentin and tubulin (avilov2023phosphoproteomicsidentifiestargets pages 1-3, singh1997mosandthe pages 1-2).

## Structure

The kinase domain of MOS is located in the C-terminal region, starting at approximately residue 100 (singh1997mosandthe pages 1-2). Molecular modeling of *Xenopus* Mos, based on the PKA crystal structure, shows a canonical bilobal kinase fold with the active site at the interface of the two lobes (robertson1996identificationofan pages 2-2, robertson1996identificationofan pages 2-3). The AlphaFold predicted 3D structure of human MOS shows a conserved kinase fold with a C-helix, an activation loop, and a conserved hydrophobic spine that connects the N- and C-lobes to stabilize the active conformation (yue2006mechanisticstudiesof pages 1-2, robertson1996identificationofan pages 2-3). The position of helix C, which contains a conserved serine residue (Ser-105 in *Xenopus*), is critical for kinase activation (yue2006mechanisticstudiesof pages 1-2). A distinctive feature of MOS is an autoinhibitory region within the activation loop that blocks the active site, thereby preventing substrate and ATP binding (robertson1996identificationofan pages 1-2, robertson1996identificationofan pages 6-7). This loop, located between the β9 strand and αF helix, contains residues such as C-227 and T-228 that are critical for maintaining its inhibitory conformation (robertson1996identificationofan pages 2-3, robertson1996identificationofan pages 6-7).

## Regulation

MOS activity is regulated by phosphorylation, protein interactions, and conformational changes. **Phosphorylation**: \* **Activating modifications**: Autophosphorylation at Ser-3 stabilizes the protein by preventing ubiquitin-mediated degradation and enhances its interaction with MKK (chen1995ser3isimportant pages 1-2, chen1995ser3isimportant pages 2-2, singh1997mosandthe pages 2-4). Phosphorylation at Ser-16 by MPF and possibly MAPK also stabilizes the protein and promotes its activity (singh1997mosandthe pages 2-4, pham1999evidenceforan pages 1-2). Dephosphorylation at Ser-105, located at the start of helix C, contributes to a conformational change necessary for activation (yue2006mechanisticstudiesof pages 1-2). \* **Inhibitory modifications**: PKA phosphorylates and inhibits Mos; in v-Mos, this occurs at Ser-263, while in c-Mos, PKA-mediated phosphorylation at Ser-232 is inhibitory (yang1996inhibitionofvmos pages 1-1, singh1997mosandthe pages 2-4). Phosphorylation at Ser-25 may inhibit activation by competing with phosphorylation at Ser-3 (singh1997mosandthe pages 2-4).

**Protein Interactions and Conformation**: \* MOS activity is inhibited by binding to the beta subunit of casein kinase II (CKIIb) (chen1997thecaseinkinase pages 1-1). \* The kinase is regulated by an autoinhibitory activation loop that blocks the active site. Activation requires displacement of this loop (robertson1996identificationofan pages 6-7, robertson1996identificationofan pages 7-7). Repositioning of helix C is also critical for activation (yue2006mechanisticstudiesof pages 1-2). \* MOS protein levels are controlled by synthesis during oocyte maturation and degradation via the ubiquitin-proteasome system upon fertilization (shibuya1993mosinducesthe pages 1-2, singh1997mosandthe pages 2-4).

## Function

MOS is a germ cell-specific kinase, with expression highly restricted to oocytes and testes (avilov2023phosphoproteomicsidentifiestargets pages 1-3, chen1995ser3isimportant pages 1-2, singh1997mosandthe pages 1-2). It is a key activator of the MAPK pathway, where it directly phosphorylates and activates MAPKK (MEK1), which in turn activates MAPK (avilov2023phosphoproteomicsidentifiestargets pages 1-3, dupre2011mosinthe pages 1-2, chen1997thecaseinkinase pages 1-1). This signaling cascade controls critical meiotic processes, including oocyte maturation, germinal vesicle breakdown (GVBD), and the establishment of cytostatic factor (CSF) arrest at metaphase II (avilov2023phosphoproteomicsidentifiestargets pages 1-3, chen1997thecaseinkinase pages 1-1). MOS maintains meiotic arrest by sustaining the activity of M-phase promoting factor (MPF; Cyclin B-Cdk1) (dupre2011mosinthe pages 1-2, singh1997mosandthe pages 1-2). This is achieved by enhancing Cyclin B translation and by inhibiting the Anaphase-Promoting Complex/Cyclosome (APC/C) via the effector Erp1/Emi2, thereby preventing Cyclin B degradation (avilov2023phosphoproteomicsidentifiestargets pages 1-3, avilov2023phosphoproteomicsidentifiestargets pages 3-4). MOS also regulates the organization of the meiotic spindle (avilov2023phosphoproteomicsidentifiestargets pages 1-3). Downstream effectors of the MOS-MAPK pathway include p90RSK (avilov2023phosphoproteomicsidentifiestargets pages 1-3).

## Inhibitors

The experimental compound U0126 is an inhibitor of the MOS-MAPK pathway that acts by targeting the downstream kinase MEK1 (avilov2023phosphoproteomicsidentifiestargets pages 3-4).

## Other Comments

Aberrant expression of MOS in somatic cells is oncogenic, leading to cellular transformation, as first identified with the viral oncogene v-mos from the Moloney murine sarcoma virus (avilov2023phosphoproteomicsidentifiestargets pages 1-3, dupre2011mosinthe pages 1-2, shibuya1993mosinducesthe pages 1-2). In germ cells, MOS acts as a tumor suppressor by preventing parthenogenetic activation of unfertilized eggs, which can lead to ovarian teratomas in mice (dupre2011mosinthe pages 2-3, singh1997mosandthe pages 1-2). Mutations that abolish its kinase activity eliminate its biological functions (dupre2011mosinthe pages 1-2). In mice, Mos mutations cause meiotic defects and reduced fertility (chen1997thecaseinkinase pages 1-1).

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