Phylogeny  
• MOS is a germ-cell serine/threonine protein kinase that functions as a MAP kinase kinase kinase (MAPKKK) within the MAPK cascade and is functionally equivalent to Raf-1 (Dupré et al., 2011; Avilov et al., 2023).  
• Sometimes grouped with the STE family of MAPKKKs or placed in a cluster containing other MAP3Ks and MLKs, although its exact family assignment is debated (Dupré et al., 2011; Johnson et al., 2023; Chen et al., 1997).  
• Orthologues are conserved in vertebrates (e.g., Xenopus, mouse, starfish) and in some invertebrates, but the gene is absent or non-essential in Drosophila and C. elegans (Avilov et al., 2023; Dupré et al., 2011).

Reaction Catalyzed  
ATP + [protein] ⇌ ADP + [phospho-protein] (Robertson & Donoghue, 1996; Shibuya & Ruderman, 1993; Singh & Arlinghaus, 1992).

Cofactor Requirements  
• Requires divalent cations; Mn²⁺ or Mg²⁺ support activity in vitro (Robertson & Donoghue, 1996; Shibuya & Ruderman, 1993).  
• Reducing agent dithiothreitol is routinely included in assays (Robertson & Donoghue, 1996).

Substrate Specificity  
• Directly phosphorylates MEK1 on Ser-218 and Ser-222 (Chen & Cooper, 1995; Dupré et al., 2011).  
• Additional reported substrates include Cyclin B, CPEB, vimentin and tubulin, consistent with roles in translation and spindle organisation (Avilov et al., 2023; Singh & Arlinghaus, 1997).  
• Phospho-motif profiling is inconsistent: MOS appears in a kinome-wide clustering analysis but no consensus motif or PSSM has been defined (Johnson et al., 2023).

Structure  
• Catalytic domain resides in the C-terminal half (from ~residue 100) and adopts a canonical bilobal kinase fold (Robertson & Donoghue, 1996; Yue & Ferrell, 2006).  
• AlphaFold and homology models reveal a conserved C-helix, activation loop and hydrophobic spine (Yue & Ferrell, 2006).  
• An autoinhibitory segment within the activation loop (between β9 and αF; residues C227/T228 in Xenopus) occludes the active site until displaced (Robertson & Donoghue, 1996).  
• Positioning of helix C (Ser-105 in Xenopus) is critical for activation (Yue & Ferrell, 2006).

Regulation  
Phosphorylation  
– Activating: Ser-3 autophosphorylation; Ser-16 phosphorylation by MPF/MAPK; dephosphorylation at Ser-105 promotes an active conformation (Chen & Cooper, 1995; Pham et al., 1999; Yue & Ferrell, 2006).  
– Inhibitory: PKA phosphorylates Ser-232 (c-Mos) or Ser-263 (v-Mos); Ser-25 phosphorylation may antagonise Ser-3 activation (Yang et al., 1996; Singh & Arlinghaus, 1997).

Protein interactions & conformational control  
• Binding of the casein kinase II β-subunit inhibits MOS (Chen et al., 1997).  
• Autoinhibitory activation loop and helix C repositioning govern catalytic competence (Robertson & Donoghue, 1996; Yue & Ferrell, 2006).  
• Protein levels rise during oocyte maturation and are eliminated after fertilisation via ubiquitin-mediated degradation (Shibuya & Ruderman, 1993; Singh & Arlinghaus, 1997).

Function  
• Expression is highly restricted to oocytes and testes (Avilov et al., 2023; Chen & Cooper, 1995).  
• Serves as the trigger kinase for the oocyte MAPK pathway: MOS → MEK1 → MAPK → p90RSK (Avilov et al., 2023; Dupré et al., 2011).  
• Controls meiotic processes—germinal vesicle breakdown, spindle assembly and establishment/maintenance of cytostatic factor (CSF) arrest in metaphase II (Avilov et al., 2023; Chen et al., 1997).  
• Sustains M-phase–promoting factor (Cyclin B–Cdk1) by stimulating Cyclin B translation and inhibiting APC/C via Erp1/Emi2 (Avilov et al., 2023; Dupré et al., 2011).

Inhibitors  
• U0126 blocks the MOS-MEK-MAPK pathway by inhibiting the downstream kinase MEK1 (Avilov et al., 2023).

Other Comments  
• Mis-expression in somatic cells is oncogenic; v-Mos was first identified as a retroviral oncogene (Dupré et al., 2011; Shibuya & Ruderman, 1993).  
• In germ cells MOS acts as a tumour suppressor by preventing parthenogenetic activation; Mos-null mice exhibit meiotic defects and reduced fertility (Singh & Arlinghaus, 1997; Chen et al., 1997).  
• Kinase-dead mutations abolish all known biological functions (Dupré et al., 2011).

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