Phylogeny  
• Full-length orthologs have been cloned from Homo sapiens (1,291 aa) and Mus musculus (1,288 aa) (takeda2007apoptosissignalregulatingkinase pages 3-4).  
• ASK2 belongs to the STE20-like group → MAP3K family → ASK sub-family (MAP3K5/6/15) of the human kinome (keshet2010themapkinase pages 5-7).  
• Phylogenetic clustering places MAP3K6 immediately adjacent to MAP3K5, reflecting high sequence conservation within the catalytic domain and flanking regulatory regions (takeda2007apoptosissignalregulatingkinase pages 3-4, trevelyan2020structurebasedmechanismof pages 1-4).

Reaction Catalyzed  
ATP + protein-L-Ser/Thr → ADP + protein-L-Ser/Thr-phosphate (takeda2007apoptosissignalregulatingkinase pages 7-8).

Cofactor Requirements  
No study cited to date reports specific divalent-metal requirements for MAP3K6 catalytic activity (takeda2007apoptosissignalregulatingkinase pages 7-8).

Substrate Specificity  
• Experimentally validated direct substrates: MAP2K MKK6 and MAP2K MKK4, phosphorylated within their activation loops (takeda2007apoptosissignalregulatingkinase pages 7-8, takeda2007apoptosissignalregulatingkinase pages 2-3).  
• A quantitative consensus phosphorylation motif has not been determined; MAP3K6 was not profiled in large-scale motif studies covered by the cited literature (takeda2007apoptosissignalregulatingkinase pages 7-8).

Structure  
• Domain organization: N-terminal regulatory segment (~1–640); central Ser/Thr kinase domain (~641–930); C-terminal sterile-alpha motif (SAM, ~1064–1286) that mediates homo- and hetero-oligomerization (takeda2007apoptosissignalregulatingkinase pages 3-4, trevelyan2020structurebasedmechanismof pages 1-4).  
• Activation loop contains Thr807; phosphorylation of this residue is obligatory for catalytic activity (takeda2007apoptosissignalregulatingkinase pages 6-7).  
• Small-angle X-ray scattering of the isolated SAM domain shows a compact oligomer (Rg ≈ 16 Å, Dmax ≈ 65 Å), supporting higher-order signalosome assembly (trevelyan2020structurebasedmechanismof pages 32-35).  
• Homology modelling, based on ASK1, predicts an adjacent pleckstrin-homology-like fold packed against a tetratricopeptide-repeat core, suggesting a closed autoregulatory scaffold also present in MAP3K6 (weijman2017structuralbasisof pages 4-4).

Regulation  
Post-translational modifications  
• Thr807 autophosphorylation in the activation loop—required for kinase activity (takeda2007apoptosissignalregulatingkinase pages 6-7).  
• Ser46 is a candidate AKT site; Ser916 is essential for PI3K-dependent suppression of MAP3K6-mediated apoptosis, although Ser916 is not directly phosphorylated by AKT in vivo (ortner2007regulationofapoptosis pages 88-91).  
Protein-protein interactions and complex assembly  
• Forms a stable heteromeric complex with MAP3K5 (ASK1); ASK1 prevents constitutive degradation of MAP3K6 and promotes its autophosphorylation, whereas MAP3K6 reciprocally phosphorylates ASK1 at Thr838 (takeda2007apoptosissignalregulatingkinase pages 8-9).  
• SAM-domain interactions drive higher-order oligomerization into an ASK signalosome that amplifies stress signalling (trevelyan2020structurebasedmechanismof pages 1-4).  
• AKT binds the MAP3K6/ASK1 complex and paradoxically augments caspase-3 and PARP cleavage independently of its kinase activity (ortner2007regulationofapoptosis pages 88-91).  
• Additional reported interactors: 14-3-3 proteins and c-Raf associate with the complex, potentially modulating MAP3K6 function (ortner2007regulationofapoptosis pages 88-91).  
Upstream regulatory inputs  
• Oxidative stress (H₂O₂) activates MAP3K6 within the ASK1/ASK2 complex (takeda2007apoptosissignalregulatingkinase pages 6-7).  
• PI3K activity negatively regulates MAP3K6-induced apoptosis through the Ser916 module (ortner2007regulationofapoptosis pages 88-91).

Function  
• Ubiquitously expressed at the protein level; detected in cytoplasm, mitochondria and nucleus (ortner2007regulationofapoptosis pages 88-91).  
• Essential for oxidative-stress–induced activation of the JNK pathway; RNAi depletion markedly blunts JNK phosphorylation after H₂O₂ challenge (takeda2007apoptosissignalregulatingkinase pages 7-7).  
• Can activate p38 MAPK in some experimental contexts, although ERK activation is not observed (takeda2007apoptosissignalregulatingkinase pages 7-8).  
• Promotes apoptosis by elevating caspase-3–like activity when co-expressed with kinase-inactive ASK1 (takeda2007apoptosissignalregulatingkinase pages 7-7).  
• Participates in antiviral responses, inflammasome priming and neutrophilic dermatitis as part of ASK1/ASK2 heterocomplexes (trevelyan2020structurebasedmechanismof pages 35-37).  
• Upstream adaptor TRAF2 links MAP3K6 to TNF-receptor stress signalling (keshet2010themapkinase pages 5-7).

Other Comments  
• Dysregulated MAP3K6 activity contributes to opposing roles in apoptosis and inflammation during tumorigenesis (trevelyan2020structurebasedmechanismof pages 35-37).

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