## Phylogeny

Full-length orthologues (Homo sapiens, 1 291 aa; Mus musculus, 1 288 aa) have been cloned (Takeda et al., 2007). MAP3K6/ASK2 clusters within the STE20-like branch of the MAP3K family, specifically the ASK sub-family comprising MAP3K5, MAP3K6 and MAP3K15 (Keshet & Seger, 2010). Phylogenetic analyses place MAP3K6 immediately adjacent to MAP3K5, consistent with strong sequence conservation across the catalytic core and neighbouring regulatory segments (Takeda et al., 2007; Trevelyan et al., 2020).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Takeda et al., 2007).

## Cofactor Requirements

No specific divalent-metal requirement has been reported to date for MAP3K6 catalytic activity (Takeda et al., 2007).

## Substrate Specificity

Verified direct substrates are MAP2Ks MKK6 and MKK4, phosphorylated within their activation loops (Takeda et al., 2007). A quantitative consensus motif has not been determined, and MAP3K6 has not been included in large-scale motif-profiling studies covered by the cited literature.

## Structure

• Modular organisation: N-terminal regulatory region (~1–640); central Ser/Thr kinase domain (~641–930); C-terminal sterile-alpha motif (SAM, ~1 064–1 286) that mediates homo- and hetero-oligomerisation (Takeda et al., 2007; Trevelyan et al., 2020).  
• Activation loop Thr807 autophosphorylation is obligatory for activity (Takeda et al., 2007).  
• Small-angle X-ray scattering of the isolated SAM domain reveals a compact oligomer (Rg ≈ 16 Å, D\_max ≈ 65 Å), supporting higher-order signalosome assembly (Trevelyan et al., 2020).  
• Homology modelling, based on ASK1, predicts a pleckstrin-homology-like fold packed against a tetratricopeptide-repeat core, suggesting a closed autoinhibitory scaffold also present in MAP3K6 (Weijman et al., 2017).

## Regulation

Post-translational modifications  
– Thr807 autophosphorylation: required for catalytic competence (Takeda et al., 2007).  
– Ser46 (candidate AKT site) and Ser916: Ser916 is essential for PI3K-dependent suppression of MAP3K6-driven apoptosis, although not directly phosphorylated by AKT in vivo (Ortner, 2007).

Protein-protein interactions and complex assembly  
– Forms a stable heteromeric complex with MAP3K5/ASK1; ASK1 stabilises MAP3K6 and promotes its autophosphorylation, while MAP3K6 reciprocally phosphorylates ASK1 at Thr838 (Takeda et al., 2007).  
– SAM-domain contacts drive higher-order oligomerisation into an ASK signalosome (Trevelyan et al., 2020).  
– AKT associates with the MAP3K6/ASK1 complex and enhances caspase-3 and PARP cleavage independently of AKT kinase activity (Ortner, 2007).  
– Additional interactors include 14-3-3 proteins and c-Raf (Ortner, 2007).

Upstream regulatory inputs  
– Oxidative stress (H₂O₂) activates MAP3K6 within the ASK1/ASK2 complex (Takeda et al., 2007).  
– Class I PI3K activity negatively regulates MAP3K6-mediated apoptosis via the Ser916 module (Ortner, 2007).

## Function

MAP3K6 protein is ubiquitously expressed and detected in cytoplasm, mitochondria and nucleus (Ortner, 2007). It is essential for oxidative-stress–induced activation of the JNK pathway; RNAi depletion markedly reduces JNK phosphorylation after H₂O₂ exposure (Takeda et al., 2007). MAP3K6 can also activate p38 MAPK, whereas ERK activation has not been observed (Takeda et al., 2007). Co-expression with kinase-inactive ASK1 elevates caspase-3–like activity, indicating a pro-apoptotic role (Takeda et al., 2007). ASK1/ASK2 heterocomplexes contribute to antiviral responses, inflammasome priming and neutrophilic dermatitis (Trevelyan et al., 2020). TRAF2 links MAP3K6 to TNF-receptor stress signalling (Keshet & Seger, 2010).

## Other Comments

Dysregulated MAP3K6 activity exhibits opposing effects on apoptosis and inflammation during tumour development (Trevelyan et al., 2020).

## 9. References

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