## Phylogeny

MAP3K2 (MEKK2) is a member of the mitogen-activated protein kinase kinase kinase family, specifically the MEKK/STE11 subfamily (Zhang et al., 2006). Orthology with Mus musculus Map3k2 has been confirmed; knockout mice are viable and retain conserved catalytic function (Ahmad et al., 2018). The closest paralogue is MAP3K3 (MEKK3), with high catalytic-domain identity and overlapping inhibitor sensitivity (Ahmad et al., 2018).

## Reaction Catalyzed

ATP + MAP2K5/7 (unphosphorylated) ⇌ ADP + MAP2K5/7-P (phosphorylated on Ser/Thr within the activation loop) (Ahmad et al., 2018).

## Cofactor Requirements

No specific divalent-cation requirement was detected in the reported biochemical assays (Ahmad et al., 2018; Zhang et al., 2006).

## Substrate Specificity

Confirmed direct substrates include MAP2K5 (MEK5), MAP2K7 (MEK7), MAP2K4 (MKK4) and c-Jun (Cargnello & Roux, 2011; Hammaker et al., 2004). A consensus sequence has not been defined; specificity appears to rely on docking interactions typical of MAP3Ks (Cargnello & Roux, 2011).

## Structure

The protein comprises an N-terminal regulatory segment followed by a C-terminal Ser/Thr kinase domain (Zhang et al., 2006). Ser519 in the activation loop is the principal regulatory phosphosite required for activity (Zhang et al., 2006). Catalytic-domain homodimerisation is necessary for full activation (Zhang et al., 2006). No crystallographic structures have been reported; structural insights derive from recombinant catalytic-domain studies used for inhibitor profiling (Ahmad et al., 2018).

## Regulation

• Autophosphorylation on Ser519 is essential for activation (Zhang et al., 2006).  
• IL-1 stimulation enhances activity towards MKK4/MKK7 in fibroblast-like synoviocytes (Hammaker et al., 2004).  
• Toll-like receptor engagement triggers TRAF6-dependent Ser519 phosphorylation (Zhang et al., 2006).  
• XIAP and cIAP1 ubiquitinate MEKK2, modulating the MEKK2/3-MEK5-ERK5 module (Takeda et al., 2014).  
• SMYD3-mediated lysine methylation augments kinase activity in Ras-driven carcinoma models (Nguyen et al., 2022).  
• Catalytic-domain dimerisation provides an additional allosteric activation layer (Zhang et al., 2006).

## Function

Expression: MAP3K2 is elevated in prostate, breast, colorectal, gastric, lung and hepatocellular carcinomas, as well as in triple-negative breast cancer and rheumatoid-arthritis synovial tissue (Ahmad et al., 2018; Hammaker et al., 2004; Nguyen et al., 2022).  
Upstream regulators: WNK1, IL-1 receptor signalling, TRAF6-coupled Toll-like receptors and Rac1/2 GTPases (Cargnello & Roux, 2011; Hammaker et al., 2004; Takeda et al., 2014; Zhang et al., 2006).  
Downstream pathways:  
– MEK5 → ERK5 promotes proliferation, survival and migration (Ahmad et al., 2018; Cargnello & Roux, 2011).  
– MEK7/MKK4 → JNK → c-Jun drives AP-1-dependent gene expression (Hammaker et al., 2004).  
– Contributes to IKK–NF-κB activation (Zhang et al., 2006).  
Cellular/physiological roles: Regulates focal-adhesion turnover and cell migration; knock-down stabilises adhesions (Ahmad et al., 2018). Supports IL-2 production in T cells (Zhang et al., 2006) and induces matrix-degrading enzymes in rheumatoid-arthritis synoviocytes (Hammaker et al., 2004). Mekk2-null mice are viable, indicating non-essentiality for embryogenesis (Ahmad et al., 2018).

## Inhibitors

• Iminocoumarin scaffold: biochemical IC₅₀ ≈ 8 nM; CF₃ substitution confers selectivity (Ahmad et al., 2018).  
• Compound 1s: cellular IC₅₀ ≈ 60 nM for blocking MEKK2-dependent ERK5 phosphorylation; cross-reactive with MEKK3 (Ahmad et al., 2018).  
• Ponatinib: multi-kinase inhibitor with limited MEKK2 selectivity (Ahmad et al., 2018).

## Other Comments

MEKK2 knock-down or pharmacological inhibition reduces tumour growth and metastasis in vivo (Ahmad et al., 2018). Elevated MAP3K2 mRNA correlates with poor survival across multiple cancers and promotes epithelial-mesenchymal transition and invasion (Nguyen et al., 2022). MEKK2 is a key inflammatory mediator in rheumatoid arthritis, highlighting its therapeutic potential for joint preservation (Hammaker et al., 2004).

## 9. References

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