Phylogeny  
• Orthologs confirmed: Mus musculus Map3k2; knockout mice are viable and retain conserved kinase function (ahmad2018discoveryandcharacterization pages 1-6).  
• Closest paralog: MAP3K3 (MEKK3); high catalytic-domain identity and shared inhibitor susceptibility (ahmad2018discoveryandcharacterization pages 10-15).  
• Kinome placement: Member of the MAPK kinase kinase (MAP3K) family, MEKK/STE11 subfamily (zhang2006identificationofmekk23 pages 1-2).

Reaction Catalyzed  
ATP + MAP2K5/7 (unphosphorylated) ⇌ ADP + MAP2K5/7-P (phosphorylated on Ser/Thr in the activation loop) (ahmad2018discoveryandcharacterization pages 1-6).

Cofactor Requirements  
No specific divalent-cation requirement has been reported in the cited biochemical studies (ahmad2018discoveryandcharacterization pages 1-6, zhang2006identificationofmekk23 pages 1-2).

Substrate Specificity  
• Direct substrates: MAP2K5 (MEK5) (cargnello2011activationandfunction pages 6-8), MAP2K7 (MEK7) (ahmad2018discoveryandcharacterization pages 1-6), MAP2K4 (MKK4) (hammaker2004regulationofcjun pages 6-7), and c-Jun (hammaker2004regulationofcjun pages 1-2).  
• A consensus phosphorylation motif has not been experimentally defined; docking interactions typical of MAP3Ks appear to dictate specificity (cargnello2011activationandfunction pages 6-8).

Structure  
• Domain organization: N-terminal regulatory segment followed by a C-terminal Ser/Thr kinase domain (zhang2006identificationofmekk23 pages 10-11).  
• Activation segment: Ser519 (human numbering) within the activation loop is the principal regulatory phosphosite required for catalytic activity (zhang2006identificationofmekk23 pages 2-3).  
• Oligomeric state: Catalytic-domain dimerization is necessary for activation (zhang2006identificationofmekk23 pages 10-11).  
• Structural coverage: No crystallographic structures reported; biochemical assays employed recombinant catalytic domains for inhibitor profiling (ahmad2018discoveryandcharacterization pages 10-15).

Regulation  
• Autophosphorylation: Ser519 phosphorylation is essential for kinase activation (zhang2006identificationofmekk23 pages 2-3).  
• Cytokine signaling: IL-1 markedly increases MEKK2 activity toward MKK4/MKK7 in fibroblast-like synoviocytes (hammaker2004regulationofcjun pages 6-7).  
• TLR/stress input: TRAF6-dependent phosphorylation at Ser519 following Toll-like receptor engagement (zhang2006identificationofmekk23 pages 1-2).  
• Ubiquitination: XIAP and cIAP1 catalyze ubiquitin attachment, modulating the MEKK2/3-MEK5-ERK5 module (takeda2014ubiquitin‐dependentregulationof pages 18-18).  
• Lysine methylation: SMYD3 methylates MEKK2, enhancing kinase activity in Ras-driven carcinoma models (nguyen2022map3kfamilyreview pages 2-3).  
• Allosteric control: Homodimerization of the catalytic domain is required for full activation (zhang2006identificationofmekk23 pages 10-11).

Function  
• Expression: Elevated in prostate, breast, colorectal, gastric, lung, hepatocellular and triple-negative breast cancers (ahmad2018discoveryandcharacterization pages 1-6, nguyen2022map3kfamilyreview pages 2-3); highly expressed in rheumatoid-arthritis synovial tissue/fibroblast-like synoviocytes (hammaker2004regulationofcjun pages 1-2).  
• Upstream regulators: WNK1 kinase (cargnello2011activationandfunction pages 6-8), IL-1 receptor signaling (hammaker2004regulationofcjun pages 6-7), Toll-like receptors via TRAF6 (zhang2006identificationofmekk23 pages 1-2), Rac1/2 GTPases (takeda2014ubiquitin‐dependentregulationof pages 18-18).  
• Downstream pathways:  
– MEK5 → ERK5 cascade controlling proliferation, survival and migration (cargnello2011activationandfunction pages 6-8, ahmad2018discoveryandcharacterization pages 1-6).  
– MEK7/MKK4 → JNK → c-Jun axis driving AP-1 and matrix metalloproteinase expression (hammaker2004regulationofcjun pages 1-2, hammaker2004regulationofcjun pages 6-7).  
– Contributes to IKK–NF-κB activation (zhang2006identificationofmekk23 pages 1-2).  
• Cellular roles: Regulates focal-adhesion turnover; knock-down stabilizes adhesions and suppresses cell migration (ahmad2018discoveryandcharacterization pages 1-6).  
• Physiological roles: Supports IL-2 production in T cells (zhang2006identificationofmekk23 pages 10-11); drives matrix-degrading enzyme expression in rheumatoid arthritis synoviocytes (hammaker2004regulationofcjun pages 1-2).  
• Genetic evidence: Mekk2-null mice are viable, indicating non-essentiality for embryogenesis (ahmad2018discoveryandcharacterization pages 1-6).

Inhibitors  
• Iminocoumarin scaffold: Lead compound IC50 = 8 nM (biochemical); CF3 substitution confers high selectivity (ahmad2018discoveryandcharacterization pages 10-15).  
• Compound 1s: Cellular IC50 ≈ 60 nM for blockade of MEKK2-dependent ERK5 phosphorylation; cross-reactive with MEKK3 (ahmad2018discoveryandcharacterization pages 10-15).  
• Ponatinib: Multi-kinase inhibitor that also targets MEKK2 with limited selectivity (ahmad2018discoveryandcharacterization pages 1-6).

Other Comments  
• Knock-down or pharmacological inhibition of MEKK2 reduces tumor growth and metastasis in vivo (ahmad2018discoveryandcharacterization pages 1-6).  
• Elevated MAP3K2 mRNA correlates with poor survival across multiple cancer types (nguyen2022map3kfamilyreview pages 2-3).  
• MEKK2 activity drives epithelial-mesenchymal transition and invasion in solid tumors (nguyen2022map3kfamilyreview pages 2-3).  
• MEKK2 is a key inflammatory mediator in rheumatoid arthritis, making it a potential therapeutic target for joint preservation (hammaker2004regulationofcjun pages 1-2).

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