## Phylogeny

• Classified within the STE group, MAP2K (Ste7) family of the human kinome (manning2002theproteinkinase pages 1-2)  
• Closest human paralogs are MAP2K3 (~80 % identity) and MAP2K4 (~40 % identity) (han1996characterizationofthe pages 1-2, han1996characterizationofthe pages 2-4)  
• Murine ortholog Mkk6c shares 97.6 % identity with human MAP2K6 (han1996characterizationofthe pages 2-4)  
• Additional vertebrate orthologs reported in rat, Xenopus and zebrafish (manning2002theproteinkinase pages 3-3)  
• Invertebrate orthologs such as Drosophila hemipterous indicate deep metazoan conservation (manning2002theproteinkinase pages 3-3)  
• Yeast MAPKK PBS2p represents a distant ortholog in the same evolutionary branch (han1996characterizationofthe pages 1-2)

## Reaction Catalyzed

ATP + protein-Thr/Tyr-OH ⇌ ADP + protein-Thr/Tyr-O-PO₃²⁻ (matsumoto2012crystalstructureof pages 4-5)

## Cofactor Requirements

• Mg²⁺ required for ATP coordination and catalysis (matsumoto2012crystalstructureof pages 4-5)

## Substrate Specificity

• Dual-specificity kinase that phosphorylates the Thr-Gly-Tyr activation-loop motif of p38 MAPKs (MAPK11/12/13/14) and shows negligible activity toward ERK or JNK isoforms (han1996characterizationofthe pages 1-2, juyoux2023architectureofthe pages 15-17)  
• Specificity is driven by an N-terminal kinase-interaction motif (KIM) docking to the p38 common docking site rather than a strict linear consensus sequence (juyoux2023architectureofthe pages 7-9)  
• The serine/threonine kinome atlas clusters MAP2K6 but does not assign an explicit peptide consensus motif, underscoring docking-based selectivity (johnson2023anatlasof pages 4-5)

## Structure

• Domain architecture: N-terminal KIM/D-domain (~residues 10–30), intrinsically disordered linker, bilobal kinase core (residues 44–334), and C-terminal DVD motif within αJ/αK helices for MAP3K docking (juyoux2023architectureofthe pages 7-9, matsumoto2012crystalstructureof pages 1-2)  
• Crystal structure of non-phosphorylated MAP2K6 reveals an antiparallel autoinhibitory dimer in which the phosphate-binding ribbon of one protomer blocks the ATP site of the other and buries the activation loop (min2009thestructureof pages 1-4)  
• Activation loop residues 203–216 form three short helices (AH1–AH3) that encase the γ-phosphate of bound ATP, maintaining an inactive conformation (matsumoto2012crystalstructureof pages 5-6)  
• Phosphorylation of Ser207 and Thr211 disrupts these helices, repositions the αC-helix and permits catalytic alignment (matsumoto2012crystalstructureof pages 5-6)  
• Cryo-EM structure of the active MAP2K6–p38α complex shows a face-to-face assembly where the MAP2K6 αG helix engages a hydrophobic pocket on p38α to present the p38 activation loop for dual phosphorylation (juyoux2023architectureofthe pages 15-17)

## Regulation

• Activated by dual phosphorylation of Ser207 and Thr211 by MAP3K3 (matsumoto2012crystalstructureof pages 1-2)  
• TLR4 and TNF signaling phosphorylate MAP2K6 via MAP3K8/TPL-2 in an IKK-dependent manner (pattison2016tlrandtnfr1 pages 1-2)  
• Autoinhibitory antiparallel dimerization masks the ATP site and activation loop; binding of upstream MAP3Ks at the DVD motif or of p38 at the KIM disrupts the dimer and relieves inhibition (min2009thestructureof pages 6-8, juyoux2023architectureofthe pages 7-9)  
• Not responsive to Rac1 or Cdc42 GTPases, distinguishing its regulation from some other MAP2Ks (han1996characterizationofthe pages 2-2)

## Function

• Exists as multiple splice isoforms (MKK6, MKK6b, murine MKK6c) with tissue-specific expression patterns (han1996characterizationofthe pages 4-6)  
• Predominant activator of p38α in TNF-stimulated fibroblasts (brancho2003mechanismofp38 pages 7-8)  
• Upstream kinases: MAP3K3 and MAP3K8/TPL-2; downstream substrates: p38 MAPKs leading to phosphorylation of transcription factors ATF2, ELK1 and STAT4 (brancho2003mechanismofp38 pages 7-8, pattison2016tlrandtnfr1 pages 1-2)  
• Participates in cellular responses to pro-inflammatory cytokines, bacterial LPS, UV irradiation, heat shock and osmotic stress, modulating cytokine production, growth arrest and apoptosis (han1996characterizationofthe pages 1-2)

## Inhibitors

• A solvent-exposed pocket adjacent to the ATP γ-phosphate in the inactive structure accommodates an ATP-non-competitive inhibitor, illustrating a ligandable allosteric site (matsumoto2012crystalstructureof pages 8-8)

## Other Comments

• Hyperactivation of the MAP2K6–p38 pathway has been linked to pathological inflammation and ovarian cancer (matsumoto2012crystalstructureof pages 1-2)  
• MAP2K6 forms complexes with tau and, via p38, drives pathological tau phosphorylation at Ser396 in Alzheimer’s disease (peel2007tauphosphorylationin pages 9-12)  
• Down-regulation of MAP2K6 by miR-625-3p confers oxaliplatin resistance in colorectal adenocarcinoma cells (rasmussen2016mir6253pregulatesoxaliplatin pages 3-4)  
• Stabilization of MAP2K6 by TRIM9 short isoform enhances p38 signaling and suppresses glioblastoma progression (liu2018mutualstabilizationbetween pages 15-15)

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