## Phylogeny

• Orthologs: Homo sapiens (MAPKAPK2), Mus musculus (Mapkapk2), Rattus norvegicus, Danio rerio, Drosophila melanogaster (~60 % identity) and Caenorhabditis elegans (~60 % identity) (cargnello2011activationandfunction pages 21-23, roux2004erkandp38 pages 16-17).  
• Yeast analogs: Rck1/Rck2 in Saccharomyces cerevisiae and Srk1/Mkp2 in Schizosaccharomyces pombe act downstream of p38-like modules but are not direct orthologs (cargnello2011activationandfunction pages 21-23).  
• Kinome position: MAPKAPK2 groups with MAPKAPK3 (75 % identity) in the MAPK-activated protein kinase sub-family on the CaMK-like branch of the human kinome (roux2004erkandp38 pages 5-7, cargnello2011activationandfunction pages 21-23).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (fiore2016targetingmitogenactivatedprotein pages 10-12).

## Cofactor Requirements

• Requires Mg²⁺; standard assays use 25 mM MgCl₂ (powell2003proteomicidentificationof pages 2-2).  
• Mn²⁺ can substitute for Mg²⁺ with retained activity in crystallographic studies (fiore2016targetingmitogenactivatedprotein pages 70-73).

## Substrate Specificity

• Consensus motif: Φ-X-Arg-X₂-Ser/Thr (Φ = large hydrophobic residue) (johnson2023anatlasof pages 4-5).  
• Experimentally confirmed cellular substrates include HSP27/HSPB1, TTP/ZFP36, LIMK1, LSP1, CDC25B/C, ALOX5 and ELAVL1 (schindler2007p38pathwaykinases pages 5-6, fiore2016targetingmitogenactivatedprotein pages 51-54).

## Structure

• Domain map (isoform 1, 400 aa)  
– 10–40: Proline-rich SH3-binding segment (fiore2016targetingmitogenactivatedprotein pages 7-10).  
– 64–325: Bilobal kinase domain; gatekeeper Met138 shapes a narrow ATP pocket (fiore2016targetingmitogenactivatedprotein pages 10-12).  
– 328–364: Autoinhibitory α-helix masking the catalytic cleft (fiore2016targetingmitogenactivatedprotein pages 7-10).  
– 356–365: Nuclear export signal (singh2017biologicalfunctionsand pages 1-6).  
– 366–390: High-affinity p38 docking site (fiore2016targetingmitogenactivatedprotein pages 10-12).  
– 371–374 & 385–389: Bipartite NLS (singh2017biologicalfunctionsand pages 1-6).  
• Representative structures: apo (1KWP), ADP/staurosporine-bound (1NY3, 1NXK), active T222E mutant (3KA0), p38α-MK2 heterodimers (2OZA, 2ONL) (fiore2016targetingmitogenactivatedprotein pages 10-12).  
• Activation entails hydrophobic-spine completion and αC-helix rotation; phosphorylation displaces the autoinhibitory helix, exposing the active site and NLS (fiore2016targetingmitogenactivatedprotein pages 54-57).

## Regulation

• p38α/MAPK14 phosphorylates Thr222, Ser272 (activation loop) and Thr334 (C-terminus) to activate MK2 and unmask the NES (singh2017biologicalfunctionsand pages 1-6, roux2004erkandp38 pages 17-18).  
• Autophosphorylation occurs at Ser9, Thr25 and Ser328 (fiore2016targetingmitogenactivatedprotein pages 7-10).  
• SUMOylation at Lys353 by PIAS1 suppresses activity; K353R mutation abolishes this inhibition (fiore2016targetingmitogenactivatedprotein pages 10-12).  
• Tight p38 docking via residues 370–400 (K\_d ≈ 20 nM) is obligatory for efficient phosphorylation (fiore2016targetingmitogenactivatedprotein pages 10-12).  
• Loss-of-function mutants Lys93→Arg or Asp207→Ala abolish catalysis; phosphomimetics Thr222E/Thr334E render the kinase constitutively active (fiore2016targetingmitogenactivatedprotein pages 10-12).  
• Ubiquitination: none reported in the current literature.

## Function

• Highly expressed in heart, skeletal muscle and kidney; detectable in immune and stromal cells (roux2004erkandp38 pages 16-17).  
• Upstream cascade: stress → MKK3/6 → p38α → MK2 (singh2017biologicalfunctionsand pages 1-6).  
• Major roles:  
– Actin remodeling and cell migration via HSP27 phosphorylation (schindler2007p38pathwaykinases pages 5-6).  
– Post-transcriptional control of inflammatory cytokines by phosphorylating TTP/ZFP36 and ELAVL1 (soni2019mapkapk2themaster pages 3-4).  
– Cell-cycle and DNA-damage checkpoints through CDC25B/C and LIMK1 regulation (fiore2016targetingmitogenactivatedprotein pages 51-54).  
– Identified as a driver kinase in colitis models (strasser2019substratebasedkinaseactivity pages 13-14).

## Inhibitors

• ATP-competitive type I  
– Staurosporine (reference ligand; co-crystal 1NY3) (fiore2016targetingmitogenactivatedprotein pages 10-12).  
– PF-3644022: benzothiophene scaffold; IC₅₀ ≈ 5 nM enzymatic, ~150 nM cellular; suppresses TNF-α release in vivo (fiore2016targetingmitogenactivatedprotein pages 18-21).  
• Indirect inhibition: p38α blocker SB203580 prevents MK2 activation (schindler2007p38pathwaykinases pages 5-6).

## Other Comments

• Mapkapk2-knockout mice show impaired TNF-α/IL-6 production and resistance to endotoxic shock (schindler2007p38pathwaykinases pages 5-6).  
• Persistent MK2 signaling stabilizes oncogenic transcripts and promotes tumor progression (soni2019mapkapk2themaster pages 3-4).  
• Hyperactivation of the p38/MK2 axis contributes to inflammatory bowel disease pathology (strasser2019substratebasedkinaseactivity pages 13-14).

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