## Phylogeny

Highly conserved serine/threonine kinase with clear orthologs in Homo sapiens (MAPKAPK2), Mus musculus (Mapkapk2), Rattus norvegicus, Danio rerio and invertebrates such as Drosophila melanogaster and Caenorhabditis elegans (~60 % identity) (Cargnello & Roux, 2011; Roux & Blenis, 2004). Yeasts encode functional analogues (Rck1/Rck2 in Saccharomyces cerevisiae, Srk1/Mkp2 in Schizosaccharomyces pombe) that act downstream of p38-like modules but are not direct orthologs (Cargnello & Roux, 2011). Within the human kinome, MAPKAPK2 clusters with MAPKAPK3 (75 % identity) inside the MAPK-activated protein-kinase sub-family on the CaMK-like branch (Roux & Blenis, 2004; Cargnello & Roux, 2011).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (Fiore, Forli, & Manetti, 2016).

## Cofactor Requirements

Requires Mg²⁺ (standard assay 25 mM MgCl₂); Mn²⁺ can substitute with retained activity (Powell et al., 2003; Fiore et al., 2016).

## Substrate Specificity

Preferred consensus Φ-X-Arg-X₂-Ser/Thr (Φ = large hydrophobic) (Johnson et al., 2023). Verified cellular substrates include HSP27/HSPB1, TTP/ZFP36, LIMK1, LSP1, CDC25B/C, ALOX5 and ELAVL1 (Schindler, Monahan, & Smith, 2007; Fiore et al., 2016).

## Structure

Isoform 1 (400 aa) contains:  
• Proline-rich SH3 segment (aa 10–40)  
• Bilobal kinase core (aa 64–325) with Met138 gatekeeper creating a narrow ATP pocket  
• Autoinhibitory α-helix (aa 328–364) that occludes the active site  
• Nuclear export signal (aa 356–365)  
• High-affinity p38 docking site (aa 366–390) with overlapping bipartite NLS (aa 371–374 & 385–389) (Fiore et al., 2016; Singh, Najmi, & Dastidar, 2017)

Representative PDB entries: apo 1KWP; ADP/staurosporine-bound 1NY3, 1NXK; phosphomimetic active 3KA0; p38α–MK2 heterodimers 2OZA, 2ONL (Fiore et al., 2016). Activation involves completion of the hydrophobic spine and αC-helix rotation; phosphorylation displaces the autoinhibitory helix, exposing the catalytic cleft and NLS (Fiore et al., 2016).

## Regulation

• Activated by p38α/MAPK14 phosphorylation on Thr222, Ser272 (activation loop) and Thr334 (C-terminus), which also unmasks the NES (Singh et al., 2017; Roux & Blenis, 2004).  
• Autophosphorylation on Ser9, Thr25 and Ser328 (Fiore et al., 2016).  
• SUMOylation of Lys353 by PIAS1 suppresses activity; K353R mutation abrogates inhibition (Fiore et al., 2016).  
• Tight p38 docking via residues 370–400 (K\_d ≈ 20 nM) is essential for efficient activation (Fiore et al., 2016).  
• Catalysis is lost in Lys93→Arg or Asp207→Ala mutants; Thr222E/Thr334E phosphomimetics confer constitutive activity (Fiore et al., 2016).  
• No ubiquitination reported to date.

## Function

Highly expressed in heart, skeletal muscle and kidney; present in immune and stromal cells (Roux & Blenis, 2004). Activated stress pathway: stress → MKK3/6 → p38α → MK2 (Singh et al., 2017). Principal roles:  
– Actin cytoskeleton remodelling and cell migration via HSP27 phosphorylation (Schindler et al., 2007).  
– Post-transcriptional regulation of inflammatory cytokines through phosphorylation of TTP/ZFP36 and ELAVL1 (Soni, Anand, & Padwad, 2019).  
– Cell-cycle and DNA-damage checkpoints via CDC25B/C and LIMK1 (Fiore et al., 2016).  
– Identified as a driver kinase in murine colitis models (Strasser et al., 2019).

## Inhibitors

ATP-competitive type I: staurosporine (co-crystal 1NY3); PF-3644022 (IC₅₀ ≈ 5 nM enzymatic, ~150 nM cellular) suppresses TNF-α release in vivo (Fiore et al., 2016). Indirect inhibition: p38α blocker SB203580 prevents MK2 activation (Schindler et al., 2007).

## Other Comments

Mapkapk2-knockout mice exhibit reduced TNF-α/IL-6 production and resistance to endotoxic shock (Schindler et al., 2007). Persistent MK2 activity stabilises oncogenic transcripts and promotes tumour progression (Soni et al., 2019). Hyperactivation of the p38/MK2 axis contributes to inflammatory bowel disease pathology (Strasser et al., 2019).

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