## Phylogeny

Mitogen-activated protein kinase 8 (MAPK8; JNK1) belongs to the CMGC group of the eukaryotic protein-kinase superfamily and, within this group, to the highly conserved MAP kinase family (Manning et al., 2002a, 2002b). Three paralogous JNK genes (JNK1/2/3) arose after the divergence of vertebrates from invertebrates (Manning et al., 2002b). Orthologues of MAPK family members occur across metazoans, including Drosophila and Caenorhabditis, whereas MAPK8 itself is generally absent from yeast (Manning et al., 2002a).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇄ ADP + O-phospho-L-seryl/threonyl-[protein] (Sabapathy, 2012).

## Cofactor Requirements

Requires Mg²⁺ for ATP coordination and catalysis (Cicenas et al., 2017; Sabapathy, 2012; Shaw et al., 2008).

## Substrate Specificity

Positional scanning peptide-array analysis classifies MAPK8 as a proline-directed kinase that prefers Ser/Thr followed immediately (+1) by Pro. Hydrophobic residues N-terminal to the phosphorylation site enhance recognition, whereas charged residues at several positions are disfavoured (Johnson et al., 2023).

## Structure

MAPK8 adopts the canonical bilobal protein-kinase fold with a β-rich N-lobe and predominantly α-helical C-lobe (Unknown Authors, 2023; Sabapathy, 2012). Key elements include:  
• N-lobe Gly-rich loop (res. 33–40) forming the ATP-binding ceiling (Sabapathy, 2012; Yan et al., 2011).  
• αC-helix that orients catalytic residues.  
• Hydrophobic spine spanning both lobes and stabilising the active conformation (Heo et al., 2004; Sabapathy, 2012).  
• Activation segment (res. 169–195) containing Thr183 and Tyr185, the dual-phosphorylation sites required for activity (Yan et al., 2011; Sabapathy, 2012).  
• MAP-kinase insert in the C-lobe implicated in regulatory interactions (Shaw et al., 2008).  
Experimental structures are available in the PDB, and a high-confidence AlphaFold model has been generated (Sabapathy, 2012).

## Regulation

Activation: Dual phosphorylation of Thr183 and Tyr185 within the TPY motif by MAP2K4 (prefers Tyr185) and MAP2K7 (prefers Thr183); the two kinases act synergistically (Cicenas et al., 2017; Unknown Authors, 2023).  
Inactivation: Dephosphorylation by dual-specificity phosphatases DUSP1/2/3/7/8, MKP5 and MKP7 (Ha et al., 2019; Liu et al., 2016).  
Scaffolding: JIP1 organises the JNK module, retains JNK1 in the cytoplasm and can allosterically reduce ATP affinity (Heo et al., 2004).

## Function

Ubiquitously expressed in cytoplasm and nucleus, MAPK8 integrates responses to UV irradiation, oxidative stress and inflammatory cues as a core component of the stress-activated protein kinase/JNK pathway (Chen, 2011). Upon activation by MAP2K4/7, it phosphorylates transcription factors c-Jun (Ser63/73), ATF-2, Elk-1 and p53, thereby modulating gene expression that governs proliferation, differentiation, apoptosis and migration (Chen, 2011). JNK1-mediated apoptosis influences both extrinsic (Fas) and intrinsic pathways via phosphorylation of Bcl-2 family proteins and p53 (Chen, 2011). In neurons, JNK1 phosphorylates microtubule-associated proteins and is required for microtubule maintenance (Chang et al., 2003).

## Inhibitors

ATP-competitive inhibitors: SP600125, AS601245, CC-401 (Cicenas et al., 2017).  
Covalent inhibitors: JNK-IN-8, JNK-IN-12 targeting a conserved cysteine in the ATP pocket (Zhang et al., 2012).  
Allosteric peptide inhibitors: JIP1-derived peptides such as pepJIP1 (Heo et al., 2004).

## Other Comments

Dysregulated MAPK8 signalling is linked to cancer, inflammatory disorders, obesity, insulin resistance, and neurodegenerative diseases (Chen, 2011; Cicenas et al., 2017). Associations with autoimmune conditions (e.g., rheumatoid arthritis, type 1 diabetes) have also been reported (Shaw et al., 2008). No specific disease-causing MAPK8 mutations are detailed in the current dataset (Chen, 2011).

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