## Phylogeny

MAPK14 (p38 α) is a member of the p38 sub-family of stress-activated protein kinases (SAPKs) that also includes p38 β, p38 γ and p38 δ. The four paralogues form a distinct branch within the CMGC group of serine/threonine kinases and descend from the yeast stress-responsive HOG1 kinase (Cargnello & Roux, 2011, pp. 4–5; Martín-Blanco, 2000, pp. 1–2; Widmann et al., 1999, pp. 5–6). Approximately 50 % sequence identity with ERK2 and conservation of the dual-phosphorylation TGY motif indicate deep evolutionary conservation across vertebrates (Kültz, 1998, pp. 2–3; Widmann et al., 1999, pp. 5–6).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Widmann et al., 1999, pp. 1–2; Orand, 2023, pp. 33–38).

## Cofactor Requirements

Requires Mg²⁺ for ATP coordination and efficient phosphate transfer (Theodosiou & Ashworth, 2002, pp. 1–2).

## Substrate Specificity

MAPK14 preferentially phosphorylates Ser/Thr residues followed by Pro (S/T-P motif). Docking interactions refine recognition, allowing phosphorylation of an estimated 200–300 substrates that include transcription factors ATF1/2, MEF2, Elk-1 and TP53, and protein kinases MK2, MK3, MNK1 and MNK2 (Cargnello & Roux, 2011, pp. 4–5; Martín-Blanco, 2000, pp. 2–3; Orand, 2023, pp. 38–41).

## Structure

The kinase adopts the canonical bilobed CMGC fold: a β-stranded N-lobe and an α-helical C-lobe with a central ATP-binding cleft. The activation loop contains the conserved T 183-G-Y 185 motif that undergoes dual phosphorylation by MKK3/6, triggering conformational changes required for activity. Structural studies reveal a hydrophobic spine, key C-helix residues for catalysis and subtle docking-site differences that distinguish p38 α from its paralogues (Cargnello & Roux, 2011, pp. 4–5; Orand, 2023, pp. 41–45).

## Regulation

• Activation: dual phosphorylation of Thr183 and Tyr185 by upstream MKK3 and MKK6 in response to UV, oxidative stress and inflammatory cytokines (Cargnello & Roux, 2011, pp. 4–5; Martín-Blanco, 2000, pp. 1–2).  
• Subcellular distribution: activated MAPK14 translocates between cytoplasm and nucleus to access distinct substrates (Cargnello & Roux, 2011, pp. 23–24; Roux & Blenis, 2004, pp. 17–18).  
• Negative regulation: MAP kinase phosphatases dephosphorylate the activation loop; casein kinase II and other protein interactions modulate autophosphorylation and activity (Theodosiou & Ashworth, 2002, pp. 1–2; Roux & Blenis, 2004, pp. 17–18).

## Function

MAPK14 is a central mediator of cellular responses to pro-inflammatory cytokines and environmental stress. By phosphorylating nuclear transcription factors (ATF1/2, MEF2, Elk-1, TP53) it drives immediate-early gene expression and chromatin remodelling (Cargnello & Roux, 2011, pp. 19–20; Orand, 2023, pp. 25–29). Cytoplasmic targets include MK2/3 and MNK1/2 as well as proteins involved in protein degradation (e.g., SIAH2) and receptor endocytosis/shedding (e.g., ADAM17), thereby influencing inflammation, cell-cycle progression and receptor signalling (Cargnello & Roux, 2011, pp. 23–25; Widmann et al., 1999, pp. 22–24).

## Inhibitors

Competitive ATP-site inhibitors SB203580 and SB202190 are widely used experimental tools to block MAPK14 activity (Martín-Blanco, 2000, pp. 1–2; New et al., 1998, pp. 1–3).

## Other Comments

Aberrant MAPK14 signalling is linked to inflammatory diseases, cancers and developmental disorders, making the kinase an attractive target for anti-inflammatory and anti-cancer drug development (Widmann et al., 1999, pp. 24–25; Roux & Blenis, 2004, pp. 16–17; Cargnello & Roux, 2011, pp. 24–25).

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