## Phylogeny

Mitogen-activated protein kinase 13 (MAPK13; p38δ/SAPK4) is one of four members of the p38 MAPK sub-family (p38α /MAPK14, p38β /MAPK11, p38γ /MAPK12, p38δ /MAPK13). The four p38 isoforms form a distinct branch of the eukaryotic protein kinase super-family that emerged early in eukaryotic evolution and is conserved in mammals (Arbabi & Maier, 2002; Kyriakis & Avruch, 2001). MAPK13 shares ~60 % overall amino-acid identity with p38α/β and is more divergent from p38γ (Cerezo-Guisado & Cuenda, 2011). Conservation centres on the catalytic domain and activation-loop motif, reflecting their common role in stress-activated signalling (Pearson et al., 2001).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Johnson & Lapadat, 2002).

## Cofactor Requirements

Mg²⁺ is essential for ATP binding and catalysis (Zarubin & Han, 2005; Roux & Blenis, 2004).

## Substrate Specificity

MAPK13 phosphorylates Ser/Thr residues in 200–300 cellular proteins. Documented substrates include transcription factors ELK1 and ATF2, the downstream kinase MAPKAPK2, translation regulator EEF2K, and cytoskeletal proteins MAPT (tau) and STMN1 (stathmin) (Cerezo-Guisado & Cuenda, 2011; Arbabi & Maier, 2002). Although a unique consensus motif has not been fully defined, its preference aligns with motifs recognised by other p38 isoforms.

## Structure

MAPK13 is a 365-residue, ~40 kDa serine/threonine kinase that adopts the canonical bilobal protein kinase fold (Tibbles & Woodgett, 1999). The activation loop contains the conserved Thr-Gly-Tyr (TGY) motif; dual phosphorylation of Thr180 and Tyr182 is required for full activity (Cerezo-Guisado & Cuenda, 2011; Zarubin & Han, 2005). The N-terminal C-helix contributes to the hydrophobic spine, and docking sites on the kinase surface mediate interaction with upstream MKK3/MKK6 and substrates (Roux & Blenis, 2004). No additional domains beyond the catalytic core have been reported; isoform-specific surface variations influence substrate and inhibitor binding (Cerezo-Guisado & Cuenda, 2011).

## Regulation

Activation is achieved by MKK3- or MKK6-mediated dual phosphorylation of the TGY motif. Cell-type–dependent preference for MKK3 versus MKK6 has been noted (Cerezo-Guisado & Cuenda, 2011; Zarubin & Han, 2005). Feedback control by downstream kinases (e.g., MAPKAPK2) and dephosphorylation by protein phosphatases ensure transient activation (Dodeller & Schulze-Koops, 2006; Kyriakis & Avruch, 2001). Compared with p38α/β, MAPK13 displays distinct sensitivity to small-molecule inhibitors, suggesting unique conformational regulation of the ATP-binding site (Zarubin & Han, 2005; Pearson et al., 2001).

## Function

MAPK13 integrates stress and inflammatory signals to modulate transcription, translation, cytoskeletal dynamics and metabolic processes.  
• Expression: widely detected in testes, pancreas, kidney and small intestine; localises to cytoplasm and nucleus (Cerezo-Guisado & Cuenda, 2011).  
• Upstream kinases: MKK3 and MKK6.  
• Downstream substrates/partners: ELK1, ATF2, MAPKAPK2, EEF2K, MAPT, STMN1 (Cerezo-Guisado & Cuenda, 2011; Arbabi & Maier, 2002).  
• Signalling roles:  
 – Transcriptional activation of inflammatory and stress-response genes (Cerezo-Guisado & Cuenda, 2011).  
 – Control of protein synthesis via EEF2K inhibition (Cerezo-Guisado & Cuenda, 2011).  
 – Cytoskeletal remodelling through phosphorylation of tau and stathmin (Arbabi & Maier, 2002).  
 – Regulation of keratinocyte differentiation, UV-induced gene expression and skin tumour development (Bachstetter, 2010; Cerezo-Guisado & Cuenda, 2011).  
 – Modulation of insulin secretion in pancreatic β-cells via PRKD1 down-regulation (Cerezo-Guisado & Cuenda, 2011).

## Inhibitors

Classic pyridinyl-imidazole inhibitors (e.g., SB203580) that potently block p38α/β show poor efficacy toward MAPK13, indicating isoform-specific structural differences in the ATP pocket (Zarubin & Han, 2005; Pearson et al., 2001).

## Other Comments

Altered MAPK13 activity is associated with inflammatory disorders, psoriasis, skin tumorigenesis, metabolic dysfunction linked to impaired insulin secretion, cancer and neurodegenerative diseases involving tau/stathmin regulation (Cerezo-Guisado & Cuenda, 2011; Bachstetter, 2010; Dodeller & Schulze-Koops, 2006).

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