## Proposed EC/sub-subclass:

— (not specified in the source material)

## Accepted name:

Mitogen-activated protein kinase 12 (MAPK12)

## Synonyms:

ERK6; SAPK3; p38 γ (p38 gamma)

## Phylogeny

MAPK12 belongs to the p38 mitogen-activated protein kinase subfamily, which also includes the p38 α, β and δ isoforms (Arbabi & Maier, 2002; Cargnello & Roux, 2011). Orthologs are conserved across vertebrates—e.g., human, mouse and rat—where similar stress-signalling roles are maintained (Cargnello & Roux, 2011; Kültz, 1998). Within the kinome, MAPK12 clusters on the p38 branch, distinct from ERK and JNK families, consistent with phylogenetic analyses tracing MAPK modules from early eukaryotes (Kyriakis & Avruch, 1996; Kültz, 1998).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇄ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Johnson & Lapadat, 2002; Arbabi & Maier, 2002)

## Cofactor requirements

Mg²⁺ is essential for ATP binding and phosphoryl transfer (Cuschieri & Maier, 2005).

## Substrate Specificity

MAPK12 is a proline-directed Ser/Thr kinase that preferentially phosphorylates sites with the consensus [S/T]P motif (Enslen et al., 1998; Tibbles & Woodgett, 1999). Documented cellular substrates include transcription factors ATF2 and ELK1 and the downstream kinase MAPKAPK2; overall, up to ~200–300 potential substrates are estimated for p38 isoforms (Arbabi & Maier, 2002; Cargnello & Roux, 2011; Goedert et al., 1997).

## Structure

MAPK12 comprises a canonical ~300–370-residue kinase domain flanked by variable N- and C-termini (Cargnello & Roux, 2011; Kültz, 1998). Key structural elements include:  
• An N-terminal lobe harbouring the glycine-rich ATP-binding loop  
• A C-terminal lobe that forms the substrate-binding cleft  
• A dual-phosphorylation Thr-Gly-Tyr (TGY) motif in the activation loop, required for activity (Arbabi & Maier, 2002; Cuenda et al., 1997)  
Distinct residues around the ATP pocket render MAPK12 resistant to pyridinyl-imidazole inhibitors that target other p38 isoforms (Kyriakis & Avruch, 2001; Cuenda et al., 1997). Homology models based on related p38 structures predict the characteristic N-terminal β-sheet and C-terminal α-helical fold (Cargnello & Roux, 2011).

## Regulation

Activation occurs via a three-tier MAPK cascade: upstream MAP2Ks MKK6 (primary) and MKK3 (secondary) dually phosphorylate the TGY motif (Cuenda et al., 1997; Arbabi & Maier, 2002). Cellular stresses (e.g., osmotic shock) and pro-inflammatory cytokines stimulate this pathway (Cargnello & Roux, 2011). Additional regulatory features include:  
• Nuclear translocation and binding to DLG1 after osmotic stress, modulating DLG1–SFPQ complexes independently of catalytic activity (Arbabi & Maier, 2002).  
• Roles in DNA-damage checkpoints, UV-repair and G2 arrest after γ-irradiation (Kyriakis & Avruch, 2001; Tibbles & Woodgett, 1999).  
• Negative modulation of c-Jun phosphorylation, influencing AP-1 activity (Kyriakis & Avruch, 2001).  
Phosphatases (MAPK phosphatases) and scaffold proteins further fine-tune signalling dynamics (Cuenda et al., 1997; Kyriakis & Avruch, 2001).

## Function

MAPK12 orchestrates cellular responses to pro-inflammatory cytokines and diverse physical stresses. Documented roles include:  
• Phosphorylation of ELK1 and ATF2 to trigger stress-responsive gene expression (Arbabi & Maier, 2002; Cargnello & Roux, 2011).  
• Essential contribution to myoblast differentiation and skeletal-muscle regeneration (Cargnello & Roux, 2011; Tibbles & Woodgett, 1999).  
• Hypoxia-induced down-regulation of cyclin D1 in adrenal cells, linking MAPK12 to proliferation control (Arbabi & Maier, 2002; Kyriakis & Avruch, 2001).  
• Regulation of osmotic-shock adaptation via disruption of DLG1–SFPQ nuclear complexes (Arbabi & Maier, 2002).  
• Maintenance of chromosomal stability through control of PLK1 kinetochore localisation during mitosis (Kyriakis & Avruch, 2001).  
• Modulation of glucose transporter (SLC2A1, SLC2A4) expression, affecting basal and contraction-mediated glucose uptake in muscle (Arbabi & Maier, 2002; Tibbles & Woodgett, 1999).

## Inhibitors

Pyridinyl-imidazole compounds (e.g., SB203580) potently inhibit p38 α/β/δ but are ineffective against MAPK12 owing to unique residues in the ATP pocket (Cuenda et al., 1997; Kyriakis & Avruch, 2001). This differential sensitivity provides an avenue for developing MAPK12-selective modulators (Roux & Blenis, 2004; Sugden & Clerk, 1998).

## Other Comments

Aberrant MAPK12 signalling is linked to inflammatory disorders, dysregulated proliferation and impaired DNA-repair processes that may contribute to cancer and metabolic diseases (Arbabi & Maier, 2002; Kyriakis & Avruch, 2001; Tibbles & Woodgett, 1999). No specific disease-causing mutations are detailed in the source material.

## References

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