## Proposed EC/Sub-subclass

2.7.11.24

## Accepted name

Mitogen-activated protein kinase 14

## Synonyms

p38 α; p38 MAPK; MAP kinase 14

## 1. Phylogeny

Member of the p38 subfamily of stress-activated protein kinases, which comprises p38 α (MAPK14), β, γ and δ. These isoforms are conserved throughout vertebrate evolution and share ancestry with the yeast stress-responsive kinase HOG1. MAPK14 shows ~50 % sequence identity with ERK2 and resides in the CMGC group of Ser/Thr kinases. Phylogenetic analyses based on the dual-phosphorylation motif and docking regions place MAPK14 on a distinct, ancient branch that has retained key functional residues over hundreds of millions of years (PMID: 21372320, 10881912, 9922379, 9560430).

## 2. Reaction catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (PMID: 9922379, 21372320).

## 3. Cofactor requirements

Mg²⁺ is essential for ATP coordination and catalysis (PMID: 12057199).

## 4. Substrate specificity

Selectively phosphorylates Ser/Thr residues followed by Pro (S/T-P motif). Docking interactions further refine recognition, enabling phosphorylation of an estimated 200-300 substrates that include transcription factors (ATF1, ATF2, MEF2, Elk-1, TP53) and downstream kinases (MK2, MK3, MNK1, MNK2) (PMID: 21372320, 10881912).

## 5. Structure

Consists solely of the canonical protein-kinase bilobed catalytic domain: a β-sheet-rich N-lobe and an α-helical C-lobe. The activation loop harbours the conserved Thr-Gly-Tyr (TGY) motif; dual phosphorylation here triggers the conformational change required for full activity. Crystal structures reveal a defined ATP-binding cleft, a hydrophobic spine and C-helix residues that participate in substrate binding; subtle differences in docking sites distinguish p38 α from its paralogues (PMID: 21372320, 9922379).

## 6. Regulation

Activated by dual phosphorylation of Thr183 and Tyr185 by MKK3 and MKK6 in response to UV, oxidative stress and inflammatory cytokines. Upon activation, MAPK14 translocates between cytoplasm and nucleus. Dephosphorylated and inactivated by MAP kinase phosphatases (MKPs). Interactions with other regulators, such as casein kinase II, modulate autophosphorylation and overall activity (PMID: 21372320, 10881912, 15187184, 12057199).

## 7. Function

Key mediator of stress and inflammatory signalling. Through phosphorylation of transcription factors, downstream kinases and chromatin-associated proteins, MAPK14 controls immediate-early gene expression, chromatin remodelling, cell-cycle checkpoints, protein turnover and receptor endocytosis (PMID: 21372320, 9922379).

## 8. Other comments

Widely used ATP-competitive inhibitors include SB203580 and SB202190; these compounds block MAPK14 activity in cells and are tools for dissecting p38 signalling. Dysregulated MAPK14 activity is linked to inflammatory diseases, certain cancers and developmental disorders, making the kinase an ongoing therapeutic target (PMID: 10881912, 9649428, 15187184, 21372320).

## 9. References

PMID 21372320 – Cargnello M & Roux PP, 2011  
PMID 10881912 – Martín-Blanco E, 2000  
PMID 9922379 – Widmann C et al., 1999  
PMID 9560430 – Kültz D, 1998  
PMID 12057199 – Theodosiou A & Ashworth A, 2002  
PMID 15187184 – Roux PP & Blenis J, 2004  
PMID 9649428 – New L et al., 1998

(In-text citations correspond to the PMIDs listed above.)