## Proposed EC/sub-subclass:

2.7.11.– *(serine/threonine-protein kinase; subclass not specified in source)*

## Accepted name:

Mitogen-activated protein kinase 14

## Synonyms:

p38 α (p38 alpha)

## Phylogeny:

Member of the p38 subfamily of stress-activated protein kinases (SAPKs); paralogues are p38 β, p38 γ and p38 δ. Closely related to the yeast HOG1 kinase and shows ~50 % sequence identity with ERK2. Dual-phosphorylation motif and docking regions define a distinct, highly conserved evolutionary branch that has retained key functional residues across vertebrates and other species.

## Reaction catalysed:

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein]

## Cofactor requirements:

Mg²⁺ (essential for ATP coordination and catalysis)

## Specificity:

Phosphorylates Ser/Thr residues followed by Pro (S/T-P motif). Docking interactions refine recognition and allow phosphorylation of an estimated 200–300 substrates, including transcription factors (ATF1, ATF2, MEF2, Elk-1, TP53) and downstream kinases (MK2, MK3, MNK1, MNK2).

## Structure:

Typical bilobed CMGC-family catalytic domain with a β-stranded N-lobe and α-helical C-lobe. Activation loop bears the conserved Thr-Gly-Tyr (TGY) motif that is dually phosphorylated for full activation. Crystal structures show an ATP-binding cleft, hydrophobic spine, and C-helix residues crucial for catalysis; subtle differences in docking sites distinguish p38 α from its paralogues.

## Regulation:

Activated by dual phosphorylation of Thr183 and Tyr185 by the upstream MAPKKs MKK3 and MKK6 in response to UV, oxidative stress and inflammatory cytokines. Translocates between cytoplasm and nucleus upon activation. Inactivated by MAP kinase phosphatases (MKPs); additional modulation by interacting proteins such as casein kinase II.

## Function:

Central mediator of cellular stress and inflammatory signalling. Through phosphorylation of transcription factors and downstream kinases, controls inflammation, cell-cycle progression, protein turnover, receptor endocytosis, immediate-early gene induction, chromatin remodelling and regulation of protein degradation pathways (e.g. SIAH2, ADAM17).

## Inhibitors:

ATP-competitive compounds SB203580 and SB202190 are widely used experimental inhibitors of MAPK14.

## Other comments:

Aberrant MAPK14 activity is linked to inflammatory disorders, certain cancers and developmental anomalies owing to its roles in cytokine expression, apoptosis and stress responses.

## References:

Inline citations to cargnello2011activationandfunction; martinblanco2000p38mapksignalling; widmann1999mitogenactivatedproteinkinase; kultz1998phylogeneticandfunctional; orand2023revealingthemechanism; theodosiou2002mapkinasephosphatases; roux2004erkandp38; new1998prakanovel.