## Phylogeny

Mitogen-activated protein kinase 14 (MAPK14, p38 α) is a member of the p38 subfamily of stress-activated protein kinases (SAPKs), which also includes the β, γ and δ isoforms. The entire p38 branch is conserved throughout vertebrate evolution and is phylogenetically related to the yeast stress-responsive kinase HOG1. MAPK14 shares ~50 % sequence identity with ERK2 and, together with other MAPKs, resides in the conserved CMGC group of serine/threonine kinases. Conserved dual-phosphorylation motifs and docking regions place MAPK14 on a distinct evolutionary branch that has retained critical functional residues for cellular stress responses over hundreds of millions of years.

## Reaction Catalyzed

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

## Cofactor Requirements

Mg²⁺

## Substrate Specificity

MAPK14 preferentially phosphorylates serine or threonine residues immediately followed by proline (S/T-P motif). Docking interactions between the kinase and its targets refine this core preference, allowing phosphorylation of an estimated 200–300 substrates, including:  
• Transcription factors: ATF1, ATF2, MEF2, Elk-1, TP53  
• Down-stream kinases: MK2, MK3, MNK1, MNK2

## Structure

MAPK14 possesses the bilobed protein-kinase fold characteristic of CMGC kinases: a β-strand-rich N-terminal lobe and an α-helical C-terminal lobe. The activation loop carries the conserved Thr-Gly-Tyr (TGY) motif that is dually phosphorylated for full activation. Crystal structures reveal a defined ATP-binding cleft, a hydrophobic spine and key catalytic residues within the C-helix; subtle variations in docking sites distinguish p38 α from its paralogues.

## Regulation

• Activation: dual phosphorylation of Thr183 and Tyr185 by the upstream MAPKKs MKK3 and MKK6 in response to stimuli such as UV light, oxidative stress and inflammatory cytokines.  
• Localization: stress-induced shuttling between cytoplasm and nucleus.  
• Negative regulation: dephosphorylation by MAP kinase phosphatases (MKPs).  
• Additional modulation: interactions with proteins such as casein kinase II can influence autophosphorylation and activity.

## Function

MAPK14 is a core component of MAPK signalling cascades that mediate cellular responses to pro-inflammatory cytokines and environmental stress. By phosphorylating numerous substrates (e.g. ATF1/2, MEF2, TP53, MK2/3, MNK1/2), it controls inflammation, cell-cycle regulation, protein turnover and receptor endocytosis. In the nucleus, it promotes immediate-early gene induction and chromatin remodelling; in the cytoplasm, it regulates protein degradation pathways through substrates such as the ubiquitin ligase SIAH2 and the metalloprotease ADAM17.

## Inhibitors

ATP-competitive inhibitors SB203580 and SB202190 are widely used experimental compounds that block MAPK14 catalytic activity.

## Other Comments

Aberrant MAPK14 activity is linked to inflammatory diseases, certain cancers and developmental defects, motivating ongoing efforts to develop anti-inflammatory and anti-cancer therapeutics targeting this kinase.

## 9. References

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