## Phylogeny

MAPK11 (p38 β) is an evolutionarily conserved member of the p38 MAPK subfamily. Across vertebrates it is consistently found in a gene cluster that also encodes the closely related MAPK14 (p38 α) and the more divergent p38 γ and p38 δ isoforms, reflecting a segmental duplication event that split the p38 lineage into two branches, one of which includes MAPK11 and MAPK14 (Li, Liu, & Zhang, 2011; Escós, Risco, Alsina-Beauchamp, & Cuenda, 2016; Roux & Blenis, 2004). Conservation of MAPK11 in multiple species underscores its role as part of an evolutionary core set of stress-responsive kinases (Li et al., 2011).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Cargnello & Roux, 2011; Shi & Gaestel, 2002).

## Cofactor Requirements

Catalysis requires Mg²⁺ to coordinate ATP at the active site (Machado, Machado, & Pascutti, 2021; Shi & Gaestel, 2002).

## Substrate Specificity

MAPK11 is a Ser/Thr kinase that preferentially phosphorylates substrates containing a Ser/Thr-Pro motif. Its relatively relaxed sequence preference allows phosphorylation of an estimated 200–300 substrates, including transcription factors and regulatory enzymes involved in stress and inflammatory responses (Cargnello & Roux, 2011; Burton et al., 2021; Shi & Gaestel, 2002).

## Structure

MAPK11 adopts the canonical bilobal protein kinase fold: a β-sheet-rich N-terminal lobe and an α-helical C-terminal lobe. Key structural features include:  
• An activation loop bearing the dual-phosphorylation Thr-Gly-Tyr (TGY) motif required for activation.  
• A docking site (DPED motif) that mediates interactions with upstream MKK3/MKK6 and downstream substrates.  
• An ATP-binding cleft bordered by a regulatory C-helix and adjacent hydrophobic pockets that accommodate ATP or small-molecule inhibitors (Cargnello & Roux, 2011; Roux & Blenis, 2004; Shi & Gaestel, 2002).

## Regulation

Activation is achieved through dual phosphorylation of the TGY motif by the MAP2Ks MKK3 and MKK6. Inactivation occurs via MAP kinase phosphatases that dephosphorylate this loop. Scaffold/adaptor proteins modulate sub-cellular localisation and timing of activation, and ATP-competitive inhibitors can allosterically restrain catalytic activity (Cargnello & Roux, 2011; Burton et al., 2021; Shi & Gaestel, 2002).

## Function

MAPK11 is a central component of the cellular stress-response pathway. Upon stimulation by environmental stressors or pro-inflammatory cytokines it phosphorylates:  
• Downstream kinases MAPKAPK2/3 and MNK1/2, propagating signals that regulate mRNA stability and translation.  
• Nuclear transcription factors (e.g., ATF1/2, p53, NF-κB family members) to drive immediate-early gene expression.  
• Proteins controlling mRNA processing, protein turnover, and metalloprotease-mediated ectodomain shedding, thereby influencing inflammatory cascades (Cargnello & Roux, 2011; Burton et al., 2021; Koul, Pal, & Koul, 2013; Shi & Gaestel, 2002).  
Although its signalling spectrum overlaps with MAPK14, differential tissue expression of MAPK11 provides additional layers of pathway fine-tuning (Cargnello & Roux, 2011).

## Inhibitors

ATP-competitive compounds such as SB203580 and SB202190 inhibit both MAPK11 and MAPK14 by occupying the conserved ATP-binding pocket (Cargnello & Roux, 2011; Machado et al., 2021).

## Other Comments

Because MAPK11 participates broadly in stress and inflammatory signalling, dysregulation of its activity has been linked to various pathologies, and p38 inhibitors remain under investigation as therapeutic agents (Burton et al., 2021; Machado et al., 2021).

## 9. References

Burton, J. C., Antoniades, W., Okalova, J., Roos, M. M., & Grimsey, N. J. (2021). Atypical p38 signaling, activation, and implications for disease. International Journal of Molecular Sciences, 22, 4183. https://doi.org/10.3390/ijms22084183

Cargnello, M., & Roux, P. P. (2011). Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. Microbiology and Molecular Biology Reviews, 75, 50–83. https://doi.org/10.1128/MMBR.00031-10

Escós, A., Risco, A., Alsina-Beauchamp, D., & Cuenda, A. (2016). p38γ and p38δ mitogen-activated protein kinases (MAPKs), new stars in the MAPK galaxy. Frontiers in Cell and Developmental Biology, 4, 31. https://doi.org/10.3389/fcell.2016.00031

Koul, H., Pal, M., & Koul, S. (2013). Role of p38 MAP kinase signal transduction in solid tumors. Genes & Cancer, 4, 342–359. https://doi.org/10.1177/1947601913507951

Li, M., Liu, J., & Zhang, C. (2011). Evolutionary history of the vertebrate mitogen-activated protein kinases family. PLoS ONE, 6, e26999. https://doi.org/10.1371/journal.pone.0026999

Machado, T. R., Machado, T. R., & Pascutti, P. G. (2021). The p38 MAPK inhibitors and their role in inflammatory diseases. ChemistrySelect, 6, 5729–5742. https://doi.org/10.1002/slct.202100406

Roux, P. P., & Blenis, J. (2004). ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiology and Molecular Biology Reviews, 68, 320–344. https://doi.org/10.1128/MMBR.68.2.320-344.2004

Shi, Y., & Gaestel, M. (2002). In the cellular garden of forking paths: how p38 MAPKs signal for downstream assistance. Biological Chemistry, 383, 1519–1536. https://doi.org/10.1515/BC.2002.173