## Phylogeny

MAPK11 (p38β) belongs to the p38 mitogen-activated protein kinase family within the CMGC group of the human kinome (Cánovas & Nebreda, 2021; Cuadrado & Nebreda, 2010; Li et al., 2011). Four vertebrate p38 isoforms arose through gene duplication: p38α (MAPK14), p38β (MAPK11), p38γ (MAPK12) and p38δ (MAPK13) (O’Callaghan et al., 2014). p38β is most closely related to p38α, sharing ~75 % amino-acid identity (Roche et al., 2020; Cuenda & Rousseau, 2007). Orthologues are reported in mammals (*Homo sapiens*, *Macaca mulatta*, *Mus musculus*, *Rattus norvegicus*), zebrafish and *C. elegans* (Li et al., 2011; Cuadrado & Nebreda, 2010; Shabardina et al., 2023).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Cánovas & Nebreda, 2021; Roche et al., 2020; O’Callaghan et al., 2014).

## Cofactor Requirements

Requires Mg²⁺ for ATP binding and phosphotransferase activity (Cánovas & Nebreda, 2021; Maik-Rachline et al., 2020; O’Callaghan et al., 2014; Roche et al., 2020).

## Substrate Specificity

• Proline-directed Ser/Thr kinase with minimal consensus Ser/Thr-Pro (SP/TP) (Roche et al., 2020; Madkour et al., 2021; Maik-Rachline et al., 2020; Burton et al., 2021).  
• Phosphoproteomics indicates additional preferences: Pro at P-3, Lys/Arg at P-2, hydrophobic residue at P-1, and a small/polar residue at P + 1 (Cuadrado & Nebreda, 2010).  
• Docking interactions through substrate D-domains (Arg/Lys₂-X₂-₆-Φ-X-Φ) and DEF motifs (FxF) enhance recognition (Maik-Rachline et al., 2020).

## Structure

Canonical bilobal kinase fold: a β-sheet-rich N-lobe (residues 1–105), α-helical C-lobe (114–316) and a flexible hinge (106–113) forming the ATP-binding cleft (Cánovas & Nebreda, 2021; Roche et al., 2020). Conserved hydrophobic spine and C-helix maintain the active conformation (Cuadrado & Nebreda, 2010; Li et al., 2011). The activation loop contains the Thr-Gly-Tyr (TGY) motif (Cánovas & Nebreda, 2021). Compared with p38α, p38β has a slightly smaller ATP-binding pocket due to altered N-/C-lobe orientation (Roche et al., 2020; Cuadrado & Nebreda, 2010). High-homology structures of p38α (PDB: 5ETC, 1A9U, 3GCU) serve as models for p38β (Cánovas & Nebreda, 2021; Roche et al., 2020).

## Regulation

Full activation requires dual phosphorylation of Thr180 and Tyr182 within the TGY motif by the MAP2Ks MKK3 and, more efficiently, MKK6 (Cánovas & Nebreda, 2021; Maik-Rachline et al., 2020; Zarubin & Han, 2005). MKK6 shows strong selectivity for p38β; MKK3 acts less efficiently (Roche et al., 2020; Zarubin & Han, 2005). Thr180 can also undergo autophosphorylation, modulating basal activity (Roche et al., 2020). Dephosphorylation and inactivation are mediated by MAP kinase phosphatases (Zarubin & Han, 2005).

## Function

Ubiquitously expressed but lower than p38α, with higher levels in endothelial cells, brain, heart and lung; absent in macrophages and monocytes (Roche et al., 2020; Burton et al., 2021). Activated by pro-inflammatory cytokines (e.g., IL-1β, TNF) and environmental stresses (UV, osmotic shock) and regulates gene expression, mRNA stability, cell-cycle progression and apoptosis (Cánovas & Nebreda, 2021; Roche et al., 2020). Shares many substrates with p38α, including downstream kinases MK2/3, MSK1/2, MNK1/2 and transcription factors ATF family, c-Myc, c-Fos, STAT1 and p53 (Cánovas & Nebreda, 2021; Roche et al., 2020). Unique reported substrates are glycogen synthase and Raptor, linking p38β to metabolism and mTORC1 signalling (Roche et al., 2020). Displays functional redundancy with MAPK14/p38α (Cánovas & Nebreda, 2021; Li et al., 2011).

## Inhibitors

Pyridinyl-imidazoles SB203580 and SB202190 are potent ATP-competitive inhibitors of p38α/β; sensitivity depends on Thr106 in the binding pocket (Cánovas & Nebreda, 2021; O’Callaghan et al., 2014; Cuenda & Rousseau, 2007). Losmapimod also targets both isoforms (Romero-Becerra et al., 2020). No inhibitors discriminate specifically between p38β and p38α (Roche et al., 2020).

## Other Comments

Implicated in inflammatory diseases, cancers, neurodegeneration, cardiac hypertrophy, Huntington’s disease and viral infections such as SARS-CoV-2 (Cánovas & Nebreda, 2021; Maik-Rachline et al., 2020; O’Callaghan et al., 2014; Roche et al., 2020). In cancer, p38β can act as tumour suppressor or promoter depending on context (Maik-Rachline et al., 2020; Roche et al., 2020). Mouse knockouts show p38α is embryonic lethal, whereas p38β knockout mice are viable, indicating non-redundant developmental functions (Roche et al., 2020; Kumar et al., 2003).

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