Protein: Mitogen-activated protein kinase 12 (MAPK12, p38γ/ERK6/SAPK3) UniProt: P53778

## Phylogeny

CMGC group ▸ MAP kinase family ▸ p38 sub-family ▸ p38γ/δ branch (cuenda2007p38mapkinasespathway pages 1-2).  
Gene-duplication analysis places MAPK11/12 as a derivative of the ancestral MAPK13/14 cluster (yokota2016p38mapkinases pages 1-2).  
Verified vertebrate orthologs include Mus musculus Mapk12 (qi2023p38γmapkinflammatory pages 7-8), Rattus norvegicus Mapk12 (kumar2003p38mapkinases pages 2-3), and human MAPK12; no invertebrate orthologs are reported in the cited literature.

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (machado2021thep38mapk pages 1-2).

## Cofactor Requirements

Catalysis requires a divalent cation, with Mg²⁺ coordinating ATP in the active site (goldsmith2004structureofmapks. pages 6-7).

## Substrate Specificity

• Proline-directed consensus motif: ‑P-X-(S/T)-P- (cuenda2007p38mapkinasespathway pages 1-2).  
• C-terminal KETXL PDZ-binding motif docks the kinase to PDZ-domain substrates such as α1-syntrophin, SAP90/PSD95 and SAP97/hDlg, enhancing phosphorylation efficiency (risco2012newinsightsinto pages 1-2).  
• p38γ/δ preferentially phosphorylate Tau, α1-syntrophin and SAP90/PSD95, whereas MAPKAPK2/3 are favored by p38α/β (cuenda2007p38mapkinasespathway pages 1-2).  
• Additional validated sites: HSP90α Ser595, β-catenin Ser605, PFKFB3 Ser467, retinoblastoma Ser807/Ser811 and p53 Ser33 (qi2023p38γmapkinflammatory pages 5-7).

## Structure

Length: 367 aa; crystallizes as a monomer with the canonical bilobed kinase fold (risco2012newinsightsinto pages 1-2).  
N-lobe: β-sheet plus Gly-rich loop (residues 30-37) forming part of the ATP pocket (goldsmith2004structureofmapks. pages 6-7).  
C-lobe: α-helical, harboring the catalytic loop (HRD motif) and DFG motif Asp168-Phe169-Gly170 (goldsmith2004structureofmapks. pages 6-7).  
Activation loop contains the Thr-Gly-Tyr motif; dual phosphorylation induces an active-loop conformation essentially superimposable on active ERK2 yet lacking a dimer interface, indicating a monomeric active state (cuadrado2010mechanismsandfunctions pages 2-3).  
Unique elements:  
• 38-residue MAPK insertion characteristic of MAPKs, contributing to substrate docking (goldsmith2004structureofmapks. pages 6-7).  
• Gatekeeper position is occupied by a bulky residue (not Thr106 as in p38α) that sterically blocks binding of pyridinyl-imidazole inhibitors (cuenda2007p38mapkinasespathway pages 1-2).  
• C-terminal KETXL sequence provides a PDZ-binding surface unique to p38γ (risco2012newinsightsinto pages 1-2).  
Hinge and αC-helix rearrangements upon phosphorylation create an accessible ATP site; comparisons among p38 isoforms reveal hinge plasticity relevant for isoform-selective inhibitor design (yurtsever2015thecrystalstructure pages 1-2).

## Regulation

Activation: Dual phosphorylation of Thr-Gly-Tyr motif (Thr180/Tyr182 numbering relative to p38α) by MAP2Ks MKK3 or MKK6; MKK4 can substitute under specific stimuli (risco2012newinsightsinto pages 1-2, cuadrado2010mechanismsandfunctions pages 2-3).  
Upstream MAP3Ks: ASK1, TAK1, TAO1/2, MLKs and MEKK family members funnel stress and cytokine signals to MKK3/6 (risco2012newinsightsinto pages 1-2, cuadrado2010mechanismsandfunctions pages 2-3).  
Alternative activation: TAB1-induced autophosphorylation reported for p38 isoforms including p38γ (machado2021thep38mapk pages 1-2).  
No additional post-translational modifications (ubiquitination, acetylation, SUMOylation) are documented in the referenced literature.

## Function

Expression: Highest in skeletal muscle; detectable in nervous tissue and cardiac myocytes (chen2001mapkinases. pages 17-18, yokota2016p38mapkinases pages 1-2, kumar2003p38mapkinases pages 2-3).  
Physiological roles:  
• Drives myoblast differentiation and muscle regeneration (risco2012newinsightsinto pages 1-2).  
• Modulates cytokine production under inflammatory stimuli (machado2021thep38mapk pages 1-2).  
• Contributes to down-regulation of cyclin D1 during hypoxia in adrenal cells (Information section).  
Signaling context: Activated by environmental stressors and pro-inflammatory cytokines; downstream targets include ELK1, ATF2 and PDZ-domain scaffolds, linking p38γ to transcriptional and cytoskeletal control (cuenda2007p38mapkinasespathway pages 1-2, risco2012newinsightsinto pages 1-2).

## Inhibitors

• SB203580 and related pyridinyl-imidazoles inhibit p38α/β but not p38γ owing to the bulky gatekeeper residue (cuenda2007p38mapkinasespathway pages 1-2).  
• Pirfenidone selectively inhibits p38γ over p38α/β; high dosing (500 mg kg⁻¹ daily) suppresses tumorigenesis in mice (qi2023p38γmapkinflammatory pages 7-8).  
• BIRB796 acts as a pan-p38 blocker in vivo yet preferentially inhibits p38γ in vitro; effective at 10 mg kg⁻¹ in xenograft models (qi2023p38γmapkinflammatory pages 7-8).  
• PIK75 (IC50 ≈ 0.34–0.42 µM) targets p38γ but also potently inhibits PI3K; active in vivo at 2 mg kg⁻¹ (qi2023p38γmapkinflammatory pages 7-8).  
• CSH71 binds a non-ATP lipid-binding pocket of p38γ (IC50 ≈ 2 µM) in T-cell lines (qi2023p38γmapkinflammatory pages 7-8).  
• AD80 inhibits p38γ/δ more strongly than p38α/β; suppresses hepatocellular carcinoma xenografts at 20 mg kg⁻¹ (qi2023p38γmapkinflammatory pages 7-8).  
• Structural similarity to CDKs permits inhibition by certain CDK-directed chemotypes (machado2021thep38mapk pages 1-2).

## Other Comments

Disease associations: Elevated p38γ signaling supports oncogenic pathways in colon, pancreatic, liver and mammary tumors via phosphorylation of HSP90α, β-catenin, PFKFB3, Rb and p53 (qi2023p38γmapkinflammatory pages 5-7).  
Mapk12-null mice are viable yet display diminished cytokine output to LPS and resistance to chemically induced carcinogenesis (qi2023p38γmapkinflammatory pages 7-8).  
p38γ expression is increased in hypertrophic rat and human myocardium, linking the kinase to cardiac remodeling (kumar2003p38mapkinases pages 2-3, yokota2016p38mapkinases pages 1-2).

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