## Phylogeny

Mitogen-activated protein kinase 13 (MAPK13) is a member of the p38 MAPK family, which is a subgroup within the mitogen-activated protein kinase (MAPK) family (cuadrado2010mechanismsandfunctions pages 2-3, zarubin2005activationandsignaling pages 1-2). According to the Manning et al. 2002 classification, the p38 family belongs to the MAPK group within the CMGC kinase family (cuenda2007p38mapkinasespathway pages 1-2, cuadrado2010mechanismsandfunctions pages 1-1). One source classifies p38δ MAPK within the CAMK group (o’callaghan2014p38δmapkemerging pages 7-8). The four mammalian p38 isoforms are p38α (MAPK14), p38β (MAPK11), p38γ (MAPK12), and p38δ (MAPK13) (cuenda2007p38mapkinasespathway pages 1-2). MAPK13 shares approximately 61% amino acid identity with p38α and p38β, and is most similar to p38γ at ~70% identity (cuenda2007p38mapkinasespathway pages 1-2). Broader p38 orthologs have been identified in yeast (Hog1), worms (pmk-2), and flies (p38a,b,c), indicating evolutionary conservation (zarubin2005activationandsignaling pages 1-2). MAPK13 orthologs are found across mammals and other vertebrates; however, MAPK13 has not been identified in teleosts (cuenda2007p38mapkinasespathway pages 1-2, o’callaghan2014p38δmapkemerging pages 1-2). The MAPK13 gene is thought to have arisen from segmental duplication of the MAPK11-MAPK12 gene unit (o’callaghan2014p38δmapkemerging pages 1-2).

## Reaction Catalyzed

The enzyme catalyzes a phosphotransferase reaction, transferring the γ-phosphate group from ATP to the hydroxyl groups of specific serine and/or threonine residues within substrate proteins (cuadrado2010mechanismsandfunctions pages 2-3, cuenda2007p38mapkinasespathway pages 1-2, risco2012newinsightsinto pages 8-9).

## Cofactor Requirements

Catalytic activity requires divalent cations, typically Mg²⁺ or Mn²⁺, to facilitate ATP coordination and catalysis (cuadrado2010mechanismsandfunctions pages 2-3, cuenda2007p38mapkinasespathway pages 1-2, risco2012newinsightsinto pages 8-9).

## Substrate Specificity

MAPK13 is a proline-directed kinase (johnson2023anatlasof pages 2-3). Profiling of substrate specificities for human serine/threonine kinases revealed that MAPK family kinases, including MAPK13, belong to a cluster characterized by strong selectivity for a proline residue at the +1 position relative to the phospho-acceptor site (johnson2023anatlasof pages 2-3). The consensus substrate phosphorylation motif for MAPK13 is therefore pS/pT-P, indicating a phosphorylated serine or threonine followed immediately by proline (johnson2023anatlasof pages 2-3). While this +1 proline is a hallmark, amino acid preferences at other positions can modulate specificity (johnson2023anatlasof pages 2-3). p38δ shows distinct substrate preferences compared to other p38 isoforms, phosphorylating targets such as microtubule-associated protein Tau and scaffold proteins like SAP97/hDlg more efficiently than p38α (cuenda2007p38mapkinasespathway pages 1-2).

## Structure

MAPK13 has the canonical kinase architecture with two lobes forming a catalytic groove (cuadrado2010mechanismsandfunctions pages 2-3). It comprises a smaller N-terminal lobe, which consists mainly of β-sheets and includes the regulatory C-helix, and a larger, mostly α-helical C-terminal lobe (cuenda2007p38mapkinasespathway pages 1-2). Key regulatory features include the activation loop, which contains the conserved Thr-Gly-Tyr (TGY) dual phosphorylation motif in kinase subdomain VIII, and a hydrophobic spine that helps stabilize the active conformation (cuenda2007p38mapkinasespathway pages 1-2, o’callaghan2014p38δmapkemerging pages 2-3). Phosphorylation of the activation loop stabilizes an open conformation that is required for substrate binding (cuadrado2010mechanismsandfunctions pages 2-3). Structural insights are available from PDB entries such as 3F9Y and 1A9U (risco2012newinsightsinto pages 8-9).

## Regulation

MAPK13 activation requires dual phosphorylation on the threonine and tyrosine residues within the TGY motif of its activation loop (cuadrado2010mechanismsandfunctions pages 2-3, cuenda2007p38mapkinasespathway pages 1-2). This phosphorylation is mediated by upstream MAP kinase kinases (MKKs), primarily MKK3 and MKK6 (cuadrado2010mechanismsandfunctions pages 2-3, cuenda2007p38mapkinasespathway pages 1-2). While MKK4 can activate p38α, its role with p38δ is less clear, though some sources suggest it can contribute to its activation (cuadrado2010mechanismsandfunctions pages 2-3, risco2012newinsightsinto pages 1-2). One source states p38δ can be activated by four MKKs: MKK3, MKK6, MKK4, and MKK7 (o’callaghan2014p38δmapkemerging pages 2-3). Deactivation is mediated by protein phosphatases such as PP1 and PP2A (o’callaghan2014p38δmapkemerging pages 2-3). However, p38δ is reported to be resistant to all known dual-specificity phosphatases (MKPs) that negatively regulate other MAPKs (zarubin2005activationandsignaling pages 1-2). Other post-translational modifications, such as methylation and acetylation, may also regulate its function (canovas2021diversityandversatility pages 18-18). The MAPK13 gene can also be epigenetically regulated via promoter hypermethylation, leading to its downregulation in certain cancers (o’callaghan2014p38δmapkemerging pages 7-8).

## Function

MAPK13 expression is tissue-specific, unlike the ubiquitously expressed p38α (cuenda2007p38mapkinasespathway pages 1-2). High expression is found in the testis, pancreas, kidney, small intestine, lung, and endocrine glands like the salivary, pituitary, and adrenal glands (cuenda2007p38mapkinasespathway pages 1-2, o’callaghan2014p38δmapkemerging pages 2-3). MAPK13 is a canonical stress-activated kinase, activated by environmental stresses (e.g., osmotic changes, UV irradiation) and proinflammatory cytokines (e.g., TNF-α, IL-1) (o’callaghan2014p38δmapkemerging pages 1-2). It participates in signaling pathways controlling inflammation, cytoskeletal remodeling, differentiation, and apoptosis (cuadrado2010mechanismsandfunctions pages 2-3, o’callaghan2014p38δmapkemerging pages 1-2, risco2012newinsightsinto pages 5-6). Downstream substrates include other kinases (MAPKAPK2, eEF2K), transcription factors (ATF2, AP1, p53), and structural and scaffold proteins (Tau, Stathmin, synapse-associated protein 97/hDlg) (cuadrado2010mechanismsandfunctions pages 2-3, cuenda2007p38mapkinasespathway pages 1-2, o’callaghan2014p38δmapkemerging pages 2-3).

## Inhibitors

The pyridinyl-imidazole compound SB203580, which inhibits p38α and p38β, is ineffective against p38δ (cuenda2007p38mapkinasespathway pages 1-2). This insensitivity is due to a methionine residue (Met106) in the ATP-binding pocket of p38δ, which replaces the smaller threonine found in sensitive isoforms and prevents inhibitor binding (o’callaghan2014p38δmapkemerging pages 1-2). BIRB796 is an allosteric inhibitor that can affect p38δ at high concentrations but is non-specific and also inhibits other p38 isoforms (o’callaghan2014p38δmapkemerging pages 1-2, o’callaghan2014p38δmapkemerging pages 2-3). Currently, selective inhibitors for MAPK13 are limited or have not been identified (o’callaghan2014p38δmapkemerging pages 1-2, o’callaghan2014p38δmapkemerging pages 7-8).

## Other Comments

MAPK13 is implicated in multiple pathological conditions, including neurodegenerative disorders, diabetes, inflammatory diseases such as psoriasis, and cancer, where it can act as both a tumor promoter and suppressor (o’callaghan2014p38δmapkemerging pages 1-2, risco2012newinsightsinto pages 5-6). Altered expression has been observed in oesophageal squamous cell carcinoma and triple-negative breast cancer (o’callaghan2014p38δmapkemerging pages 7-8). Unlike p38α, which is essential for embryonic development, knockout mice lacking p38δ are viable and fertile, suggesting functional redundancy with other p38 isoforms during development (o’callaghan2014p38δmapkemerging pages 1-2).

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