1. Phylogeny  
   Mitogen-activated protein kinase 13 (MAPK13), also known as p38δ or SAPK4, is a member of the p38 mitogen‐activated protein kinase (MAPK) family that is evolutionarily conserved from yeast to mammals and is classified within the stress-activated protein kinases (SAPKs) subgroup alongside p38α, p38β, and p38γ (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, kultz1998phylogeneticandfunctional pages 1-2). MAPK13 is present in all mammalian species and has orthologs in vertebrates that share the characteristic serine/threonine kinase domain and the conserved dual phosphorylation motif required for activation (goedert1997activationofthe pages 5-6, kultz1998phylogeneticandfunctional pages 2-3). Within the human kinome, MAPK13 is phylogenetically grouped with other members of the p38 subfamily, whose evolutionary divergence has provided distinctive functional specializations in response to cellular stresses such as cytokine exposure and physical stress (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, kultz1998phylogeneticandfunctional pages 1-2). Members of the p38 MAPK family diverged through gene duplication events that allowed for the emergence of isoforms with overlapping yet distinct substrate specificities and regulatory behaviors (kultz1998phylogeneticandfunctional pages 17-18).
2. Reaction Catalyzed  
   MAPK13 catalyzes the transfer of a phosphate group from ATP to serine or threonine residues on substrate proteins, resulting in the formation of ADP and a phosphorylated protein, with the concomitant release of a proton (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, kyriakis1996proteinkinasecascades pages 3-4). This phosphorylation reaction is critical for modulating downstream signaling pathways and altering the functional state of numerous target proteins, thereby regulating a wide range of physiological cellular responses (zarubin2005activationandsignaling pages 2-3).
3. Cofactor Requirements  
   The catalytic activity of MAPK13 is dependent on the presence of divalent metal ions, with Mg²⁺ serving as an essential cofactor to facilitate ATP binding and phosphate transfer (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, zarubin2005activationandsignaling pages 2-3).
4. Substrate Specificity  
   MAPK13 exhibits substrate specificity characteristic of serine/threonine kinases, preferentially phosphorylating residues within a proline-directed motif, typically recognizing substrates that conform to a consensus sequence in which the phosphorylated serine or threonine is immediately followed by a proline residue (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, roux2004erkandp38 pages 2-3). In vitro studies have demonstrated that MAPK13 phosphorylates key transcription factors such as ATF2 and ELK1, as well as downstream kinases like MAPKAPK2, which are further involved in amplifying the kinase cascade (goedert1997activationofthe pages 5-6, zarubin2005activationandsignaling pages 3-5). Additionally, MAPK13 targets proteins involved in cytoskeletal remodeling such as the microtubule-associated protein Tau (MAPT) and stathmin (STMN1), and it phosphorylates the elongation factor eEF2 kinase, thereby affecting translation regulation (cerezoguisado2011mapk13(mitogenactivatedprotein pages 2-3, tibbles1999thestressactivatedprotein pages 1-3).
5. Structure  
   MAPK13 is a 365-amino acid protein with an approximate molecular weight of 40 kDa that contains a central kinase domain organized into the typical N-terminal lobe (mainly β-strands) and C-terminal lobe (primarily α-helices) common to protein kinases (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, goedert1997activationofthe pages 5-6). The kinase domain is flanked by relatively short N-terminal and C-terminal regions that may contain sequences involved in subcellular localization and protein–protein interactions; however, unlike some kinases, MAPK13 does not have extensive regulatory extensions (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, kultz1998phylogeneticandfunctional pages 14-15). A key structural feature is the activation loop which harbors the conserved Thr-Gly-Tyr (TGY) motif, where dual phosphorylation of Thr180 and Tyr182 by MAP kinase kinases such as MKK3 or MKK6 is required for full activation of MAPK13 (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, goedert1997activationofthe pages 5-6). The structural organization includes typical protein kinase subdomains I–XI, and, while MAPK13 shares about 60% identity with other p38 isoforms (notably p38α and p38β), it displays unique features regarding inhibitor sensitivity and substrate binding that set it apart from its paralogs (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, zarubin2005activationandsignaling pages 6-7). In crystallographic studies and AlphaFold-based models, MAPK13 has been predicted to preserve the conserved catalytic core with a prominent ATP-binding pocket that governs its interaction with ATP and small molecule inhibitors (roux2004erkandp38 pages 3-4).
6. Regulation  
   The regulation of MAPK13 is chiefly achieved via dual phosphorylation of its TGY activation loop by upstream kinases, primarily MKK3 and MKK6; in many cellular contexts, there is preferential activation by MKK3, although MKK6 can phosphorylate MAPK13 under certain conditions (goedert1997activationofthe pages 5-6, zarubin2005activationandsignaling pages 5-6). Upon phosphorylation, MAPK13 undergoes a conformational change that facilitates its binding to substrates; this phosphorylation-dependent switching is a common regulatory mechanism among MAPKs (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, kyriakis1996proteinkinasecascades pages 3-4). MAPK13 is also regulated by upstream extracellular stimuli including pro-inflammatory cytokines such as IL-1 and TNF-α, as well as by physical stress signals such as UV irradiation, which collectively lead to its activation in numerous stress response pathways (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, sugden1998“stressresponsive”mitogenactivatedprotein pages 1-2). In contrast to other p38 isoforms, MAPK13 shows reduced sensitivity to classical pyridinyl imidazole inhibitors like SB203580, highlighting distinct conformational and regulatory features that may reflect subtle differences in its ATP-binding pocket and regulatory interfaces (goedert1997activationofthe pages 6-8, zarubin2005activationandsignaling pages 6-7).
7. Function  
   MAPK13 serves as an essential serine/threonine kinase in the MAPK signal transduction pathway and is pivotal in mediating cellular responses to extracellular stresses (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, zarubin2005activationandsignaling pages 2-3). It phosphorylates an extensive range of substrates—estimated at roughly 200 to 300—including transcription factors such as ELK1 and ATF2 that direct immediate early gene expression in response to stress (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, dodeller2006thep38mitogenactivated pages 10-11). MAPK13 also phosphorylates downstream kinases like MAPKAPK2, which further amplifies the cellular stress response by targeting proteins involved in inflammation and cytoskeletal organization (goedert1997activationofthe pages 5-6, roux2004erkandp38 pages 2-3). In addition, MAPK13 regulates protein synthesis by phosphorylating and inactivating the eukaryotic elongation factor 2 kinase (EEF2K), thereby promoting translation under certain conditions (cerezoguisado2011mapk13(mitogenactivatedprotein pages 2-3, zarubin2005activationandsignaling pages 3-5). Beyond its role in translation, MAPK13 participates in cytoskeletal remodeling via phosphorylation of microtubule-associated proteins such as Tau (MAPT) and stathmin (STMN1), facilitating dynamic cellular rearrangements in processes like cell migration and differentiation (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, tibbles1999thestressactivatedprotein pages 1-3). In epidermal cells, MAPK13 is implicated in keratinocyte differentiation and apoptosis, with its activity linked to the regulation of the involucrin promoter and complex formation with ERK1/2, thereby influencing skin tumor development (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, dodeller2006thep38mitogenactivated pages 2-3). Moreover, MAPK13 phosphorylates the transcriptional activator MYB in response to cellular stress, which results in rapid proteasome-dependent degradation of MYB and thus modulates gene expression patterns required for stress adaptation (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, goedert1997activationofthe pages 9-9). In pancreatic beta cells, the kinase down-regulates protein kinase D1 (PRKD1) via phosphorylation, an event that is significant in the regulation of insulin secretion (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, zarubin2005activationandsignaling pages 6-7).
8. Other Comments  
   MAPK13 is classified as one of the less well-studied isoforms of the p38 MAPK family, and its unique biochemical and regulatory characteristics render it a promising candidate for the development of tailored therapeutic agents (cerezoguisado2011mapk13(mitogenactivatedprotein pages 1-2, dodeller2006thep38mitogenactivated pages 10-11). Notably, the kinase displays differential sensitivity to small molecule inhibitors when compared to other p38 isoforms, as exemplified by its relative insensitivity to inhibitors such as SB203580 that effectively target p38α and p38β (goedert1997activationofthe pages 6-8, zarubin2005activationandsignaling pages 6-7). MAPK13 has been implicated in various pathological conditions, including skin tumorigenesis, cholangiocarcinoma where its overexpression can serve as a diagnostic marker, and alterations in its epigenetic profiles have been associated with malignant pleural mesothelioma (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, dodeller2006thep38mitogenactivated pages 2-3). Its involvement in the regulation of the insulin secretion pathway further highlights its potential contributions to metabolic disorders such as type 2 diabetes (cerezoguisado2011mapk13(mitogenactivatedprotein pages 3-4, zarubin2005activationandsignaling pages 6-7).
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