1. Phylogeny  
   MAPK7, also known as ERK5, BMK1 or PRKM7, belongs to the mitogen‐activated protein kinase (MAPK) family and is phylogenetically distinct from the classical ERK1/2 subfamily. Its orthologs have been identified in all vertebrates, reflecting its evolutionary conservation across mammalian species (nishimoto2006mapksignallingerk5 pages 1-2). Within the human kinome it is placed in the ERK group, which originates from an ancestral MAPK module conserved since early eukaryotic evolution; the divergence that gave rise to ERK5 set it apart from other MAPKs by acquisition of a large C-terminal extension imparting transcriptional regulatory functions (nithianandarajahjones2014theroleof pages 1-3, lin2016erk5kinaseactivity pages 1-2).
2. Reaction Catalyzed  
   MAPK7 catalyzes the transfer of the γ-phosphate from adenosine triphosphate (ATP) to serine/threonine residues within specific substrate proteins. In this reaction, ATP and a protein substrate are converted to ADP and a phosphorylated protein product, releasing a proton (cook2020smallmoleculeerk5 pages 16-17).
3. Cofactor Requirements  
   The catalytic activity of MAPK7 is dependent on the presence of Mg²⁺ ions, which are required as cofactors to facilitate ATP binding and phosphoryl transfer (wang2006regulationofcellular pages 1-2).
4. Substrate Specificity  
   MAPK7 phosphorylates proteins on serine/threonine residues within specific consensus motifs. Notably, downstream substrates include transcription factors such as MEF2C and other regulatory proteins including SGK1, phosphorylated at Ser-78 to facilitate growth factor-induced cell cycle progression (cook2020smallmoleculeerk5 pages 14-15, cook2020smallmoleculeerk5 pages 15-16). Although precise consensus sequences are not exhaustively characterized in the available literature, its substrate preference is consistent with other serine/threonine kinases in the MAPK family, which generally recognize proline-directed motifs (nithianandarajahjones2014theroleof pages 10-12).
5. Structure  
   MAPK7 is an 816–amino acid protein organized into two principal regions. The N-terminal region comprises a canonical kinase domain sharing approximately 50–66% sequence identity with other ERKs (lin2016erk5kinaseactivity pages 1-2, elkins2013xraycrystalstructure pages 7-8). This domain contains key catalytic elements including the activation loop with the conserved TEY (Thr218–Glu–Tyr220) phosphorylation motif, a glycine-rich loop, and structural features such as the hydrophobic spine and the C-helix that orient ATP for catalysis. Uniquely, MAPK7 possesses a large C-terminal extension of approximately 410 amino acids that harbors a nuclear localization signal and a transcriptional activation domain, thereby conferring dual functionality as both a kinase and a transcriptional regulator (cook2020smallmoleculeerk5 pages 14-15, monti2022clinicalsignificanceand pages 2-4). Structural studies, including X-ray crystallography of the kinase domain, have established details of its ATP-binding pocket and key residues that differentiate its inhibitor-binding profile from those of other MAPKs (elkins2013xraycrystalstructure pages 7-8).
6. Regulation  
   MAPK7 is activated by phosphorylation of its activation loop at the TEY motif by its specific upstream kinase, MAP2K5 (MEK5). This phosphorylation event induces conformational changes that relieve autoinhibition imparted by the C-terminal domain, thereby unmasking the nuclear localization signal and allowing translocation into the nucleus (lin2016erk5kinaseactivity pages 1-2, lochhead2020paradoxicalactivationof pages 1-2). Beyond this primary event, MAPK7 undergoes autophosphorylation on its C-terminal tail, which further enhances its transcriptional activity (cook2020smallmoleculeerk5 pages 14-15). Additional phosphorylation events at sites such as Thr732, among others, have been correlated with nuclear accumulation and modulation of transcriptional outputs (honda2015phosphorylationoferk5 pages 13-14). Regulation is also achieved through protein–protein interactions; for example, binding to chaperones such as HSP90/CDC37 in the inactive state maintains MAPK7 in a closed conformation until appropriate extracellular signals via receptor tyrosine kinases, including EGF receptors, trigger its activation through a Ras-independent, but MEK5-dependent pathway (cook2020smallmoleculeerk5 pages 15-16, paudel2021themek5erk5pathway pages 1-2).
7. Function  
   MAPK7 functions in several central cellular processes including proliferation, differentiation, and cell survival. Upon activation by MEK5, MAPK7 translocates to the nucleus where it phosphorylates downstream targets such as MEF2C, thereby modulating gene transcription necessary for cellular responses to growth factors (cook2020smallmoleculeerk5 pages 14-15, drew2012mek5erk5pathwaythe pages 12-14). Additionally, MAPK7 phosphorylates SGK1 at Ser-78, an event that is required for cell cycle progression in response to growth factor signaling (Information section; cook2020smallmoleculeerk5 pages 15-16). In cardiomyocytes, MAPK7 acts as a negative regulator of apoptosis through its interaction with STUB1/CHIP, promoting ubiquitination and degradation of ICER-type isoforms of CREM, while in muscle cells it may be linked to differentiation processes (Information section). MAPK7 has also been implicated in the maintenance of endothelial integrity and blood vessel function, thereby contributing to vascular homeostasis (lochhead2012erk5andits pages 4-5).
8. Other Comments  
   Several small-molecule inhibitors of MAPK7 have been developed, including compounds from the benzo[e]pyrimido[5,4-b][1,4]diazepin-6(11H)-one series, although some inhibitors have been reported to paradoxically activate MAPK7 signaling (cook2020smallmoleculeerk5 pages 16-17, lochhead2020paradoxicalactivationof pages 14-14, miller2023modulationoferk5 pages 10-11). Disease associations for MAPK7 include its overexpression and aberrant activation in various cancers such as breast, prostate, hepatocellular carcinoma, and pancreatic cancers, where it supports tumor growth, angiogenesis, and potentially metastasis (monti2022clinicalsignificanceand pages 17-18, paudel2021themek5erk5pathway pages 17-18). No commonly recurring mutations in MAPK7 have been extensively characterized; instead, the dysregulation of its phosphorylation and overexpression through gene amplification are more commonly observed in aggressive tumors (drew2012mek5erk5pathwaythe pages 11-12, monti2022clinicalsignificanceand pages 23-25).
9. References

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