## Phylogeny

MAPK7 (also called ERK5, BMK1 or PRKM7) is a mitogen-activated protein kinase that forms a distinct branch within the ERK group of the MAPK family. Orthologues are present in all vertebrates, underscoring strong evolutionary conservation (Nishimoto & Nishida, 2006). Divergence from other MAPKs was accompanied by acquisition of an extended C-terminal region that confers transcriptional-regulatory functions (Nithianandarajah-Jones et al., 2014; Lin et al., 2016).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Cook et al., 2020).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Wang & Tournier, 2006).

## Substrate Specificity

MAPK7 phosphorylates Ser/Thr residues within proline-directed motifs. Documented substrates include transcription factors (e.g., MEF2C) and regulatory proteins such as SGK1 at Ser-78 (Cook et al., 2020). Motif definition is incomplete but resembles other MAPKs with a preference for Pro at +1 (Nithianandarajah-Jones et al., 2014).

## Structure

The 816-residue protein comprises:  
• N-terminal kinase domain (~1–406 aa) that shares 50–66 % identity with ERK1/2 and contains the TEY activation motif (Thr218-Glu-Tyr220), glycine-rich loop, C-helix and hydrophobic spine (Lin et al., 2016; Elkins et al., 2013).  
• C-terminal extension (~410 aa) harbouring a nuclear-localization signal and transcriptional-activation domain, enabling dual kinase/transcription-factor roles (Cook et al., 2020; Monti et al., 2022).  
X-ray structures of the kinase domain delineate an ATP-binding pocket with residues that dictate inhibitor selectivity (Elkins et al., 2013).

## Regulation

Activation requires MAP2K5 (MEK5)-mediated phosphorylation of the TEY motif, relieving C-terminal autoinhibition and exposing the nuclear-localization signal (Lin et al., 2016; Lochhead et al., 2020). Additional regulation includes:  
• C-terminal autophosphorylation enhancing transcriptional activity (Cook et al., 2020).  
• Phosphorylation at Thr732 promoting nuclear accumulation (Honda et al., 2015).  
• Association with HSP90/CDC37 in the inactive state; growth-factor signals via receptor tyrosine kinases stimulate MEK5-dependent activation in a Ras-independent manner (Cook et al., 2020; Paudel et al., 2021).

## Function

Upon activation, MAPK7 translocates to the nucleus to modulate gene expression required for cell proliferation, differentiation and survival. Key roles include:  
• Phosphorylation of MEF2C and SGK1 to drive growth-factor-induced cell-cycle progression (Cook et al., 2020; Drew et al., 2012).  
• Anti-apoptotic effects in cardiomyocytes via STUB1/CHIP-mediated degradation of ICER isoforms (information cited in Nomenclature).  
• Maintenance of endothelial integrity and vascular homeostasis (Lochhead et al., 2012; Nithianandarajah-Jones et al., 2014).

## Inhibitors

Several ATP-competitive small molecules (e.g., benzo[e]pyrimido[5,4-b][1,4]diazepin-6(11H)-ones) inhibit MAPK7, yet some compounds paradoxically activate MAPK7 signalling (Cook et al., 2020; Lochhead et al., 2020; Miller et al., 2023).

## Other Comments

Over-expression or hyperactivation of MAPK7 is observed in multiple cancers (breast, prostate, hepatocellular, pancreatic) where it supports tumour growth, angiogenesis and metastasis. Dysregulation typically arises from gene amplification or aberrant phosphorylation rather than recurrent point mutations (Monti et al., 2022; Drew et al., 2012).

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