## Phylogeny

MAP kinase-interacting kinase-1 (MNK1) and its paralog MNK2 form the MNK family within the CAMK group of the eukaryotic kinome, but unlike most CAMKs they do not bind calmodulin (Cargnello & Roux, 2011; Jin et al., 2021). MNK1 shares ~70–80 % amino-acid identity with MNK2 (Cargnello & Roux, 2011; Dreas et al., 2017). Orthologues are present from invertebrates to mammals: human MNK1 is ~51 % identical to Drosophila LK6, ~46 % to Caenorhabditis elegans mnk-1, and ~94 % to mouse Mnk1 (Cargnello & Roux, 2011; Prabhu et al., 2020). Loss of mnk-1 function is embryonic-lethal in C. elegans (Cargnello & Roux, 2011).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Dreas et al., 2017; Pinto-Díez et al., 2020).

## Cofactor requirements

Mg²⁺ is required for catalysis (Dreas et al., 2017; Pinto-Díez et al., 2020).

## Substrate specificity

Human MNK1 is a basophilic Ser/Thr kinase (Johnson et al., 2023). It prefers Lys or Arg residues flanking the phospho-acceptor site, generating a positively charged environment that insulates its substrates from non-cognate kinases (Johnson et al., 2023).

## Structure

MNK1 adopts the classical bilobal protein-kinase fold with an N-terminal β-sheet-rich lobe, a helical C-terminal lobe and an ATP-binding hinge (Dreas et al., 2017).

• N-terminal tail: poly-basic sequence acting as a nuclear localisation signal and eIF4G-binding site (Hou et al., 2012; Pinto-Díez et al., 2020).  
• Catalytic domain: contains an αC helix and two short inserts unique to MNKs (Cargnello & Roux, 2011).  
• C-terminal extension (MNK1a only): MAPK-binding motif (Leu-Ala-Arg-Arg-Arg) and a nuclear-export signal; both are absent in the shorter MNK1b isoform (Cargnello & Roux, 2011; Unknown authors, 2015).  
Key features:  
– Activation loop carries an atypical Asp-Phe-Asp (DFD) motif that adopts a DFG-out-like conformation, lowering ATP affinity (Cargnello & Roux, 2011; Unknown authors, 2015).  
– Autoinhibition: Phe230 repositions Phe192 of the DFD motif into the ATP pocket (Pinto-Díez et al., 2020; Bou-Petit et al., 2022).  
– A zinc-binding module formed by four Cys residues lies near the C-terminus (Dreas et al., 2017; Jauch et al., 2005).

## Regulation

ERK1/2 and p38 MAPKs phosphorylate MNK1a on Thr209 and Thr214 within the activation loop to relieve autoinhibition and activate the kinase (Cargnello & Roux, 2011; Hou et al., 2012; Xie et al., 2019). A third site, Thr344, modulates activity; a phosphomimetic mutation at this position renders the enzyme constitutively active (Cargnello & Roux, 2011). Isoform specificity: MNK1a, which contains the MAPK-binding domain, is strongly inducible by MAPKs, whereas MNK1b lacks this domain and shows low, MAPK-independent basal activity (Dreas et al., 2017; Xie et al., 2019).

## Function

MNK1 is a downstream effector of ERK1/2 and p38 pathways that controls cap-dependent mRNA translation (Dreas et al., 2017; Hou et al., 2012).

Expression/localisation: broadly expressed (liver, pancreas, heart, placenta; high in skeletal muscle) but not detected in brain (Cargnello & Roux, 2011; Pinto-Díez et al., 2020). MNK1a is mainly cytoplasmic; MNK1b is both nuclear and cytoplasmic (Pinto-Díez et al., 2020).

Upstream kinases: ERK1/2, p38 MAPKs (Dreas et al., 2017).

Principal substrate: eIF4E, phosphorylated exclusively on Ser209 after recruitment via eIF4G (Dreas et al., 2017; Hou et al., 2012). Phosphorylation increases eIF4E affinity for the 5′-mRNA cap, promoting translation of mRNAs encoding Cyclin D1, VEGF, MCL-1 and other growth-promoting proteins (Dreas et al., 2017). Additional substrates include hnRNP A1 and LARP1 (Pinto-Díez et al., 2020; Unknown authors, 2023).

## Inhibitors

Early tool compounds: CGP57380 and cercosporamide (Dreas et al., 2017; Cargnello & Roux, 2011).  
Conformation-selective inhibitor: EB1 binds the inactive DFD-out state (Bou-Petit et al., 2022).  
Clinical-stage agents: tomivosertib (eFT508, phase II) and BAY 1143269 (phase I). Additional investigational inhibitors include SEL-201, QL-X-138 and merestinib (Xie et al., 2019; Jin et al., 2021; Dreas et al., 2017).

## Other comments

Elevated MNK1 levels and increased eIF4E phosphorylation correlate with poor prognosis in numerous cancers, especially those with Ras activation, c-Myc amplification or PTEN loss (Dreas et al., 2017; Hou et al., 2012; Jin et al., 2021). Double knockout of MNK1/2 in mice is viable and confers resistance to oncogenic transformation, supporting MNK inhibition as a potentially safe anticancer strategy (Dreas et al., 2017; Hou et al., 2012).

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