## Phylogeny

MAP kinase-interacting serine/threonine-protein kinase 2 (MNK2) belongs to the MAPK-interacting kinases (MNK) within the Ca2+/calmodulin-dependent protein kinase (CaMK) family of protein kinases, which is part of the CMGC kinome group (cargnello2011activationandfunction pages 20-21, joshi2014mnkkinasepathway pages 1-2, jauch2005crystalstructuresof pages 1-2, dreas2017mitogenactivatedproteinkinase pages 2-3). Although classified within the CaMK group based on kinase domain sequence, MNKs are not regulated by Ca2+/calmodulin (jauch2005crystalstructuresof pages 1-2, jin2021progressindeveloping pages 2-3). MNK2 shares approximately 70-80% amino acid identity with its paralog MNK1 (cargnello2011activationandfunction pages 20-21, dreas2017mitogenactivatedproteinkinase pages 2-3, kannan2015probingthebinding pages 1-2). The MNK catalytic domains are homologous to those of RSKs, other Ca2+/calmodulin-dependent kinases, and Mapkap kinases (waskiewicz1997mitogenactivatedproteinkinases pages 1-2, cargnello2011activationandfunction pages 20-21). Orthologs of MNK2 exist in species including *Drosophila melanogaster* (LK6) and *Caenorhabditis elegans* (mnk-1), as well as in mice (cargnello2011activationandfunction pages 20-21, jauch2005crystalstructuresof pages 1-2, jin2021progressindeveloping pages 2-3).

## Reaction Catalyzed

MNK2 is a serine/threonine kinase that catalyzes the ATP-dependent phosphorylation of protein substrates (jin2021progressindeveloping pages 2-3, pintodiez2020deepinginthe pages 23-25). The reaction involves the transfer of a phosphate group from ATP to a serine or threonine residue on the target protein (jin2021progressindeveloping pages 1-2, xie2019themapkinaseinteracting pages 31-36).

## Cofactor Requirements

The catalytic activity of MNK2 requires divalent cations, typically Mg²⁺ or Mn²⁺ (jin2021progressindeveloping pages 2-3, kannan2015probingthebinding pages 1-2, pintodiez2020deepinginthe pages 23-25, joshi2014mnkkinasepathway pages 1-2, xie2019themapkinaseinteracting pages 20-22).

## Substrate Specificity

MKNK2 is categorized as a basophilic kinase based on analysis of its substrate specificity (johnson2023anatlasof pages 4-4). The consensus phosphorylation motif for MKNK2 indicates a preference for positively charged (basic) residues, such as lysine (K) or arginine (R), at positions N-terminal to the phosphorylated site (johnson2023anatlasof pages 4-4). This preference is particularly strong for positions -3 to -1 relative to the phosphorylated serine (S) or threonine (T) (johnson2023anatlasof pages 4-4). The enrichment of basophilic residues in the upstream flanking positions is a key feature for substrate recognition (johnson2023anatlasof pages 4-4).

## Structure

The MNK2 kinase domain (residues 72–385) has a typical bilobal architecture, comprising an N-terminal β-sheet-rich domain and a predominantly helical C-terminal domain connected by a hinge region (dreas2017mitogenactivatedproteinkinase pages 2-3, kannan2015probingthebinding pages 1-2, jauch2005crystalstructuresof pages 1-2). The N-terminal lobe contains the glycine-rich P-loop (residues 86-97), a conserved catalytic lysine (Lys113) in strand β3, and a conserved glutamic acid (Glu129) in the αC helix (kannan2015probingthebinding pages 1-2). The crystal structure (PDB ID 2AC3, 2.1 Å resolution) reveals several unique features (jauch2005crystalstructuresof pages 1-2, kannan2015probingthebinding pages 1-2). MNK2 contains a distinct Asp-Phe-Asp (DFD) motif (Asp226-Phe227-Asp228) in the magnesium-binding loop, which replaces the canonical Asp-Phe-Gly (DFG) motif found in most other kinases (cargnello2011activationandfunction pages 20-21, dreas2017mitogenactivatedproteinkinase pages 2-3, kannan2015probingthebinding pages 1-2). In the inactive “DFD-out” conformation, the phenylalanine of this motif occludes the ATP-binding pocket (jauch2005crystalstructuresof pages 1-2, kannan2015probingthebinding pages 1-2). The kinase domain also contains unique short inserts in the activation loop and after the APE motif (cargnello2011activationandfunction pages 20-21). Atypical zinc-binding motifs formed by a cluster of four cysteines are located near the C-terminus (dreas2017mitogenactivatedproteinkinase pages 2-3, jauch2005crystalstructuresof pages 1-2). Two main splice isoforms, MNK2a and MNK2b, have different domain organizations; MNK2a contains a C-terminal D domain for MAPK binding, which is absent in MNK2b (cargnello2011activationandfunction pages 20-21, jin2021progressindeveloping pages 2-3). Both isoforms have N-terminal polybasic regions that function as a nuclear localization signal (NLS) and an eIF4G binding motif (cargnello2011activationandfunction pages 20-21, jauch2005crystalstructuresof pages 1-2).

## Regulation

MNK2 is activated downstream of the MAPK pathways by the kinases ERK1/2 and p38, which phosphorylate it on key residues (cargnello2011activationandfunction pages 20-21, waskiewicz1997mitogenactivatedproteinkinases pages 1-2, scheper2001themitogenactivatedprotein pages 3-4). Phosphorylation at proline-directed sites Thr209 and Thr214 in the activation loop is vital for activity (cargnello2011activationandfunction pages 20-21). Other identified phosphorylation sites include Ser27, Thr197, and Thr202 (scheper2001themitogenactivatedprotein pages 3-4). Thr344 is essential for the activity of the MNK2a isoform (cargnello2011activationandfunction pages 20-21). Regulation also occurs via the mTORC1 pathway, which directly phosphorylates MNK2 on Ser74, leading to suppressed kinase activity and reduced binding to the scaffold protein eIF4G (jin2021progressindeveloping pages 2-3, xie2021reciprocalsignalingbetween pages 1-2). The two major splice variants are regulated differently: MNK2a contains a MAPK-binding domain, associates with ERK1/2, and exhibits relatively high basal kinase activity that is only slightly enhanced by MAPK stimulation (cargnello2011activationandfunction pages 20-21, xie2019themapkinaseinteracting pages 6-9). MNK2b lacks this domain and is mostly inactive under typical stimulations (cargnello2011activationandfunction pages 20-21). Autoinhibition is mediated by the activation segment and C-terminal domain (pintodiez2020deepinginthe pages 23-25).

## Function

MNK2 is broadly expressed in adult tissues, with the exception of the brain where its expression is low, and it is more abundant in skeletal muscle and pancreas (cargnello2011activationandfunction pages 20-21, cargnello2011activationandfunction pages 21-23, pintodiez2020deepinginthe pages 1-3). As a downstream effector of the ERK1/2 and p38 MAPK pathways, MNK2 regulates cellular processes primarily through the phosphorylation of its substrates (jauch2005crystalstructuresof pages 1-2). Its main function is to regulate translation initiation by phosphorylating eIF4E at Ser209 (cargnello2011activationandfunction pages 21-23, dreas2017mitogenactivatedproteinkinase pages 2-3). MNKs are recruited to the eIF4F translation initiation complex via an interaction with the scaffold protein eIF4G, which facilitates the phosphorylation of eIF4E (cargnello2011activationandfunction pages 21-23, dreas2017mitogenactivatedproteinkinase pages 2-3). In addition to controlling translation, MNK2 is involved in mRNA metabolism through the phosphorylation of RNA-binding proteins like hnRNP A1 and PSF (cargnello2011activationandfunction pages 21-23). It also participates in inflammatory responses, pro-inflammatory cytokine production, and the regulation of TNF-alpha biosynthesis (cargnello2011activationandfunction pages 21-23, pintodiez2020deepinginthe pages 23-25). MNK2 shuttles between the cytoplasm and nucleus, and its splice isoforms exhibit distinct localizations and functions: MNK2a is mainly cytoplasmic and can act as a tumor suppressor, while MNK2b is predominantly nuclear and can act as a proto-oncoprotein (cargnello2011activationandfunction pages 20-21, xie2019themapkinaseinteracting pages 6-9, dreas2017mitogenactivatedproteinkinase pages 1-2).

## Inhibitors

Several experimental inhibitors of MNK2 have been reported. CGP57380 inhibits both MNK1 and MNK2 but is characterized as a relatively weak and non-specific inhibitor (cargnello2011activationandfunction pages 20-21, joshi2014mnkkinasepathway pages 8-10). Cercosporamide exhibits higher specificity for MNK2 than CGP57380 (joshi2014mnkkinasepathway pages 8-10). More recent and selective inhibitors developed for cancer therapy include eFT508 (tomivosertib), BAY 1143269, and SEL-201 (dreas2017mitogenactivatedproteinkinase pages 1-2, xie2019themapkinaseinteracting pages 31-36). Other reported compounds include QL-X-138, merestinib, AST-487 derivatives, and novel imidazopyridine and imidazopyrazine derivatives (jin2021progressindeveloping pages 2-3, kannan2015probingthebinding pages 1-2). In addition, MNK2 activity can be indirectly blocked by inhibiting its upstream activators, ERK1/2 and p38, with compounds such as PD98059 and SB203580, respectively (scheper2001themitogenactivatedprotein pages 3-4).

## Other Comments

MNK2 is implicated in numerous diseases, particularly in cancer. Its activity is linked to various solid tumors and hematologic malignancies, including breast, lung, colon, prostate, pancreatic, ovarian cancers, gliomas, melanoma, and acute myeloid leukemia (dreas2017mitogenactivatedproteinkinase pages 2-3, xie2019themapkinaseinteracting pages 31-36, pintodiez2020deepinginthe pages 23-25). It is also associated with autoimmune and inflammatory disorders, sepsis, cardiovascular disease, neurodegeneration, and obesity (jin2021progressindeveloping pages 2-3, joshi2014mnkkinasepathway pages 8-10). The two main splice isoforms, MNK2a and MNK2b, have opposing roles in oncogenesis, with MNK2a often acting as a tumor suppressor and MNK2b as a proto-oncoprotein (dreas2017mitogenactivatedproteinkinase pages 2-3, xie2019themapkinaseinteracting pages 6-9). Despite its role in pathological states, genetic knockout of both *Mnk1* and *Mnk2* in mice results in no major developmental defects or adverse effects under normal conditions, indicating functional redundancy or specialized roles (cargnello2011activationandfunction pages 21-23, jauch2005crystalstructuresof pages 1-2, jin2021progressindeveloping pages 1-2).

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