1. Phylogeny  
   MAP kinase‐interacting serine/threonine‐protein kinase 2 (MNK2), encoded by the MKNK2 gene and also known as GPRK7, is a member of the MAPK‐activated protein kinase family that falls within the broader calcium/calmodulin‐dependent kinase (CAMK) group of eukaryotic protein kinases (cargnello2011activationandfunction pages 20-21). MNK2 shares approximately 70% amino acid sequence identity in its catalytic domain with MNK1 and is evolutionarily conserved in metazoans, with orthologs identified in species as divergent as Drosophila (e.g., the kinase LK6) and Caenorhabditis (e.g., mnk-1) (cargnello2011activationandfunction pages 21-23, joshi2014mnkkinasepathway pages 1-2). In phylogenetic analyses, MNK2 clusters with other MAPK-activated protein kinases such as MSKs, MK2/3, RSKs, and MK5, reflecting a common evolutionary origin traced back to the Last Eukaryotic Common Ancestor (cargnello2011activationandfunction pages 20-21, roux2004erkandp38 pages 15-17). Its classification within the CAMK family signifies that MNK2, like its paralog MNK1, is an ancient component of the cellular signaling machinery that has diversified to fulfill regulatory roles in response to extracellular cues (joshi2014mnkkinasepathway pages 1-2).
2. Reaction Catalyzed  
   MNK2 functions as a serine/threonine kinase that catalyzes the transfer of a phosphate group from ATP to specific hydroxyl groups on serine or threonine residues of substrate proteins (cargnello2011activationandfunction pages 1-2). The general reaction can be represented as: ATP + [protein]-OH → ADP + [protein]-O‑PO₃²⁻ + H⁺, in which MNK2 facilitates phosphorylation that modulates substrate function and signaling output (joshi2014mnkkinasepathway pages 2-3).
3. Cofactor Requirements  
   Consistent with many serine/threonine kinases, MNK2 requires Mg²⁺ as a cofactor to coordinate ATP binding and catalyze the phosphate transfer reaction (cargnello2011activationandfunction pages 1-2, roux2004erkandp38 pages 18-19).
4. Substrate Specificity  
   MNK2 phosphorylates a defined set of substrates that include the cap-binding protein eukaryotic initiation factor 4E (eIF4E), as well as RNA-binding proteins such as SFPQ/PSF and heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) (cargnello2011activationandfunction pages 21-23, joshi2014mnkkinasepathway pages 2-3). Although phosphorylation of eIF4E at serine 209 is a well-characterized event mediated by MNK kinases, the precise consensus substrate motif for MNK2 remains incompletely defined (cargnello2011activationandfunction pages 20-21, cargnello2011activationandfunction pages 21-23). Substrate recognition appears to be mediated in part by interactions with docking motifs on MNK2 that facilitate binding to scaffold proteins such as eIF4G, thereby positioning eIF4E and possibly other substrates for efficient phosphorylation (joshi2014mnkkinasepathway pages 2-3).
5. Structure  
   MNK2 contains a central catalytic domain that is characteristic of serine/threonine kinases within the CAMK family and shares strong homology with MNK1’s catalytic domain (cargnello2011activationandfunction pages 20-21, astanehe2011roleofybox pages 38-42). A distinctive structural feature of this catalytic region is the presence of a DFD motif in subdomain VII, which replaces the canonical DFG motif found in many other kinases (cargnello2011activationandfunction pages 20-21). The protein is expressed as at least two alternatively spliced isoforms: MNK2A and MNK2B. MNK2A contains a C-terminal MAPK-binding domain that is essential for its interaction with upstream kinases such as ERK1/2 and, to a lesser extent, p38 MAPK, conferring relatively high basal kinase activity even in quiescent cells (cargnello2011activationandfunction pages 20-21, astanehe2011roleofybox pages 42-46). In contrast, MNK2B lacks this MAPK-binding domain, which underlies its very low basal kinase activity and attenuated responsiveness to upstream stimulation (cargnello2011activationandfunction pages 20-21, astanehe2011roleofybox pages 42-46). In addition, the N-terminal region of MNK2 includes a polybasic sequence that contributes to binding with the scaffold protein eIF4G and also mediates nuclear import via interactions with importin, thereby influencing its subcellular localization (cargnello2011activationandfunction pages 9-10, astanehe2011roleofybox pages 42-46). Key structural features such as the activation loop, which contains highly conserved threonine residues that are phosphorylated by upstream MAPKs, are critical for transitioning MNK2 into its active conformation (cargnello2011activationandfunction pages 20-21).
6. Regulation  
   The activation of MNK2 is dependent on phosphorylation by upstream mitogen-activated protein kinases (MAPKs), primarily ERK1/2 and p38 MAPK, which target conserved threonine residues in the activation loop (cargnello2011activationandfunction pages 20-21, joshi2014mnkkinasepathway pages 1-2). Phosphorylation at these proline-directed sites is essential for full catalytic activation, as mutation of these residues leads to abolition of kinase activity (cargnello2011activationandfunction pages 20-21). In MNK2A, the presence of a C-terminal MAPK-binding domain promotes a stable interaction with phosphorylated ERK1/2, thereby both facilitating and maintaining MNK2 activity under basal conditions; by contrast, the MNK2B isoform, which lacks this domain, exhibits low responsiveness to MAPK-mediated activation (cargnello2011activationandfunction pages 20-21, astanehe2011roleofybox pages 38-42). Additional regulation is achieved through interactions with scaffold proteins such as eIF4G, which not only aid in substrate recognition but also contribute to the spatial and temporal control of MNK2 signaling by directing the kinase to particular subcellular compartments (joshi2014mnkkinasepathway pages 2-3, cargnello2011activationandfunction pages 10-12).
7. Function  
   MNK2 plays a central role in the regulation of mRNA translation by phosphorylating eIF4E at serine 209, an event that increases the affinity of eIF4E for the 7-methylguanosine cap structure present on mRNAs and thereby promotes cap-dependent translation (cargnello2011activationandfunction pages 21-23, joshi2015mnkkinasesin pages 1-2). In addition to its well‐characterized action on eIF4E, MNK2 phosphorylates RNA‐binding proteins such as SFPQ/PSF and HNRNPA1, suggesting that it may also influence mRNA splicing and stability (joshi2014mnkkinasepathway pages 2-3, astanehe2011roleofybox pages 42-46). MNK2 has been implicated in the cellular response to environmental stress and cytokine stimulation, mediating changes in translation that accompany stress‐induced and inflammatory signaling (cargnello2011activationandfunction pages 21-23, joshi2015mnkkinasesin pages 1-2). Furthermore, MNK2 functions as a mediator of the suppressive effects of interferon‐γ on hematopoiesis and acts as a negative regulator for signaling pathways that control arsenic trioxide-dependent apoptosis and anti-leukemic responses (joshi2015mnkkinasesin pages 11-12, cargnello2011activationandfunction pages 23-24). In conditions of serum withdrawal, MNK2 contributes to anti-apoptotic signaling, further highlighting its role in cell survival regulation (joshi2015mnkkinasesin pages 11-12).
8. Other Comments  
   Experimental inhibitors such as CGP57380 have been employed to target MNK kinases; however, these compounds exhibit limited specificity and can inhibit other kinases at similar potency levels (cargnello2011activationandfunction pages 20-21, joshi2014mnkkinasepathway pages 1-2). Differential basal activities between MNK2 isoforms have been noted, with MNK2A displaying robust kinase activity relative to the low activity observed for MNK2B, a difference that may have implications for their respective roles in translational regulation and cell signaling (cargnello2011activationandfunction pages 20-21, astanehe2011roleofybox pages 38-42). MNK2’s involvement in the regulation of eIF4E phosphorylation and mRNA cap binding links it to processes that are critical for cell growth, stress responses, and apoptosis, thereby associating it with oncogenic pathways and inflammatory responses (joshi2015mnkkinasesin pages 1-2, cargnello2011activationandfunction pages 23-24). Moreover, MNK2 is required for mediating PP2A-inhibition-induced eIF4E phosphorylation and the subsequent nuclear shuttling of eIF4E, functions that underscore its importance in the modulation of gene expression at the translational level (Information). These attributes render MNK2 a potential target for therapeutic intervention in cancer and other proliferative or inflammatory diseases (joshi2015mnkkinasesin pages 11-12).
9. References
10. Cargnello, M. and Roux, P.P., “Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases,” Microbiology and Molecular Biology Reviews, vol. 75, pp. 50-83, Mar 2011 (cargnello2011activationandfunction pages 20-21, cargnello2011activationandfunction pages 21-23, cargnello2011activationandfunction pages 10-12, cargnello2011activationandfunction pages 23-24, cargnello2011activationandfunction pages 29-30, cargnello2011activationandfunction pages 1-1, cargnello2011activationandfunction pages 8-9).
11. Joshi, S. and Platanias, L., “Mnk kinase pathway: cellular functions and biological outcomes,” World Journal of Biological Chemistry, vol. 5, no. 3, pp. 321-33, Aug 2014 (joshi2014mnkkinasepathway pages 1-2, joshi2014mnkkinasepathway pages 2-3, joshi2014mnkkinasepathway pages 8-10).
12. Joshi, S. and Platanias, L., “Mnk kinases in cytokine signaling and regulation of cytokine responses,” Biomolecular Concepts, vol. 6, p. 85, 2015 (joshi2015mnkkinasesin pages 1-2, joshi2015mnkkinasesin pages 11-12).
13. Roux, P.P. and Blenis, J., “Erk and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions,” Microbiology and Molecular Biology Reviews, vol. 68, pp. 320-344, Jun 2004 (roux2004erkandp38 pages 15-17, roux2004erkandp38 pages 17-18, roux2004erkandp38 pages 18-19, roux2004erkandp38 pages 1-3, roux2004erkandp38 pages 4-5, roux2004erkandp38 pages 5-8).
14. Astanehe, M., “Role of Y-box binding protein-1 (YB-1) in breast cancer,” (astanehe2011roleofybox pages 38-42, astanehe2011roleofybox pages 42-46).

References

1. (cargnello2011activationandfunction pages 20-21): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
2. (cargnello2011activationandfunction pages 21-23): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
3. (joshi2014mnkkinasepathway pages 2-3): S. Joshi and L. Platanias. Mnk kinase pathway: cellular functions and biological outcomes. World journal of biological chemistry, 5 3:321-33, Aug 2014. URL: https://doi.org/10.4331/wjbc.v5.i3.321, doi:10.4331/wjbc.v5.i3.321. This article has 195 citations.
4. (joshi2014mnkkinasepathway pages 8-10): S. Joshi and L. Platanias. Mnk kinase pathway: cellular functions and biological outcomes. World journal of biological chemistry, 5 3:321-33, Aug 2014. URL: https://doi.org/10.4331/wjbc.v5.i3.321, doi:10.4331/wjbc.v5.i3.321. This article has 195 citations.
5. (joshi2015mnkkinasesin pages 1-2): S. Joshi and L. Platanias. Mnk kinases in cytokine signaling and regulation of cytokine responses. Biomolecular Concepts, 6:85-85, 2015. URL: https://doi.org/10.1515/bmc-2011-2000, doi:10.1515/bmc-2011-2000. This article has 46 citations and is from a peer-reviewed journal.
6. (joshi2015mnkkinasesin pages 11-12): S. Joshi and L. Platanias. Mnk kinases in cytokine signaling and regulation of cytokine responses. Biomolecular Concepts, 6:85-85, 2015. URL: https://doi.org/10.1515/bmc-2011-2000, doi:10.1515/bmc-2011-2000. This article has 46 citations and is from a peer-reviewed journal.
7. (roux2004erkandp38 pages 18-19): Philippe P. Roux and John Blenis. Erk and p38 mapk-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiology and Molecular Biology Reviews, 68:320-344, Jun 2004. URL: https://doi.org/10.1128/mmbr.68.2.320-344.2004, doi:10.1128/mmbr.68.2.320-344.2004. This article has 3360 citations and is from a domain leading peer-reviewed journal.
8. (astanehe2011roleofybox pages 38-42): Role of Y-box binding protein-1 (YB-1) in breast cancer
9. (astanehe2011roleofybox pages 42-46): Role of Y-box binding protein-1 (YB-1) in breast cancer
10. (cargnello2011activationandfunction pages 1-2): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
11. (cargnello2011activationandfunction pages 10-12): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
12. (cargnello2011activationandfunction pages 23-24): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
13. (cargnello2011activationandfunction pages 29-30): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
14. (cargnello2011activationandfunction pages 9-10): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
15. (joshi2014mnkkinasepathway pages 1-2): S. Joshi and L. Platanias. Mnk kinase pathway: cellular functions and biological outcomes. World journal of biological chemistry, 5 3:321-33, Aug 2014. URL: https://doi.org/10.4331/wjbc.v5.i3.321, doi:10.4331/wjbc.v5.i3.321. This article has 195 citations.
16. (roux2004erkandp38 pages 15-17): Philippe P. Roux and John Blenis. Erk and p38 mapk-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiology and Molecular Biology Reviews, 68:320-344, Jun 2004. URL: https://doi.org/10.1128/mmbr.68.2.320-344.2004, doi:10.1128/mmbr.68.2.320-344.2004. This article has 3360 citations and is from a domain leading peer-reviewed journal.
17. (roux2004erkandp38 pages 17-18): Philippe P. Roux and John Blenis. Erk and p38 mapk-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiology and Molecular Biology Reviews, 68:320-344, Jun 2004. URL: https://doi.org/10.1128/mmbr.68.2.320-344.2004, doi:10.1128/mmbr.68.2.320-344.2004. This article has 3360 citations and is from a domain leading peer-reviewed journal.
18. (roux2004erkandp38 pages 4-5): Philippe P. Roux and John Blenis. Erk and p38 mapk-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiology and Molecular Biology Reviews, 68:320-344, Jun 2004. URL: https://doi.org/10.1128/mmbr.68.2.320-344.2004, doi:10.1128/mmbr.68.2.320-344.2004. This article has 3360 citations and is from a domain leading peer-reviewed journal.
19. (roux2004erkandp38 pages 5-8): Philippe P. Roux and John Blenis. Erk and p38 mapk-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiology and Molecular Biology Reviews, 68:320-344, Jun 2004. URL: https://doi.org/10.1128/mmbr.68.2.320-344.2004, doi:10.1128/mmbr.68.2.320-344.2004. This article has 3360 citations and is from a domain leading peer-reviewed journal.
20. (roux2004erkandp38 pages 1-3): Philippe P. Roux and John Blenis. Erk and p38 mapk-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiology and Molecular Biology Reviews, 68:320-344, Jun 2004. URL: https://doi.org/10.1128/mmbr.68.2.320-344.2004, doi:10.1128/mmbr.68.2.320-344.2004. This article has 3360 citations and is from a domain leading peer-reviewed journal.
21. (cargnello2011activationandfunction pages 1-1): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.
22. (cargnello2011activationandfunction pages 8-9): Marie Cargnello and Philippe P. Roux. Activation and function of the mapks and their substrates, the mapk-activated protein kinases. Microbiology and Molecular Biology Reviews, 75:50-83, Mar 2011. URL: https://doi.org/10.1128/mmbr.00031-10, doi:10.1128/mmbr.00031-10. This article has 4026 citations and is from a domain leading peer-reviewed journal.