1. Phylogeny – MAP2K3, also known as MKK3, MEK3, PRKMK3, or SKK2, is a dual‐specificity kinase that belongs to the mitogen‐activated protein kinase kinase (MAP2K) family within the larger CMGC group of the human kinome. Orthologs of MAP2K3 have been identified across eukaryotic species, and phylogenetic analyses trace its evolutionary origins back to early eukaryotic signaling systems. Within mammals, MAP2K3 is closely related to its paralog MAP2K6 (commonly referred to as MEK6), and both enzymes are dedicated activators of p38 MAP kinases. These evolutionary relationships, supported by analyses described in studies on the human kinase complement, indicate that MAP2K3 arose from gene duplication events that contributed to the diversification of stress‐activated signaling cascades (ayalamarin2021quadrupleandtruncated pages 1-2, pearson2001mitogenactivatedprotein(map) pages 31-31, kyriakis2001mammalianmitogenactivatedprotein pages 15-16).
2. Reaction Catalyzed – MAP2K3 catalyzes an ATP‐dependent phosphorylation reaction in which a molecule of ATP donates a phosphate group to both a threonine and a tyrosine residue within the activation loop (TGY motif) of its substrate, the p38 MAP kinase. In this dual phosphorylation reaction, ATP is converted to ADP while the p38 kinase is modified to its active, phosphorylated form along with the release of a proton (H⁺) (ayalamarin2021quadrupleandtruncated pages 1-2, pearson2001mitogenactivatedprotein(map) pages 31-31, davies2000specificityandmechanism pages 1-2).
3. Cofactor Requirements – The catalytic activity of MAP2K3 requires the presence of divalent cations, with Mg²⁺ serving as the essential cofactor for the proper binding of ATP and for facilitating the phosphoryl transfer reaction (davies2000specificityandmechanism pages 1-2).
4. Substrate Specificity – MAP2K3 exhibits a high degree of substrate specificity by selectively phosphorylating p38 MAP kinase isoforms. It targets the conserved threonine and tyrosine residues within the activation loop (the TGY motif) of p38, a modification critical for p38 activation. Although classified as a serine/threonine kinase, its dual‐specificity nature enables MAP2K3 to catalyze phosphorylation on both serine/threonine and tyrosine residues, a property that underlies its precise regulation of p38-mediated signaling (ayalamarin2021quadrupleandtruncated pages 1-2, raman2007differentialregulationand pages 6-7, raman2007differentialregulationand pages 7-8).
5. Structure – The three-dimensional organization of MAP2K3 reveals a canonical kinase fold composed of an N-terminal lobe dominated by β-sheets and a larger, predominantly α-helical C-terminal lobe. The ATP-binding pocket is located in the cleft between these lobes, and the catalytic core includes conserved motifs such as the DFG motif and a hydrophobic spine that stabilize the active conformation. Central to its regulatory function is the activation loop, which harbors critical threonine and tyrosine residues that must be phosphorylated for full catalytic activation. In addition, MAP2K3 contains docking domains that promote selective interactions with upstream activators and downstream substrates. These structural features are consistent with experimental data and modeling studies that describe MAP2K3’s overall fold and the role of its regulatory segments in substrate recognition and kinase activation (ayalamarin2021quadrupleandtruncated pages 1-2, pearson2001mitogenactivatedprotein(map) pages 5-6, raman2007differentialregulationand pages 2-3, raman2007differentialregulationand pages 7-8).
6. Regulation – MAP2K3 is subject to multiple layers of regulation that ensure precise control of its activity. Its activation is initiated by phosphorylation at key serine and threonine residues within the activation loop by upstream MAP kinase kinase kinases (MAP3Ks). In certain disease contexts, point mutations—such as R65L, R67W in the vicinity of the ATP-binding site and R26T, P11T near the substrate-binding region—have been identified and are associated with enhanced proteasome- and protease-dependent degradation. A truncated mutant (Q73\*) has also been described, which further exemplifies the role of structural integrity in maintaining kinase stability. Additionally, the turnover of MAP2K3 protein can be modulated by inhibitors of cysteine/serine proteases, indicating that post-translational regulation through targeted degradation plays an important role in controlling its cellular levels. These regulatory mechanisms underscore the tight control of MAP2K3 activity in response to stress signals, and its altered regulation has been implicated in oncogenic processes (ayalamarin2021quadrupleandtruncated pages 1-2, ayalamarin2021quadrupleandtruncated pages 12-13, pearson2001mitogenactivatedprotein(map) pages 31-31, hammaker2004regulationofcjun pages 8-8).
7. Function – As a dual-specificity MAP kinase kinase, MAP2K3 plays a pivotal role in transmitting stress and cytokine signals to the p38 MAP kinase pathway. Activation of MAP2K3 occurs in response to cytokines and environmental stressors, as well as through receptor-mediated signals such as those initiated by the adrenergic receptor ADRA1B. Once activated, MAP2K3 phosphorylates p38 MAP kinase (MAPK14), thereby triggering a cascade that influences cellular functions including differentiation, migration, survival, apoptosis, and metabolism. In addition, MAP2K3 contributes to the regulation of inflammatory responses by modulating the expression of pro-inflammatory cytokines and gene products involved in stress responses. Alterations in MAP2K3 expression or activity, including its downregulation in cancers such as breast, colon, liver, esophageal, and thyroid carcinomas, further highlight its role as a tumor suppressor and its importance in maintaining normal cellular homeostasis. Moreover, in hematopoietic malignancies, dysregulation of the p38 pathway downstream of MAP2K3 has been linked to therapy resistance, emphasizing its biological significance in a range of physiological and pathological processes (ayalamarin2021quadrupleandtruncated pages 1-2, raman2007differentialregulationand pages 7-8, pearson2001mitogenactivatedprotein(map) pages 31-31, danquah2015identificationandcharacterization pages 2-4).
8. Other Comments – Although selective inhibitors directly targeting MAP2K3 have not been comprehensively detailed in the literature, downstream elements of the MAP2K3-p38 pathway are amenable to pharmacological modulation through agents such as pyridinyl imidazole inhibitors (e.g., SB203580), which inhibit p38 MAP kinase activity. In the context of disease, mutations in MAP2K3, including point mutations and truncations, have been implicated in the development of acute lymphoblastic leukemia by promoting protein degradation and enhancing cell proliferation. Furthermore, the frequent downregulation of MAP2K3 observed in various cancers points to its potential utility as a therapeutic target in oncology and hematological malignancies (ayalamarin2021quadrupleandtruncated pages 1-2, ayalamarin2021quadrupleandtruncated pages 13-14, rocco2022anti‑oncogenicandpro‑myogenic pages 15-15, yustein2003comparativestudiesof pages 1-2).
9. References
10. ayalamarin2021quadrupleandtruncated pages 1-2
11. ayalamarin2021quadrupleandtruncated pages 12-13
12. ayalamarin2021quadrupleandtruncated pages 13-14
13. pearson2001mitogenactivatedprotein(map) pages 31-31
14. raman2007differentialregulationand pages 6-7
15. raman2007differentialregulationand pages 7-8
16. davies2000specificityandmechanism pages 1-2
17. davies2000specificityandmechanism pages 2-3
18. hammaker2004regulationofcjun pages 8-8
19. kyriakis2001mammalianmitogenactivatedprotein pages 15-16
20. danquah2015identificationandcharacterization pages 2-4
21. rocco2022anti‑oncogenicandpro‑myogenic pages 15-15
22. yustein2003comparativestudiesof pages 1-2

References

1. (ayalamarin2021quadrupleandtruncated pages 1-2): Yoshira M. Ayala-Marín, Alice H. Grant, Georgialina Rodriguez, and R. Kirken. Quadruple and truncated mek3 mutants identified from acute lymphoblastic leukemia promote degradation and enhance proliferation. International Journal of Molecular Sciences, Nov 2021. URL: https://doi.org/10.3390/ijms222212210, doi:10.3390/ijms222212210. This article has 2 citations and is from a peer-reviewed journal.
2. (pearson2001mitogenactivatedprotein(map) pages 31-31): G. Pearson, Fred L Robinson, T. Gibson, Bing-e Xu, M. Karandikar, K. Berman, and M. Cobb. Mitogen-activated protein (map) kinase pathways: regulation and physiological functions. Endocrine Reviews, 22:153-183, Apr 2001. URL: https://doi.org/10.1210/er.22.2.153, doi:10.1210/er.22.2.153. This article has 5942 citations and is from a domain leading peer-reviewed journal.
3. (raman2007differentialregulationand pages 6-7): Malavika Raman, Wei Chen, and M. Cobb. Differential regulation and properties of mapks. Oncogene, 26:3100-3112, May 2007. URL: https://doi.org/10.1038/sj.onc.1210392, doi:10.1038/sj.onc.1210392. This article has 1965 citations and is from a domain leading peer-reviewed journal.
4. (raman2007differentialregulationand pages 7-8): Malavika Raman, Wei Chen, and M. Cobb. Differential regulation and properties of mapks. Oncogene, 26:3100-3112, May 2007. URL: https://doi.org/10.1038/sj.onc.1210392, doi:10.1038/sj.onc.1210392. This article has 1965 citations and is from a domain leading peer-reviewed journal.
5. (ayalamarin2021quadrupleandtruncated pages 12-13): Yoshira M. Ayala-Marín, Alice H. Grant, Georgialina Rodriguez, and R. Kirken. Quadruple and truncated mek3 mutants identified from acute lymphoblastic leukemia promote degradation and enhance proliferation. International Journal of Molecular Sciences, Nov 2021. URL: https://doi.org/10.3390/ijms222212210, doi:10.3390/ijms222212210. This article has 2 citations and is from a peer-reviewed journal.
6. (ayalamarin2021quadrupleandtruncated pages 13-14): Yoshira M. Ayala-Marín, Alice H. Grant, Georgialina Rodriguez, and R. Kirken. Quadruple and truncated mek3 mutants identified from acute lymphoblastic leukemia promote degradation and enhance proliferation. International Journal of Molecular Sciences, Nov 2021. URL: https://doi.org/10.3390/ijms222212210, doi:10.3390/ijms222212210. This article has 2 citations and is from a peer-reviewed journal.
7. (danquah2015identificationandcharacterization pages 2-4): A. Danquah, Axel de Zélicourt, Marie Boudsocq, Jorinde Neubauer, Nicolas Frei dit Frey, N. Leonhardt, Stéphanie Pateyron, Frederik Gwinner, J. Tamby, D. Ortiz-Masia, M. J. Marcote, H. Hirt, and J. Colcombet. Identification and characterization of an aba-activated map kinase cascade in arabidopsis thaliana. The Plant journal : for cell and molecular biology, 82 2:232-44, Apr 2015. URL: https://doi.org/10.1111/tpj.12808, doi:10.1111/tpj.12808. This article has 253 citations.
8. (davies2000specificityandmechanism pages 1-2): Stephen P. DAVIES, Helen REDDY, Matilde CAIVANO, and Philip COHEN. Specificity and mechanism of action of some commonly used protein kinase inhibitors. Biochemical Journal, 351:95-105, Sep 2000. URL: https://doi.org/10.1042/bj3510095, doi:10.1042/bj3510095. This article has 5476 citations and is from a domain leading peer-reviewed journal.
9. (davies2000specificityandmechanism pages 2-3): Stephen P. DAVIES, Helen REDDY, Matilde CAIVANO, and Philip COHEN. Specificity and mechanism of action of some commonly used protein kinase inhibitors. Biochemical Journal, 351:95-105, Sep 2000. URL: https://doi.org/10.1042/bj3510095, doi:10.1042/bj3510095. This article has 5476 citations and is from a domain leading peer-reviewed journal.
10. (hammaker2004regulationofcjun pages 8-8): Deepa R. Hammaker, David L. Boyle, Martine Chabaud-Riou, and Gary S. Firestein. Regulation of c-jun n-terminal kinase by mekk-2 and mitogen-activated protein kinase kinase kinases in rheumatoid arthritis. The Journal of Immunology, 172:1612-1618, Feb 2004. URL: https://doi.org/10.4049/jimmunol.172.3.1612, doi:10.4049/jimmunol.172.3.1612. This article has 110 citations.
11. (kyriakis2001mammalianmitogenactivatedprotein pages 15-16): John M. Kyriakis and Joseph Avruch. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiological Reviews, 81:807-869, Apr 2001. URL: https://doi.org/10.1152/physrev.2001.81.2.807, doi:10.1152/physrev.2001.81.2.807. This article has 4491 citations and is from a highest quality peer-reviewed journal.
12. (pearson2001mitogenactivatedprotein(map) pages 5-6): G. Pearson, Fred L Robinson, T. Gibson, Bing-e Xu, M. Karandikar, K. Berman, and M. Cobb. Mitogen-activated protein (map) kinase pathways: regulation and physiological functions. Endocrine Reviews, 22:153-183, Apr 2001. URL: https://doi.org/10.1210/er.22.2.153, doi:10.1210/er.22.2.153. This article has 5942 citations and is from a domain leading peer-reviewed journal.
13. (raman2007differentialregulationand pages 2-3): Malavika Raman, Wei Chen, and M. Cobb. Differential regulation and properties of mapks. Oncogene, 26:3100-3112, May 2007. URL: https://doi.org/10.1038/sj.onc.1210392, doi:10.1038/sj.onc.1210392. This article has 1965 citations and is from a domain leading peer-reviewed journal.
14. (rocco2022anti‑oncogenicandpro‑myogenic pages 15-15): Agnese Di Rocco, Simona Camero, Anna Benedetti, Biliana Lozanoska‑ochser, Francesca Megiorni, Cinzia Marchese, Lorenzo Stramucci, Carmela Ciccarelli, Marina Bouché, Gianluca Bossi, Francesco Marampon, and Bianca Zani. Anti‑oncogenic and pro‑myogenic action of the mkk6/p38/akt axis induced by targeting mek/erk in embryonal rhabdomyosarcoma. Oncology Reports, Jul 2022. URL: https://doi.org/10.3892/or.2022.8363, doi:10.3892/or.2022.8363. This article has 4 citations and is from a peer-reviewed journal.
15. (yustein2003comparativestudiesof pages 1-2): J. Yustein, L. Xia, J. M. Kahlenburg, D. Robinson, D. Templeton, and H. Kung. Comparative studies of a new subfamily of human ste20-like kinases: homodimerization, subcellular localization, and selective activation of mkk3 and p38. Oncogene, 22:6129-6141, Sep 2003. URL: https://doi.org/10.1038/sj.onc.1206605, doi:10.1038/sj.onc.1206605. This article has 63 citations and is from a domain leading peer-reviewed journal.