1. Phylogeny  
   MAP2K5, also known as MEK5 or MKK5, is a dual‐specificity kinase that belongs to the mitogen-activated protein kinase kinase (MAP2K) family and is evolutionarily related to MEK1 and MEK2 as well as to the fission yeast homolog Byr1, demonstrating conservation across eukaryotes (english1995isolationofmek5 pages 1-3). Orthologs of MAP2K5 have been identified in a wide range of species, confirming that its fundamental role in signal transduction is maintained from yeast to mammals (english1995isolationofmek5 pages 1-3, glatz2013structuralmechanismfor pages 1-2). In phylogenetic analyses, MAP2K5 clusters separately from other MAP2Ks that activate ERK1/2 or p38, thereby forming a dedicated signaling branch that specifically regulates ERK5 activity (nishimoto2006mapksignallingerk5 pages 1-2). The protein is further characterized by the presence of a PB1 domain in its N-terminal region, which distinguishes it as a mediator of selective protein–protein interactions in the ERK5 module (seyfried2005anovelmitogenactivated pages 1-2).
2. Reaction Catalyzed  
   MAP2K5 is an enzyme that catalyzes the phosphate transfer reaction from ATP to its target substrate, specifically phosphorylating the dual phosphorylation motif (TEY) located in the activation loop of ERK5 (mody2003ananalysisof pages 7-8). The chemical reaction can be represented as follows: ATP + ERK5 (contain­ing unphosphorylated threonine and tyrosine residues) → ADP + ERK5 (phosphorylated at both threonine and tyrosine) + H⁺ (nishimoto2006mapksignallingerk5 pages 1-2, mody2003ananalysisof pages 9-9).
3. Cofactor Requirements  
   The catalytic activity of MAP2K5 is dependent on ATP as the phosphate donor and requires divalent metal ions for optimal function. In particular, Mg²⁺ is necessary to coordinate ATP binding and facilitate the phosphoryl transfer reaction within the kinase active site (glatz2013structuralmechanismfor pages 7-8, mody2003ananalysisof pages 7-8).
4. Substrate Specificity  
   MAP2K5 exhibits a high degree of substrate specificity by selectively targeting ERK5 for phosphorylation. This selectivity is mediated by the recognition of a specific docking region within ERK5 that includes the conserved TEY motif, which is essential for its activation (seyfried2005anovelmitogenactivated pages 1-2). The enzyme’s unique interaction with ERK5 is further enhanced by the cooperative contributions of its PB1 domain and a linear docking (D-) motif, which together ensure that phosphorylation occurs exclusively on ERK5 (mody2003ananalysisof pages 7-8).
5. Structure  
   MAP2K5 is composed of an N-terminal region that includes a PB1 (Phox and Bem1) domain, a linear D-motif, and a central kinase domain. The PB1 domain is responsible for mediating protein–protein interactions with upstream MAP3K activators and with its downstream substrate ERK5, forming part of a signaling-competent ternary complex (seyfried2005anovelmitogenactivated pages 1-2, english1995isolationofmek5 pages 3-4). The D-motif, which is located adjacent to the PB1 domain, strengthens the binding affinity between MAP2K5 and ERK5 by providing additional docking interactions. The catalytic kinase domain displays the conserved bilobal architecture common to protein kinases, with an N-terminal lobe primarily composed of β-sheets and a larger C-terminal lobe containing α-helices and the regulatory C-helix. Structural studies have revealed the presence of an activation loop within the kinase domain that must undergo phosphorylation to achieve full catalytic competency; additional conserved structural features, such as the hydrophobic spine, are also present and essential for proper alignment of catalytic residues (glatz2013structuralmechanismfor pages 4-5, glatz2013structuralmechanismfor pages 7-8). High-resolution crystallographic analyses of the MAP2K5–ERK5 complex have demonstrated that the PB1 domain and the D-motif cooperate to form a stable interface, resulting in a significant buried surface area that is indicative of a robust interaction network (glatz2013structuralmechanismfor pages 9-11). Furthermore, alternative splicing gives rise to at least two isoforms—MEK5α and MEK5β—that differ in their N-terminal sequences and subcellular localization properties, with MEK5α possessing an extended N-terminal region that includes additional regulatory elements (english1995isolationofmek5 pages 3-4, seyfried2005anovelmitogenactivated pages 1-2).
6. Regulation  
   MAP2K5 activity is tightly regulated by multiple mechanisms that ensure precise control over ERK5 activation. Phosphorylation is the primary regulatory mechanism, with upstream MAP kinase kinase kinases (MAP3Ks) such as MEKK2 and MEKK3 directly phosphorylating MAP2K5 on specific serine and threonine residues, notably including Ser311 and Thr315, to stimulate its catalytic activity (mody2003ananalysisof pages 7-8, seyfried2005anovelmitogenactivated pages 5-6). In addition to this phosphorylation, the PB1 domain of MAP2K5 mediates critical scaffold interactions that facilitate the assembly of a ternary complex with MAP3Ks and ERK5, thereby enabling efficient and selective signal transduction (seyfried2005anovelmitogenactivated pages 5-6, glatz2013structuralmechanismfor pages 9-11). Regulatory interactions with atypical protein kinase C isoforms have also been documented, wherein binding of aPKCs promotes MEK5 autophosphorylation and further enhances its activity (diazmeco2001mek5anew pages 6-8). Moreover, feedback regulation is observed within the ERK5 pathway; sustained ERK5 activation can lead to modulation of upstream signaling components and influence further MAP2K5 activity, although detailed mechanisms of such feedback loops remain to be fully elucidated within the available literature (nishimoto2006mapksignallingerk5 pages 3-4).
7. Function  
   MAP2K5 plays a dual role as both an active kinase and a scaffold within the ERK5 signaling cascade. By phosphorylating ERK5 on its dual phosphorylation (TEY) motif, it initiates a signaling cascade that is critical for diverse cellular processes. Among its well-defined functions, MAP2K5 is essential for protecting cells from stress-induced apoptosis, a role that is particularly evident in neuronal and cardiac tissues (simoes2016themek5erk5signalling pages 1-2, nishimoto2006mapksignallingerk5 pages 1-2). In cardiomyocytes, MAP2K5 functions as a negative regulator of apoptosis by promoting the STUB1/CHIP-mediated ubiquitination and degradation of ICER-type isoforms of CREM, thus maintaining cell survival under stress conditions (wang2005targeteddeletionof pages 8-9, simoes2016themek5erk5signalling pages 1-2). In addition, MAP2K5 is integral to the development of the cardiovascular system and angiogenesis, as evidenced by in vivo studies showing that deletion of MEK5 leads to embryonic lethality and cardiac developmental defects (wang2005targeteddeletionof pages 8-9, nakahata2010thesignalingpathway pages 1-2). The activation of ERK5 by MAP2K5 further drives the transcriptional regulation of key factors such as the myocyte enhancer factor 2 (MEF2) family, thereby linking the kinase to the regulation of gene expression programs that control neuronal survival and endothelial cell function (nishimoto2006mapksignallingerk5 pages 1-2, simoes2016themek5erk5signalling pages 2-3).
8. Other Comments  
   Experimental efforts to target the MAP2K5/ERK5 pathway have led to the development of selective inhibitors such as BIX02188 and BIX02189, which inhibit MAP2K5 activity at low nanomolar concentrations; however, the selectivity and potency of these compounds continue to be refined (simoes2016themek5erk5signalling pages 2-3, stecca2019impactoferk5 pages 20-21). MAP2K5 has been implicated in oncogenic processes, with dysregulation of the MEK5/ERK5 signaling cascade observed in several human cancers, including breast, prostate, and hematologic malignancies; its aberrant activation has been associated with enhanced cellular proliferation, resistance to apoptosis, and increased metastatic potential (stecca2019impactoferk5 pages 20-21, wilhelmsen2015extracellularsignal–regulatedkinase pages 15-17). In addition to cancer, functional studies utilizing gene-targeted deletion of MAP2K5 in animal models have highlighted its fundamental role in embryonic development, particularly in cardiac morphogenesis and vascular integrity, where its loss results in pronounced developmental defects and increased apoptosis (wang2005targeteddeletionof pages 8-9, nakahata2010thesignalingpathway pages 1-2). The dual role of MAP2K5 as both an enzyme and a scaffold for the assembly of signaling complexes underscores its importance in ensuring the correct spatial and temporal activation of ERK5 and other downstream effectors. Although specific disease-causing mutations in MAP2K5 have not been extensively characterized, its vital role in regulating survival pathways makes it a potential target for therapeutic intervention in disorders associated with impaired apoptosis and aberrant developmental signaling (wilhelmsen2015extracellularsignal–regulatedkinase pages 17-18, mody2003ananalysisof pages 9-9).
9. References
10. English, J., Vanderbilt, C., Xu, S., Marcus, S., & Cobb, M. “Isolation of MEK5 and Differential Expression of Alternatively Spliced Forms.” The Journal of Biological Chemistry, 270, 28897–28902, Dec 1995. (english1995isolationofmek5 pages 1-3, pages 3-4, pages 6-7)
11. Glatz, G., Gógl, G., Alexa, A., & Reményi, A. “Structural Mechanism for the Specific Assembly and Activation of the Extracellular Signal Regulated Kinase 5 (ERK5) Module.” Journal of Biological Chemistry, 288, 8596–8609, Mar 2013. (glatz2013structuralmechanismfor pages 1-2, pages 4-5, pages 7-8, pages 9-11, pages 11-12)
12. Nishimoto, S. & Nishida, E. “MAPK Signalling: ERK5 versus ERK1/2.” EMBO Reports, Aug 2006. (nishimoto2006mapksignallingerk5 pages 1-2, pages 3-4)
13. Seyfried, J., Wang, X., Kharebava, G., & Tournier, C. “A Novel Mitogen-Activated Protein Kinase Docking Site in the N Terminus of MEK5α Organizes the Components of the Extracellular Signal-Regulated Kinase 5 Signaling Pathway.” Molecular and Cellular Biology, 25, 9820–9828, Nov 2005. (seyfried2005anovelmitogenactivated pages 1-2, pages 3-5, pages 5-6, pages 9-9)
14. Simões, A. E. S., Rodrigues, C. M. P., & Borralho, P. M. “The MEK5/ERK5 Signalling Pathway in Cancer: A Promising Novel Therapeutic Target.” Drug Discovery Today, 21, 1654–1663, Oct 2016. (simoes2016themek5erk5signalling pages 1-2, pages 2-3, pages 8-9)
15. Stecca, B. & Rovida, E. “Impact of ERK5 on the Hallmarks of Cancer.” International Journal of Molecular Sciences, 20, 1426, Mar 2019. (stecca2019impactoferk5 pages 13-15, pages 20-21)
16. Wang, X., Merritt, A., Seyfried, J., Guo, C., Papadakis, E., Finegan, K., Kayahara, M., Dixon, J., Boot-Handford, R., Cartwright, E., Mayer, U., & Tournier, C. “Targeted Deletion of MEK5 Causes Early Embryonic Death and Defects in the Extracellular Signal-Regulated Kinase 5/Myocyte Enhancer Factor 2 Cell Survival Pathway.” Molecular and Cellular Biology, 25, 336–345, Jan 2005. (wang2005targeteddeletionof pages 8-9, pages 10-10)
17. Wilhelmsen, K., Xu, F., Farrar, K., Tran, A., Khakpour, S., Sundar, S., Prakash, A., Wang, J., Gray, N. S., & Hellman, J. “Extracellular Signal–Regulated Kinase 5 Promotes Acute Cellular and Systemic Inflammation.” Science Signaling, 8, ra86–ra86, Aug 2015. (wilhelmsen2015extracellularsignal–regulatedkinase pages 15-17, pages 17-18, pages 18-19)
18. Mody, N., Campbell, D., Morrice, N., Peggie, M., & Cohen, P. “An Analysis of the Phosphorylation and Activation of Extracellular-Signal-Regulated Protein Kinase 5 (ERK5) by Mitogen-Activated Protein Kinase Kinase 5 (MKK5) In Vitro.” The Biochemical Journal, 372 Pt 2, 567–575, Jun 2003. (mody2003ananalysisof pages 7-8, pages 8-9, pages 9-9, pages 1-2)
19. Nakahata, N. & Obara, Y. “The Signaling Pathway Leading to Extracellular Signal-Regulated Kinase 5 (ERK5) Activation via G-Proteins and ERK5-Dependent Neurotrophic Effects.” Molecular Pharmacology, 77, 10–16, Jan 2010. (nakahata2010thesignalingpathway pages 1-2, pages 6-6)
20. Diaz-Meco, M. T. & Moscat, J. “MEK5, a New Target of the Atypical Protein Kinase C Isoforms in Mitogenic Signaling.” Molecular and Cellular Biology, 21, 1218–1227, Feb 2001. (diazmeco2001mek5anew pages 6-8)

References

1. (glatz2013structuralmechanismfor pages 4-5): Gábor Glatz, Gergő Gógl, Anita Alexa, and Attila Reményi. Structural mechanism for the specific assembly and activation of the extracellular signal regulated kinase 5 (erk5) module. Journal of Biological Chemistry, 288:8596-8609, Mar 2013. URL: https://doi.org/10.1074/jbc.m113.452235, doi:10.1074/jbc.m113.452235. This article has 50 citations and is from a domain leading peer-reviewed journal.
2. (seyfried2005anovelmitogenactivated pages 1-2): Jan Seyfried, Xin Wang, Giorgi Kharebava, and Cathy Tournier. A novel mitogen-activated protein kinase docking site in the n terminus of mek5α organizes the components of the extracellular signal-regulated kinase 5 signaling pathway. Molecular and Cellular Biology, 25:9820-9828, Nov 2005. URL: https://doi.org/10.1128/mcb.25.22.9820-9828.2005, doi:10.1128/mcb.25.22.9820-9828.2005. This article has 67 citations and is from a domain leading peer-reviewed journal.
3. (simoes2016themek5erk5signalling pages 1-2): André E.S. Simões, Cecília M.P. Rodrigues, and Pedro M. Borralho. The mek5/erk5 signalling pathway in cancer: a promising novel therapeutic target. Drug Discovery Today, 21:1654-1663, Oct 2016. URL: https://doi.org/10.1016/j.drudis.2016.06.010, doi:10.1016/j.drudis.2016.06.010. This article has 94 citations and is from a domain leading peer-reviewed journal.
4. (simoes2016themek5erk5signalling pages 2-3): André E.S. Simões, Cecília M.P. Rodrigues, and Pedro M. Borralho. The mek5/erk5 signalling pathway in cancer: a promising novel therapeutic target. Drug Discovery Today, 21:1654-1663, Oct 2016. URL: https://doi.org/10.1016/j.drudis.2016.06.010, doi:10.1016/j.drudis.2016.06.010. This article has 94 citations and is from a domain leading peer-reviewed journal.
5. (stecca2019impactoferk5 pages 13-15): Barbara Stecca and Elisabetta Rovida. Impact of erk5 on the hallmarks of cancer. International Journal of Molecular Sciences, 20:1426, Mar 2019. URL: https://doi.org/10.3390/ijms20061426, doi:10.3390/ijms20061426. This article has 111 citations and is from a peer-reviewed journal.
6. (wilhelmsen2015extracellularsignal–regulatedkinase pages 15-17): Kevin Wilhelmsen, Fengyun Xu, Katherine Farrar, Alphonso Tran, Samira Khakpour, Shirin Sundar, Arun Prakash, Jinhua Wang, Nathanael S. Gray, and Judith Hellman. Extracellular signal–regulated kinase 5 promotes acute cellular and systemic inflammation. Science Signaling, 8:ra86-ra86, Aug 2015. URL: https://doi.org/10.1126/scisignal.aaa3206, doi:10.1126/scisignal.aaa3206. This article has 47 citations and is from a domain leading peer-reviewed journal.
7. (wilhelmsen2015extracellularsignal–regulatedkinase pages 17-18): Kevin Wilhelmsen, Fengyun Xu, Katherine Farrar, Alphonso Tran, Samira Khakpour, Shirin Sundar, Arun Prakash, Jinhua Wang, Nathanael S. Gray, and Judith Hellman. Extracellular signal–regulated kinase 5 promotes acute cellular and systemic inflammation. Science Signaling, 8:ra86-ra86, Aug 2015. URL: https://doi.org/10.1126/scisignal.aaa3206, doi:10.1126/scisignal.aaa3206. This article has 47 citations and is from a domain leading peer-reviewed journal.
8. (diazmeco2001mek5anew pages 6-8): Marı́a T. Diaz-Meco and Jorge Moscat. Mek5, a new target of the atypical protein kinase c isoforms in mitogenic signaling. Molecular and Cellular Biology, 21:1218-1227, Feb 2001. URL: https://doi.org/10.1128/mcb.21.4.1218-1227.2001, doi:10.1128/mcb.21.4.1218-1227.2001. This article has 102 citations and is from a domain leading peer-reviewed journal.
9. (english1995isolationofmek5 pages 1-3): J. English, C. Vanderbilt, Shuichan Xu, S. Marcus, and M. Cobb. Isolation of mek5 and differential expression of alternatively spliced forms \*. The Journal of Biological Chemistry, 270:28897-28902, Dec 1995. URL: https://doi.org/10.1074/jbc.270.48.28897, doi:10.1074/jbc.270.48.28897. This article has 281 citations.
10. (english1995isolationofmek5 pages 3-4): J. English, C. Vanderbilt, Shuichan Xu, S. Marcus, and M. Cobb. Isolation of mek5 and differential expression of alternatively spliced forms \*. The Journal of Biological Chemistry, 270:28897-28902, Dec 1995. URL: https://doi.org/10.1074/jbc.270.48.28897, doi:10.1074/jbc.270.48.28897. This article has 281 citations.
11. (glatz2013structuralmechanismfor pages 1-2): Gábor Glatz, Gergő Gógl, Anita Alexa, and Attila Reményi. Structural mechanism for the specific assembly and activation of the extracellular signal regulated kinase 5 (erk5) module. Journal of Biological Chemistry, 288:8596-8609, Mar 2013. URL: https://doi.org/10.1074/jbc.m113.452235, doi:10.1074/jbc.m113.452235. This article has 50 citations and is from a domain leading peer-reviewed journal.
12. (glatz2013structuralmechanismfor pages 7-8): Gábor Glatz, Gergő Gógl, Anita Alexa, and Attila Reményi. Structural mechanism for the specific assembly and activation of the extracellular signal regulated kinase 5 (erk5) module. Journal of Biological Chemistry, 288:8596-8609, Mar 2013. URL: https://doi.org/10.1074/jbc.m113.452235, doi:10.1074/jbc.m113.452235. This article has 50 citations and is from a domain leading peer-reviewed journal.
13. (glatz2013structuralmechanismfor pages 9-11): Gábor Glatz, Gergő Gógl, Anita Alexa, and Attila Reményi. Structural mechanism for the specific assembly and activation of the extracellular signal regulated kinase 5 (erk5) module. Journal of Biological Chemistry, 288:8596-8609, Mar 2013. URL: https://doi.org/10.1074/jbc.m113.452235, doi:10.1074/jbc.m113.452235. This article has 50 citations and is from a domain leading peer-reviewed journal.
14. (mody2003ananalysisof pages 7-8): N. Mody, D. Campbell, N. Morrice, M. Peggie, and P. Cohen. An analysis of the phosphorylation and activation of extracellular-signal-regulated protein kinase 5 (erk5) by mitogen-activated protein kinase kinase 5 (mkk5) in vitro. The Biochemical journal, 372 Pt 2:567-75, Jun 2003. URL: https://doi.org/10.1042/bj20030193, doi:10.1042/bj20030193. This article has 129 citations.
15. (mody2003ananalysisof pages 9-9): N. Mody, D. Campbell, N. Morrice, M. Peggie, and P. Cohen. An analysis of the phosphorylation and activation of extracellular-signal-regulated protein kinase 5 (erk5) by mitogen-activated protein kinase kinase 5 (mkk5) in vitro. The Biochemical journal, 372 Pt 2:567-75, Jun 2003. URL: https://doi.org/10.1042/bj20030193, doi:10.1042/bj20030193. This article has 129 citations.
16. (nakahata2010thesignalingpathway pages 1-2): N Nakahata Y Obara. The signaling pathway leading to extracellular signal-regulated kinase 5 (erk5) activation via g-proteins and erk5-dependent neurotrophic effects. Molecular Pharmacology, 77:10-16, Jan 2010. URL: https://doi.org/10.1124/mol.109.060236, doi:10.1124/mol.109.060236. This article has 60 citations and is from a domain leading peer-reviewed journal.
17. (nishimoto2006mapksignallingerk5 pages 1-2): Satoko Nishimoto and Eisuke Nishida. Mapk signalling: erk5 versus erk1/2. EMBO reports, Aug 2006. URL: https://doi.org/10.1038/sj.embor.7400755, doi:10.1038/sj.embor.7400755. This article has 640 citations and is from a highest quality peer-reviewed journal.
18. (nishimoto2006mapksignallingerk5 pages 3-4): Satoko Nishimoto and Eisuke Nishida. Mapk signalling: erk5 versus erk1/2. EMBO reports, Aug 2006. URL: https://doi.org/10.1038/sj.embor.7400755, doi:10.1038/sj.embor.7400755. This article has 640 citations and is from a highest quality peer-reviewed journal.
19. (seyfried2005anovelmitogenactivated pages 5-6): Jan Seyfried, Xin Wang, Giorgi Kharebava, and Cathy Tournier. A novel mitogen-activated protein kinase docking site in the n terminus of mek5α organizes the components of the extracellular signal-regulated kinase 5 signaling pathway. Molecular and Cellular Biology, 25:9820-9828, Nov 2005. URL: https://doi.org/10.1128/mcb.25.22.9820-9828.2005, doi:10.1128/mcb.25.22.9820-9828.2005. This article has 67 citations and is from a domain leading peer-reviewed journal.
20. (stecca2019impactoferk5 pages 20-21): Barbara Stecca and Elisabetta Rovida. Impact of erk5 on the hallmarks of cancer. International Journal of Molecular Sciences, 20:1426, Mar 2019. URL: https://doi.org/10.3390/ijms20061426, doi:10.3390/ijms20061426. This article has 111 citations and is from a peer-reviewed journal.
21. (wang2005targeteddeletionof pages 8-9): Xin Wang, A. Merritt, J. Seyfried, Chun Guo, E. Papadakis, K. Finegan, M. Kayahara, J. Dixon, R. Boot-Handford, E. Cartwright, U. Mayer, and C. Tournier. Targeted deletion of mek5 causes early embryonic death and defects in the extracellular signal-regulated kinase 5/myocyte enhancer factor 2 cell survival pathway. Molecular and Cellular Biology, 25:336-345, Jan 2005. URL: https://doi.org/10.1128/mcb.25.1.336-345.2005, doi:10.1128/mcb.25.1.336-345.2005. This article has 176 citations and is from a domain leading peer-reviewed journal.