## Phylogeny

• Kinome placement: CMGC group → RCK (ros-cross-hybridizing kinase) subfamily together with MAK and ICK/MRK (chowdhury2023cmgckinasesin pages 12-13).  
• Paralogous relationships: 42.6 % identity to MRK/ICK and 40.5 % to MAK (miyata1999molecularcloningand pages 2-3).  
• Activation-segment divergence: MOK carries a TEY motif whereas MAK/ICK harbour TDY, marking a distinct clade within RCK kinases (miyata1999molecularcloningand pages 2-3).  
• Orthologs: DYF-5 (Caenorhabditis elegans), LF4 (Chlamydomonas reinhardtii), LF4A (Tetrahymena thermophila), LmxMPK9 (Leishmania mexicana) – all conserved negative regulators of axonemal length (fu2019ciliogenesisassociatedkinase pages 8-9, fu2019ciliogenesisassociatedkinase pages 9-10).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P  
(intrinsic autophosphorylation on the TEY activation loop is also observed) (miyata1999molecularcloningand pages 1-2).

## Cofactor Requirements

No experimental study has defined divalent-metal dependence; cofactor requirement remains unreported (chowdhury2023cmgckinasesin pages 12-13).

## Substrate Specificity

• Consensus motif: R-P-X-S/T-P derived from positional-scanning peptide arrays applied to RCK kinases and enriched among MOK interactors (unknownauthors2012ciliarylengthcontrol pages 62-65).  
• Validated cellular substrates  
– Brd4 Ser492, controlling microglial inflammatory/type-I IFN gene expression (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2).  
– Raptor, linking MOK to mTORC1 signalling (unknownauthors2012ciliarylengthcontrol pages 49-52).  
• The kinase efficiently phosphorylates generic MAPK reporter peptides and undergoes robust autophosphorylation when the TEY motif is intact (miyata1999molecularcloningand pages 1-2).

## Structure

• Length 419–420 aa; single catalytic domain. Non-canonical glycine-rich loop GXGXXS replaces the canonical GXGXXG (miyata1999molecularcloningand pages 2-3).  
• Catalytic core adopts the bilobal MAPK fold according to AlphaFold model AF-Q9UQ07-F1; key elements: Lys41–Glu59 salt bridge, HRD (His153-Arg154-Asp155) catalytic triad, DFG motif at residues 175-177, correctly aligned hydrophobic spine, and outward-rotated C-helix in the inactive prediction (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2).  
• Activation segment: TEY183-185; dual phosphorylation is obligatory for activity (miyata1999molecularcloningand pages 6-7).  
• No experimentally determined PDB structure is available to date (chowdhury2023cmgckinasesin pages 12-13).

## Regulation

Post-translational modifications  
• Thr183/Tyr185 dual phosphorylation activates the kinase; TEY→AEA mutation ablates activity (miyata1999molecularcloningand pages 6-7).  
• Upstream activating kinase has not been identified (chowdhury2023cmgckinasesin pages 12-13).  
• MOK performs tyrosine autophosphorylation on Tyr185 in vitro (miyata1999molecularcloningand pages 1-2).  
Signal-dependent control  
• Rapid activation by phorbol ester (TPA); no response to serum, anisomycin or hyperosmotic stress (miyata1999molecularcloningand pages 6-7).  
• Okadaic acid markedly augments activity, implicating serine/threonine phosphatases as negative regulators (miyata1999molecularcloningand pages 6-7).  
Protein interactions  
• Binds HSP90 and the co-chaperone Cdc37, indicating chaperone-assisted maturation/stability (unknownauthors2012ciliarylengthcontrol pages 70-72).

## Function

Expression  
• Broad mRNA expression in human heart, brain, lung, kidney and pancreas; highest in mouse testis (miyata1999molecularcloningand pages 2-3).  
• Present throughout the small intestine but low in colon epithelium (unknownauthors2018thelongand pages 96-100).  
• Endogenous protein detected in renal epithelial IMCD-3 cells (unknownauthors2012ciliarylengthcontrol pages 45-49).  
• Up-regulated in spinal-cord microglia from ALS patients and SOD1G93A mice (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2).  
Subcellular localisation and roles  
• Localises along the axoneme and at the basal body of primary cilia; shRNA knock-down produces ~40 % ciliary elongation, defining MOK as a negative regulator of cilium length (unknownauthors2012ciliarylengthcontrol pages 38-45).  
• Modulates intraflagellar transport frequency without altering motor velocity (jansen2012regulationofcilium pages 1-1).  
Signalling interactions  
• Phosphorylates Raptor, attenuating mTORC1; rapamycin blocks the ciliary-elongation phenotype of MOK loss (unknownauthors2012ciliarylengthcontrol pages 49-52).  
• Phosphorylates Brd4 to enhance chromatin binding at cytokine promoters and drive TNF-α/IL-6/IL-1β induction in LPS-stimulated microglia (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2).  
• Co-localises with cytoplasmic TDP-43 inclusions in ALS models (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2).  
• Proteomic pull-downs identify centrosomal/ciliary partners such as centriolin, CEP350 and rootletin, consistent with roles in microtubule anchoring (unknownauthors2012ciliarylengthcontrol pages 62-65).

## Inhibitors

• C13: research-grade small molecule that inhibits MOK-dependent Brd4 Ser492 phosphorylation and suppresses pro-inflammatory cytokine secretion in microglia (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2).

## Other Comments

• MOK protein is markedly down-regulated in mouse intestinal adenomas, suggesting loss may accompany intestinal tumorigenesis (chowdhury2023cmgckinasesin pages 12-13, unknownauthors2018thelongand pages 96-100).  
• Elevated expression in ALS microglia and functional mitigation by C13 nominate MOK as a potential neuroinflammatory target (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2).

References

1. (chowdhury2023cmgckinasesin pages 12-13): Iftekhar Chowdhury, Giovanna Dashi, and Salla Keskitalo. Cmgc kinases in health and cancer. Cancers, 15:3838, Jul 2023. URL: https://doi.org/10.3390/cancers15153838, doi:10.3390/cancers15153838. This article has 19 citations and is from a peer-reviewed journal.
2. (miyata1999molecularcloningand pages 2-3): Yoshihiko Miyata, Makoto Akashi, and Eisuke Nishida. Molecular cloning and characterization of a novel member of the map kinase superfamily. Genes to Cells, 4:299-309, May 1999. URL: https://doi.org/10.1046/j.1365-2443.1999.00261.x, doi:10.1046/j.1365-2443.1999.00261.x. This article has 74 citations and is from a peer-reviewed journal.
3. (perezcabello2023mapkmakmrkoverlappingkinase pages 1-2): Jesús A. Pérez-Cabello, Lucía Silvera-Carrasco, Jaime M. Franco, Vivian Capilla-González, Alexandros Armaos, María Gómez-Lima, Raquel García-García, Xin Wen Yap, Magdalena Leal-Lasarte, Deepti Lall, Robert H. Baloh, Salvador Martínez, Yoshihiko Miyata, Gian G. Tartaglia, Ritwick Sawarkar, Mario García-Domínguez, David Pozo, and Cintia Roodveldt. Mapk/mak/mrk overlapping kinase (mok) controls microglial inflammatory/type-i ifn responses via brd4 and is involved in als. Proceedings of the National Academy of Sciences, Jul 2023. URL: https://doi.org/10.1073/pnas.2302143120, doi:10.1073/pnas.2302143120. This article has 6 citations.
4. (unknownauthors2012ciliarylengthcontrol pages 38-45): Ciliary length control
5. (unknownauthors2012ciliarylengthcontrol pages 49-52): Ciliary length control
6. (unknownauthors2012ciliarylengthcontrol pages 70-72): Ciliary length control
7. (jansen2012regulationofcilium pages 1-1): G. Jansen and J. Broekhuis. Regulation of cilium length and intraflagellar transport by the map kinases mak, mrk, and mok. Cilia, 1:O12-O12, Nov 2012. URL: https://doi.org/10.1186/2046-2530-1-s1-o12, doi:10.1186/2046-2530-1-s1-o12. This article has 0 citations.
8. (miyata1999molecularcloningand pages 6-7): Yoshihiko Miyata, Makoto Akashi, and Eisuke Nishida. Molecular cloning and characterization of a novel member of the map kinase superfamily. Genes to Cells, 4:299-309, May 1999. URL: https://doi.org/10.1046/j.1365-2443.1999.00261.x, doi:10.1046/j.1365-2443.1999.00261.x. This article has 74 citations and is from a peer-reviewed journal.
9. (unknownauthors2012ciliarylengthcontrol pages 45-49): Ciliary length control
10. (unknownauthors2012ciliarylengthcontrol pages 62-65): Ciliary length control
11. (unknownauthors2018thelongand pages 96-100): The long and the short of it: the role of cell cycle-related kinase (CCRK) and intestinal cell kinase (ICK) in ciliogenesis and hedgehog signaling
12. (fu2019ciliogenesisassociatedkinase pages 8-9): Zheng Fu, Casey D. Gailey, Eric J. Wang, and David L. Brautigan. Ciliogenesis associated kinase 1: targets and functions in various organ systems. FEBS Letters, Nov 2019. URL: https://doi.org/10.1002/1873-3468.13600, doi:10.1002/1873-3468.13600. This article has 31 citations and is from a peer-reviewed journal.
13. (fu2019ciliogenesisassociatedkinase pages 9-10): Zheng Fu, Casey D. Gailey, Eric J. Wang, and David L. Brautigan. Ciliogenesis associated kinase 1: targets and functions in various organ systems. FEBS Letters, Nov 2019. URL: https://doi.org/10.1002/1873-3468.13600, doi:10.1002/1873-3468.13600. This article has 31 citations and is from a peer-reviewed journal.
14. (miyata1999molecularcloningand pages 1-2): Yoshihiko Miyata, Makoto Akashi, and Eisuke Nishida. Molecular cloning and characterization of a novel member of the map kinase superfamily. Genes to Cells, 4:299-309, May 1999. URL: https://doi.org/10.1046/j.1365-2443.1999.00261.x, doi:10.1046/j.1365-2443.1999.00261.x. This article has 74 citations and is from a peer-reviewed journal.