1. Phylogeny  
   MAST2, accepted as Microtubule‐associated serine/threonine‐protein kinase 2 and also known as MAST205 or KIAA0807, is classified within the AGC kinase superfamily and forms part of the MAST kinase subfamily, which in vertebrates comprises four members (MAST1–4) while many invertebrates encode a single ortholog (rumpf2023microtubuleassociatedserinethreonine(mast) pages 1-2, karpov2009bioinformaticsearchof pages 6-7). Phylogenetic analyses based on conserved catalytic domains have demonstrated that the key functional motifs in the kinase domain are highly conserved among diverse species ranging from lower eukaryotes to mammals, confirming an evolutionary relationship that dates back to the last common eukaryotic ancestor (rumpf2023microtubuleassociatedserinethreonine(mast) pages 1-2, karpov2010bioinformaticsearchof pages 7-10).
2. Reaction Catalyzed  
   MAST2 catalyzes the transfer of the γ‐phosphate from ATP to the hydroxyl group of serine or threonine residues in target proteins. The overall chemical reaction is as follows:  
     ATP + [protein]–(L‑serine or L‑threonine) → ADP + [protein]–(L‑serine/threonine)‑phosphate + H⁺ (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5).
3. Cofactor Requirements  
   The kinase activity of MAST2 is dependent on the presence of Mg²⁺, which is required to coordinate ATP binding within the active site and facilitate the phosphoryl transfer reaction (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5).
4. Substrate Specificity  
   MAST2 phosphorylates serine/threonine residues within its substrates. The substrate specificity is dictated in part by intrinsic features of its catalytic domain and is further refined by its C-terminal PDZ domain. This PDZ domain preferentially recognizes C-terminal motifs conforming to a pattern of X-S/T-X-V/I/L, thereby directing MAST2 toward proteins involved in the stabilization and regulation of the dystrophin/utrophin network (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5). In addition, MAST2 has been linked to the phosphorylation of proteins that are components of multi‐protein complexes involved in spermatid maturation and in the regulation of immune signaling in macrophages (karpov2009bioinformaticsearchof pages 6-7, lumeng1999interactionsbetweenβ2syntrophin pages 1-2).
5. Structure  
   MAST2 exhibits a characteristic modular organization that includes three major domains. At the N-terminus is the DUF1908 domain, a region enriched in serine, threonine, and tyrosine residues; although its precise function remains unresolved, it is conceivable that it serves as a regulatory module subject to phosphorylation (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5). Centrally, MAST2 contains the serine/threonine kinase domain that adopts the classical bilobular structure associated with the AGC kinase family. In this domain, key conserved motifs—including the DFG, APE, and HRD sequences—form the catalytic core required for ATP binding and phosphoryl transfer. Notably, a substitution in the glycine-rich loop, wherein the first glycine is replaced by a serine, is a distinguishing feature that may influence the regulation of kinase activity (rumpf2023microtubuleassociatedserinethreonine(mast) pages 5-7, karpov2010bioinformaticsearchof pages 4-7). At the C-terminus lies the PDZ domain, a compact module approximately 80–100 amino acids in length whose structure consists of five β-strands and two α-helices. This domain confers the ability to engage in specific protein-protein interactions by recognizing short C-terminal motifs on target proteins (rumpf2023microtubuleassociatedserinethreonine(mast) pages 7-8, lumeng1999interactionsbetweenβ2syntrophin pages 1-2). Structural models derived from experimental data and AlphaFold predictions collectively indicate that the overall three-dimensional organization of MAST2 is conserved within the MAST family, ensuring the proper spatial arrangement of its active site cleft and regulatory regions (karpov2010bioinformaticsearchof pages 7-10, sun2006identificationofa pages 1-4).
6. Regulation  
   MAST2 is subject to multiple layers of regulation. Autophosphorylation events and phosphorylation by other kinases likely occur within conserved elements of the activation loop, although specific phosphorylation sites have not been exhaustively mapped (rumpf2023microtubuleassociatedserinethreonine(mast) pages 16-17). The C-terminal PDZ domain not only mediates substrate recognition but also influences MAST2’s autophosphorylation, suggesting an inter-domain regulatory mechanism (rumpf2023microtubuleassociatedserinethreonine(mast) pages 10-11). Furthermore, interactions with regulatory proteins—such as the 14-3-3 family, which bind in a phosphorylation-dependent manner—may further modulate MAST2 activity (rumpf2023microtubuleassociatedserinethreonine(mast) pages 7-8). In macrophages, MAST2 forms a complex with TRAF6; this interaction is associated with the inhibition of TRAF6-mediated NF-κB activation, thereby affecting cytokine expression such as IL-12 (Information, rumpf2023microtubuleassociatedserinethreonine(mast) pages 10-11).
7. Function  
   MAST2 functions at the intersection of cytoskeletal organization and signal transduction. Through the PDZ-mediated association with the dystrophin/utrophin network, MAST2 plays a central role in linking microtubule filaments to membrane-associated complexes. This interaction is critical for the proper formation and function of the multi-protein complex involved in spermatid maturation, particularly at the spermatid manchette (walden1993anovel205kilodalton pages 1-2, karpov2009bioinformaticsearchof pages 7-9). Additionally, in immune cells such as macrophages, MAST2 regulates inflammatory signaling; by forming a complex with TRAF6, it modulates the lipopolysaccharide-induced synthesis of IL-12 via inhibition of NF-κB activation (Information, rumpf2023microtubuleassociatedserinethreonine(mast) pages 10-11). These roles underscore MAST2’s importance in both reproductive biology and immune regulation.
8. Other Comments  
   MAST2 is alternatively designated as MAST205, reflecting its original identification in a testis-specific context associated with microtubule structures (walden1993anovel205kilodalton pages 1-2). At present, no highly selective pharmacological inhibitors for MAST2 have been well characterized in the peer-reviewed literature provided. Although disease associations—such as potential roles in reproductive and immune system disorders—are implied by its functional involvement in spermatid maturation and cytokine regulation, detailed pathogenic mutations specific to MAST2 remain to be documented (karpov2009bioinformaticsearchof pages 7-9, rumpf2023microtubuleassociatedserinethreonine(mast) pages 7-8).
9. References
10. karpov2009bioinformaticsearchof pages 6-7
11. karpov2010bioinformaticsearchof pages 2-4
12. rumpf2023microtubuleassociatedserinethreonine(mast) pages 1-2
13. rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5
14. rumpf2023microtubuleassociatedserinethreonine(mast) pages 5-7
15. rumpf2023microtubuleassociatedserinethreonine(mast) pages 7-8
16. rumpf2023microtubuleassociatedserinethreonine(mast) pages 10-11
17. rumpf2023microtubuleassociatedserinethreonine(mast) pages 16-17
18. rumpf2023microtubuleassociatedserinethreonine(mast) pages 17-18
19. karpov2009bioinformaticsearchof pages 7-9
20. karpov2010bioinformaticsearchof pages 4-7
21. lumeng1999interactionsbetweenβ2syntrophin pages 1-2
22. walden1993anovel205kilodalton pages 1-2
23. naz2013microtubuleaffinityregulatingkinase pages 5-7
24. sun2006identificationofa pages 1-4
25. spinelli2021pathogenicmast3variants pages 11-11

References

1. (karpov2009bioinformaticsearchof pages 6-7): P. A. Karpov, E. S. Nadezhdina, A. I. Emets, V. G. Matusov, A. Yu. Nyporko, N. Yu. Shashina, and Ya. B. Blume. Bioinformatic search of plant protein kinases involved in the phosphorylation of microtubular proteins and the regulation of the cell cycle. Cytology and Genetics, 43:201-215, Jun 2009. URL: https://doi.org/10.3103/s0095452709030104, doi:10.3103/s0095452709030104. This article has 6 citations and is from a peer-reviewed journal.
2. (karpov2010bioinformaticsearchof pages 2-4): Pavel A Karpov, Elena S Nadezhdina, Alla I Yemets, Vadym G Matusov, Alexey Yu Nyporko, Nadezhda Yu Shashina, and Yaroslav B Blume. Bioinformatic search of plant microtubule-and cell cycle related serine-threonine protein kinases. BMC Genomics, 11:S14-S14, Feb 2010. URL: https://doi.org/10.1186/1471-2164-11-s1-s14, doi:10.1186/1471-2164-11-s1-s14. This article has 46 citations and is from a peer-reviewed journal.
3. (rumpf2023microtubuleassociatedserinethreonine(mast) pages 1-2): Marie Rumpf, Sabine Pautz, Benedikt Drebes, Friedrich W. Herberg, and Hans-Arno J. Müller. Microtubule-associated serine/threonine (mast) kinases in development and disease. International Journal of Molecular Sciences, 24:11913, Jul 2023. URL: https://doi.org/10.3390/ijms241511913, doi:10.3390/ijms241511913. This article has 6 citations and is from a peer-reviewed journal.
4. (rumpf2023microtubuleassociatedserinethreonine(mast) pages 10-11): Marie Rumpf, Sabine Pautz, Benedikt Drebes, Friedrich W. Herberg, and Hans-Arno J. Müller. Microtubule-associated serine/threonine (mast) kinases in development and disease. International Journal of Molecular Sciences, 24:11913, Jul 2023. URL: https://doi.org/10.3390/ijms241511913, doi:10.3390/ijms241511913. This article has 6 citations and is from a peer-reviewed journal.
5. (rumpf2023microtubuleassociatedserinethreonine(mast) pages 16-17): Marie Rumpf, Sabine Pautz, Benedikt Drebes, Friedrich W. Herberg, and Hans-Arno J. Müller. Microtubule-associated serine/threonine (mast) kinases in development and disease. International Journal of Molecular Sciences, 24:11913, Jul 2023. URL: https://doi.org/10.3390/ijms241511913, doi:10.3390/ijms241511913. This article has 6 citations and is from a peer-reviewed journal.
6. (rumpf2023microtubuleassociatedserinethreonine(mast) pages 17-18): Marie Rumpf, Sabine Pautz, Benedikt Drebes, Friedrich W. Herberg, and Hans-Arno J. Müller. Microtubule-associated serine/threonine (mast) kinases in development and disease. International Journal of Molecular Sciences, 24:11913, Jul 2023. URL: https://doi.org/10.3390/ijms241511913, doi:10.3390/ijms241511913. This article has 6 citations and is from a peer-reviewed journal.
7. (rumpf2023microtubuleassociatedserinethreonine(mast) pages 2-5): Marie Rumpf, Sabine Pautz, Benedikt Drebes, Friedrich W. Herberg, and Hans-Arno J. Müller. Microtubule-associated serine/threonine (mast) kinases in development and disease. International Journal of Molecular Sciences, 24:11913, Jul 2023. URL: https://doi.org/10.3390/ijms241511913, doi:10.3390/ijms241511913. This article has 6 citations and is from a peer-reviewed journal.
8. (rumpf2023microtubuleassociatedserinethreonine(mast) pages 5-7): Marie Rumpf, Sabine Pautz, Benedikt Drebes, Friedrich W. Herberg, and Hans-Arno J. Müller. Microtubule-associated serine/threonine (mast) kinases in development and disease. International Journal of Molecular Sciences, 24:11913, Jul 2023. URL: https://doi.org/10.3390/ijms241511913, doi:10.3390/ijms241511913. This article has 6 citations and is from a peer-reviewed journal.
9. (rumpf2023microtubuleassociatedserinethreonine(mast) pages 7-8): Marie Rumpf, Sabine Pautz, Benedikt Drebes, Friedrich W. Herberg, and Hans-Arno J. Müller. Microtubule-associated serine/threonine (mast) kinases in development and disease. International Journal of Molecular Sciences, 24:11913, Jul 2023. URL: https://doi.org/10.3390/ijms241511913, doi:10.3390/ijms241511913. This article has 6 citations and is from a peer-reviewed journal.
10. (karpov2009bioinformaticsearchof pages 7-9): P. A. Karpov, E. S. Nadezhdina, A. I. Emets, V. G. Matusov, A. Yu. Nyporko, N. Yu. Shashina, and Ya. B. Blume. Bioinformatic search of plant protein kinases involved in the phosphorylation of microtubular proteins and the regulation of the cell cycle. Cytology and Genetics, 43:201-215, Jun 2009. URL: https://doi.org/10.3103/s0095452709030104, doi:10.3103/s0095452709030104. This article has 6 citations and is from a peer-reviewed journal.
11. (karpov2010bioinformaticsearchof pages 4-7): Pavel A Karpov, Elena S Nadezhdina, Alla I Yemets, Vadym G Matusov, Alexey Yu Nyporko, Nadezhda Yu Shashina, and Yaroslav B Blume. Bioinformatic search of plant microtubule-and cell cycle related serine-threonine protein kinases. BMC Genomics, 11:S14-S14, Feb 2010. URL: https://doi.org/10.1186/1471-2164-11-s1-s14, doi:10.1186/1471-2164-11-s1-s14. This article has 46 citations and is from a peer-reviewed journal.
12. (karpov2010bioinformaticsearchof pages 7-10): Pavel A Karpov, Elena S Nadezhdina, Alla I Yemets, Vadym G Matusov, Alexey Yu Nyporko, Nadezhda Yu Shashina, and Yaroslav B Blume. Bioinformatic search of plant microtubule-and cell cycle related serine-threonine protein kinases. BMC Genomics, 11:S14-S14, Feb 2010. URL: https://doi.org/10.1186/1471-2164-11-s1-s14, doi:10.1186/1471-2164-11-s1-s14. This article has 46 citations and is from a peer-reviewed journal.
13. (lumeng1999interactionsbetweenβ2syntrophin pages 1-2): Carey Lumeng, Stephanie Phelps, Gregory E. Crawford, Paul D. Walden, Kate Barald, and Jeffrey S. Chamberlain. Interactions between β2-syntrophin and a family of microtubule-associated serine/threonine kinases. Nature Neuroscience, 2:611-617, Jul 1999. URL: https://doi.org/10.1038/10165, doi:10.1038/10165. This article has 205 citations and is from a highest quality peer-reviewed journal.
14. (walden1993anovel205kilodalton pages 1-2): Paul D. Walden and Nicholas J. Cowan. A novel 205-kilodalton testis-specific serine/threonine protein kinase associated with microtubules of the spermatid manchette. Molecular and Cellular Biology, 13:7625-7635, Dec 1993. URL: https://doi.org/10.1128/mcb.13.12.7625-7635.1993, doi:10.1128/mcb.13.12.7625-7635.1993. This article has 108 citations and is from a domain leading peer-reviewed journal.
15. (naz2013microtubuleaffinityregulatingkinase pages 5-7): Farha Naz, Farah Anjum, Asimul Islam, Faizan Ahmad, and Md. Imtaiyaz Hassan. Microtubule affinity-regulating kinase 4: structure, function, and regulation. Cell Biochemistry and Biophysics, 67:485-499, Mar 2013. URL: https://doi.org/10.1007/s12013-013-9550-7, doi:10.1007/s12013-013-9550-7. This article has 119 citations and is from a peer-reviewed journal.
16. (spinelli2021pathogenicmast3variants pages 11-11): Egidio Spinelli, Kyle R. Christensen, Emily Bryant, Amy Schneider, Jennifer Rakotomamonjy, Alison M. Muir, Jessica Giannelli, Rebecca O. Littlejohn, Elizabeth R. Roeder, Berkley Schmidt, William G. Wilson, Elysa J. Marco, Kazuhiro Iwama, Satoko Kumada, Tiziana Pisano, Carmen Barba, Annalisa Vetro, Eva H. Brilstra, Richard H. van Jaarsveld, Naomichi Matsumoto, Hadassa Goldberg‐Stern, Patrick W. Carney, P. Ian Andrews, Christelle M. El Achkar, Sam Berkovic, Lance H. Rodan, Kirsty McWalter, Renzo Guerrini, Ingrid E. Scheffer, Heather C. Mefford, Simone Mandelstam, Linda Laux, John J. Millichap, Alicia Guemez‐Gamboa, Angus C. Nairn, and Gemma L. Carvill. Pathogenic mast3 variants in the stk domain are associated with epilepsy. Annals of Neurology, 90:274-284, Jul 2021. URL: https://doi.org/10.1002/ana.26147, doi:10.1002/ana.26147. This article has 15 citations and is from a highest quality peer-reviewed journal.
17. (sun2006identificationofa pages 1-4): Liyun Sun, S. Gu, Xin Li, Yaqiong Sun, D. Zheng, K. Yu, C. Ji, R. Tang, Yi Xie†, and Y. Mao. Identification of a novel human mast4 gene, a new member of human microtubule associated serine/threonine kinase family. Molecular Biology, 40:724-731, Oct 2006. URL: https://doi.org/10.1134/s0026893306050062, doi:10.1134/s0026893306050062. This article has 18 citations and is from a peer-reviewed journal.