## Phylogeny

MuSK is classified within the Receptor Tyrosine Kinase (RTK) group of the human kinome (mammalian RTK sub-division dealing with muscle and neuromuscular signaling) (manning2002theproteinkinase pages 3-3).  
Orthologs with high primary-sequence conservation include rat MuSK (94 % identity overall, 97 % within the kinase domain) and the Torpedo californica electric-organ RTK, indicating evolutionary conservation across vertebrates (valenzuela1995receptortyrosinekinase pages 2-3).  
Phylogenetic analyses position MuSK as a sister branch to the ROR subgroup while remaining a distinct, muscle-restricted family within the RTK superfamily (valenzuela1995receptortyrosinekinase pages 4-5, valenzuela1995receptortyrosinekinase pages 9-10).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (duongly2013thehumankinome pages 3-5).

## Cofactor Requirements

Catalysis requires a divalent cation coordinated in the active site; Mg²⁺ (and, by extension, Mn²⁺) fulfills this role by orienting the ATP γ-phosphate for transfer (duongly2013thehumankinome pages 5-6).

## Substrate Specificity

High-density peptide array profiling of the human tyrosine kinome assigns MuSK to the RTK cluster that prefers hydrophobic residues (e.g., Ile/Leu) at the –1 and +3 positions flanking the target tyrosine, while disfavouring acidic residues at +3 (yaronbarir2024theintrinsicsubstrate pages 3-3).

## Structure

Domain organisation  
• Extracellular ectodomain: four Ig-like domains followed by a Frizzled-like cysteine-rich domain (CRD); Ig1–Ig2 crystal structure solved at 2.2 Å (PDB 2IEP) (stiegler2006crystalstructureof pages 1-2, stiegler2006crystalstructureof pages 12-16).  
• Single-pass transmembrane helix (valenzuela1995receptortyrosinekinase pages 3-4).  
• Cytoplasmic portion: juxtamembrane segment harbouring Tyr553 (NPXY motif) and a kinase domain containing the activation loop Tyr750/Tyr754/Tyr755 cluster (hubbard2013structureandactivation pages 2-3).

3D structural features  
• Ig1 forms a hydrophobic dimerisation interface centred on Met48, Leu83 and Ile96; mutation of these residues abrogates agrin-dependent activation (stiegler2006crystalstructureof pages 4-5).  
• Ig1 contains a unique surface-exposed disulfide (Cys98–Cys112) stabilising folding and surface transport (stiegler2006crystalstructureof pages 12-16).  
• The unphosphorylated kinase domain adopts an autoinhibited conformation in which Tyr754 occupies the catalytic cleft; trans-phosphorylation of Tyr750/Tyr754/Tyr755 unlocks the active state (hubbard2013structureandactivation pages 2-3).  
• Phosphorylated Tyr553 provides a PTB-binding site for the dimeric activator Dok7, driving juxtaposition of two kinase domains for activation-loop phosphorylation (hubbard2013structureandactivation pages 3-4).

## Regulation

Post-translational modifications  
• Autophosphorylation at Tyr553 (juxtamembrane) is essential for downstream signalling and Dok7 engagement (herbst2000thejuxtamembraneregion pages 1-2).  
• Activation-loop phosphorylation at Tyr750, Tyr754 and Tyr755 is required for full catalytic activity (hubbard2013structureandactivation pages 2-3).  
• Additional regulated phosphosites include Tyr576, Tyr599, Ser678, Ser751 and Tyr755 identified by quantitative phosphoproteomics (budayeva2022phosphoproteomeprofilingof pages 7-7, promer2025muskisa pages 2-4).  
• Ser751 is a direct substrate of CaMK2β in vitro; however, CaMK2β deletion does not impair MuSK activation in vivo (promer2025muskisa pages 2-4).  
• N-linked glycosylation of extracellular domains restricts agrin responsiveness; enzymatic deglycosylation abolishes signalling (glass1996thereceptortyrosine pages 7-8).

Allosteric/conformational control  
• Agrin binds LRP4; this complex engages MuSK and promotes receptor clustering and basal autophosphorylation (hubbard2013structureandactivation pages 4-4).  
• Dok7 binding to pTyr553 stabilises a MuSK-Dok7 dimer that catalyses activation-loop phosphorylation (hubbard2013structureandactivation pages 2-3).

## Function

Expression  
MuSK is selectively expressed in skeletal muscle, up-regulated as myoblasts fuse into myotubes, and concentrated at the postsynaptic membrane of the neuromuscular junction (dechiara1996thereceptortyrosine pages 1-2, valenzuela1995receptortyrosinekinase pages 2-3).

Upstream inputs  
• Neural agrin engaging LRP4 (dechiara1996thereceptortyrosine pages 1-2).  
• Basal Wnt binding to the CRD (non-canonical) (hubbard2013structureandactivation pages 2-3).

Downstream partners and pathways  
• PTB adaptor Dok7 (hubbard2013structureandactivation pages 2-3).  
• Crk/Crk-L, Abl1 and Src kinases propagate signals to AChR clustering machinery (fish2020multiplemusksignaling pages 2-3, wang2007musksignalingat pages 1-2).  
• Rapsyn acts as the scaffold linking MuSK activity to acetylcholine receptor aggregation (fish2020multiplemusksignaling pages 2-3).  
• Dishevelled-1, PAK1 and Rho family GTPases (Rac1, Cdc42) remodel the cytoskeleton during cluster maturation (wang2007musksignalingat pages 1-2).  
• Phosphorylation of Rab10, Rab35 and related Rab GTPases links MuSK to vesicular trafficking (budayeva2022phosphoproteomeprofilingof pages 4-5, budayeva2022phosphoproteomeprofilingof pages 8-8).

Physiological roles  
• Initiates and maintains acetylcholine receptor clustering, postsynaptic gene transcription, and synaptic cytoskeleton organisation essential for neuromuscular transmission (fish2020multiplemusksignaling pages 2-3).  
• Required for embryonic NMJ formation; genetic ablation eliminates synapse development (dechiara1996thereceptortyrosine pages 1-2).  
• Maintains NMJ stability throughout life, with down-regulation or signalling failure leading to synaptic fragmentation and muscle weakness (fish2020multiplemusksignaling pages 2-3).

## Other Comments

Autoantibodies against MuSK (primarily IgG4) cause a subset of myasthenia gravis by disrupting agrin/LRP4-dependent activation, while inherited loss-of-function mutations in MU​SK or DOK7 underlie congenital myasthenic syndromes (hubbard2013structureandactivation pages 1-2).

References

1. (budayeva2022phosphoproteomeprofilingof pages 4-5): Hanna G. Budayeva, Arundhati Sengupta-Ghosh, Lilian Phu, J. G. Moffat, Gai Ayalon, and D. Kirkpatrick. Phosphoproteome profiling of the receptor tyrosine kinase musk identifies tyrosine phosphorylation of rab gtpases. Molecular & Cellular Proteomics : MCP, Feb 2022. URL: https://doi.org/10.1016/j.mcpro.2022.100221, doi:10.1016/j.mcpro.2022.100221. This article has 11 citations.
2. (dechiara1996thereceptortyrosine pages 1-2): T. Dechiara, D. Bowen, D. Valenzuela, Mary V. Simmons, W. Poueymirou, Susan Thomas, Erika Kinetz, D. L. Compton, E. Rojas, John S. Park, Cynthia L. Smith, P. Distefano, D. Glass, S. Burden, and G. Yancopoulos. The receptor tyrosine kinase musk is required for neuromuscular junction formation in vivo. Cell, 85:501-512, May 1996. URL: https://doi.org/10.1016/s0092-8674(00)81251-9, doi:10.1016/s0092-8674(00)81251-9. This article has 1132 citations and is from a highest quality peer-reviewed journal.
3. (fish2020multiplemusksignaling pages 2-3): L. A. Fish and J. Fallon. Multiple musk signaling pathways and the aging neuromuscular junction. Neuroscience Letters, Apr 2020. URL: https://doi.org/10.1016/j.neulet.2020.135014, doi:10.1016/j.neulet.2020.135014. This article has 27 citations and is from a peer-reviewed journal.
4. (glass1996thereceptortyrosine pages 7-8): D. Glass, T. Dechiara, T. Stitt, P. Distefano, D. Valenzuela, and G. Yancopoulos. The receptor tyrosine kinase musk is required for neuromuscular junction formation and is a functional receptor for agrin. Cold Spring Harbor symposia on quantitative biology, 61:435-44, 1996. URL: https://doi.org/10.1101/sqb.1996.061.01.046, doi:10.1101/sqb.1996.061.01.046. This article has 61 citations and is from a peer-reviewed journal.
5. (herbst2000thejuxtamembraneregion pages 1-2): R. Herbst and S. Burden. The juxtamembrane region of musk has a critical role in agrin-mediated signaling. The EMBO Journal, 19:67-77, Jan 2000. URL: https://doi.org/10.1093/emboj/19.1.67, doi:10.1093/emboj/19.1.67. This article has 229 citations.
6. (hubbard2013structureandactivation pages 2-3): S. Hubbard and Kavitha Gnanasambandan. Structure and activation of musk, a receptor tyrosine kinase central to neuromuscular junction formation. Biochimica et biophysica acta, 1834 10:2166-9, Oct 2013. URL: https://doi.org/10.1016/j.bbapap.2013.02.034, doi:10.1016/j.bbapap.2013.02.034. This article has 63 citations.
7. (hubbard2013structureandactivation pages 4-4): S. Hubbard and Kavitha Gnanasambandan. Structure and activation of musk, a receptor tyrosine kinase central to neuromuscular junction formation. Biochimica et biophysica acta, 1834 10:2166-9, Oct 2013. URL: https://doi.org/10.1016/j.bbapap.2013.02.034, doi:10.1016/j.bbapap.2013.02.034. This article has 63 citations.
8. (promer2025muskisa pages 2-4): Jakob J. Prömer, Sara Wolske, Perrine Castets, Geeske M. Woerden, Cinzia Barresi, Kevin C. O’Connor, and Ruth Herbst. Musk is a substrate for camk2β but this interaction is dispensable for musk activation in vivo. Scientific Reports, Apr 2025. URL: https://doi.org/10.1038/s41598-025-95053-3, doi:10.1038/s41598-025-95053-3. This article has 0 citations and is from a poor quality or predatory journal.
9. (wang2007musksignalingat pages 1-2): Qiang Wang, Bin Zhang, W. Xiong, and L. Mei. Musk signaling at the neuromuscular junction. Journal of Molecular Neuroscience, 30:223-226, 2007. URL: https://doi.org/10.1385/jmn:30:1:223, doi:10.1385/jmn:30:1:223. This article has 24 citations and is from a peer-reviewed journal.
10. (budayeva2022phosphoproteomeprofilingof pages 7-7): Hanna G. Budayeva, Arundhati Sengupta-Ghosh, Lilian Phu, J. G. Moffat, Gai Ayalon, and D. Kirkpatrick. Phosphoproteome profiling of the receptor tyrosine kinase musk identifies tyrosine phosphorylation of rab gtpases. Molecular & Cellular Proteomics : MCP, Feb 2022. URL: https://doi.org/10.1016/j.mcpro.2022.100221, doi:10.1016/j.mcpro.2022.100221. This article has 11 citations.
11. (budayeva2022phosphoproteomeprofilingof pages 8-8): Hanna G. Budayeva, Arundhati Sengupta-Ghosh, Lilian Phu, J. G. Moffat, Gai Ayalon, and D. Kirkpatrick. Phosphoproteome profiling of the receptor tyrosine kinase musk identifies tyrosine phosphorylation of rab gtpases. Molecular & Cellular Proteomics : MCP, Feb 2022. URL: https://doi.org/10.1016/j.mcpro.2022.100221, doi:10.1016/j.mcpro.2022.100221. This article has 11 citations.
12. (duongly2013thehumankinome pages 3-5): Krisna C. Duong-Ly and J. R. Peterson. The human kinome and kinase inhibition. Current Protocols in Pharmacology, Mar 2013. URL: https://doi.org/10.1002/0471141755.ph0209s60, doi:10.1002/0471141755.ph0209s60. This article has 162 citations.
13. (duongly2013thehumankinome pages 5-6): Krisna C. Duong-Ly and J. R. Peterson. The human kinome and kinase inhibition. Current Protocols in Pharmacology, Mar 2013. URL: https://doi.org/10.1002/0471141755.ph0209s60, doi:10.1002/0471141755.ph0209s60. This article has 162 citations.
14. (hubbard2013structureandactivation pages 1-2): S. Hubbard and Kavitha Gnanasambandan. Structure and activation of musk, a receptor tyrosine kinase central to neuromuscular junction formation. Biochimica et biophysica acta, 1834 10:2166-9, Oct 2013. URL: https://doi.org/10.1016/j.bbapap.2013.02.034, doi:10.1016/j.bbapap.2013.02.034. This article has 63 citations.
15. (hubbard2013structureandactivation pages 3-4): S. Hubbard and Kavitha Gnanasambandan. Structure and activation of musk, a receptor tyrosine kinase central to neuromuscular junction formation. Biochimica et biophysica acta, 1834 10:2166-9, Oct 2013. URL: https://doi.org/10.1016/j.bbapap.2013.02.034, doi:10.1016/j.bbapap.2013.02.034. This article has 63 citations.
16. (valenzuela1995receptortyrosinekinase pages 2-3): D. Valenzuela, T. Stitt, P. Distefano, E. Rojas, Karen Mattsson, D. L. Compton, L. Nuñez, John S. Park, J. L. Stark, D. Gies, Susan Thomas, M. L. Beau, A. Fernald, N. Copeland, N. Jenkins, S. Burden, D. Glass, and G. Yancopoulos. Receptor tyrosine kinase specific for the skeletal muscle lineage: expression in embryonic muscle, at the neuromuscular junction, and after injury. Neuron, 15:573-584, Sep 1995. URL: https://doi.org/10.1016/0896-6273(95)90146-9, doi:10.1016/0896-6273(95)90146-9. This article has 542 citations and is from a highest quality peer-reviewed journal.
17. (valenzuela1995receptortyrosinekinase pages 3-4): D. Valenzuela, T. Stitt, P. Distefano, E. Rojas, Karen Mattsson, D. L. Compton, L. Nuñez, John S. Park, J. L. Stark, D. Gies, Susan Thomas, M. L. Beau, A. Fernald, N. Copeland, N. Jenkins, S. Burden, D. Glass, and G. Yancopoulos. Receptor tyrosine kinase specific for the skeletal muscle lineage: expression in embryonic muscle, at the neuromuscular junction, and after injury. Neuron, 15:573-584, Sep 1995. URL: https://doi.org/10.1016/0896-6273(95)90146-9, doi:10.1016/0896-6273(95)90146-9. This article has 542 citations and is from a highest quality peer-reviewed journal.
18. (valenzuela1995receptortyrosinekinase pages 4-5): D. Valenzuela, T. Stitt, P. Distefano, E. Rojas, Karen Mattsson, D. L. Compton, L. Nuñez, John S. Park, J. L. Stark, D. Gies, Susan Thomas, M. L. Beau, A. Fernald, N. Copeland, N. Jenkins, S. Burden, D. Glass, and G. Yancopoulos. Receptor tyrosine kinase specific for the skeletal muscle lineage: expression in embryonic muscle, at the neuromuscular junction, and after injury. Neuron, 15:573-584, Sep 1995. URL: https://doi.org/10.1016/0896-6273(95)90146-9, doi:10.1016/0896-6273(95)90146-9. This article has 542 citations and is from a highest quality peer-reviewed journal.
19. (valenzuela1995receptortyrosinekinase pages 9-10): D. Valenzuela, T. Stitt, P. Distefano, E. Rojas, Karen Mattsson, D. L. Compton, L. Nuñez, John S. Park, J. L. Stark, D. Gies, Susan Thomas, M. L. Beau, A. Fernald, N. Copeland, N. Jenkins, S. Burden, D. Glass, and G. Yancopoulos. Receptor tyrosine kinase specific for the skeletal muscle lineage: expression in embryonic muscle, at the neuromuscular junction, and after injury. Neuron, 15:573-584, Sep 1995. URL: https://doi.org/10.1016/0896-6273(95)90146-9, doi:10.1016/0896-6273(95)90146-9. This article has 542 citations and is from a highest quality peer-reviewed journal.
20. (manning2002theproteinkinase pages 3-3): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
21. (stiegler2006crystalstructureof pages 1-2): A. L. Stiegler, S. Burden, and S. Hubbard. Crystal structure of the agrin-responsive immunoglobulin-like domains 1 and 2 of the receptor tyrosine kinase musk. Journal of molecular biology, 364 3:424-33, Dec 2006. URL: https://doi.org/10.1016/j.jmb.2006.09.019, doi:10.1016/j.jmb.2006.09.019. This article has 95 citations and is from a domain leading peer-reviewed journal.
22. (stiegler2006crystalstructureof pages 12-16): A. L. Stiegler, S. Burden, and S. Hubbard. Crystal structure of the agrin-responsive immunoglobulin-like domains 1 and 2 of the receptor tyrosine kinase musk. Journal of molecular biology, 364 3:424-33, Dec 2006. URL: https://doi.org/10.1016/j.jmb.2006.09.019, doi:10.1016/j.jmb.2006.09.019. This article has 95 citations and is from a domain leading peer-reviewed journal.
23. (stiegler2006crystalstructureof pages 4-5): A. L. Stiegler, S. Burden, and S. Hubbard. Crystal structure of the agrin-responsive immunoglobulin-like domains 1 and 2 of the receptor tyrosine kinase musk. Journal of molecular biology, 364 3:424-33, Dec 2006. URL: https://doi.org/10.1016/j.jmb.2006.09.019, doi:10.1016/j.jmb.2006.09.019. This article has 95 citations and is from a domain leading peer-reviewed journal.
24. (yaronbarir2024theintrinsicsubstrate pages 3-3): Tomer M. Yaron-Barir, Brian A. Joughin, Emily M. Huntsman, Alexander Kerelsky, Daniel M. Cizin, Benjamin M. Cohen, Amit Regev, Junho Song, Neil Vasan, Ting-Yu Lin, Jose M. Orozco, Christina Schoenherr, Cari Sagum, Mark T. Bedford, R. Max Wynn, Shih-Chia Tso, David T. Chuang, Lei Li, Shawn S.-C. Li, Pau Creixell, Konstantin Krismer, Mina Takegami, Harin Lee, Bin Zhang, Jingyi Lu, Ian Cossentino, Sean D. Landry, Mohamed Uduman, John Blenis, Olivier Elemento, Margaret C. Frame, Peter V. Hornbeck, Lewis C. Cantley, Benjamin E. Turk, Michael B. Yaffe, and Jared L. Johnson. The intrinsic substrate specificity of the human tyrosine kinome. Nature, 629:1174-1181, May 2024. URL: https://doi.org/10.1038/s41586-024-07407-y, doi:10.1038/s41586-024-07407-y. This article has 59 citations and is from a highest quality peer-reviewed journal.