1. Phylogeny  
   Muscle‐specific kinase (MUSK) is a member of the receptor tyrosine kinase superfamily that appears to have evolved for a highly specialized role in vertebrate neuromuscular function. Orthologs of MUSK have been identified in many vertebrate species, including mammals and amphibians, with studies in Xenopus showing an approximate 65% sequence identity compared with mammalian MUSK (chu…1999xenopusmuscle‐specifickinase pages 1-3). This conservation reflects its specialized function in neuromuscular junction (NMJ) formation. MUSK is classified within a distinct subgroup of receptor tyrosine kinases that possess an extracellular region incorporating immunoglobulin‐like (Ig) domains and a Frizzled‐like cysteine‐rich domain. These features set it apart from classical receptor tyrosine kinases that bind soluble ligands; instead, MUSK requires an accessory co‐receptor for activation (burden2018fundamentalmoleculesand pages 13-14). In addition, evolutionary analyses indicate that MUSK shares structural motifs with other kinases within the receptor tyrosine kinase family and shows distant homology to the Ror subfamily, whose extracellular domains also contain Frizzled‐like regions (sossin2006tracingtheevolution pages 8-9). The presence of these conserved domains across different species underlines the importance of MUSK’s function in establishing synaptic contacts and maintaining NMJ integrity. Its phylogenetic distribution demonstrates that MUSK has been conserved through metazoan evolution, suggesting that the core elements required for NMJ assembly emerged early in the evolution of multicellular animals (burden2018fundamentalmoleculesand pages 13-14, chu…1999xenopusmuscle‐specifickinase pages 1-3, sossin2006tracingtheevolution pages 8-9).
2. Reaction Catalyzed  
   MUSK catalyzes the transfer of a phosphate group from ATP to specific tyrosine residues present on substrate proteins, a characteristic reaction of receptor tyrosine kinases. In the biochemical reaction, ATP and the target protein combine such that the γ‐phosphate is transferred to a hydroxyl group on a tyrosine residue, yielding ADP, a phosphorylated tyrosine‐containing protein, and a proton. In formulaic terms, the reaction can be represented as:  
     ATP + [protein]-(L-tyrosine) → ADP + [protein]-(L-tyrosine)-phosphate + H⁺  
   This reaction is central to MUSK’s function in initiating downstream signaling events that culminate in the assembly and maintenance of the neuromuscular junction, and its autophosphorylation is a key step in the receptor’s activation cascade (cheusova2006caseinkinase2dependent pages 1-2, zong2013structuralmechanismsof pages 2-4).
3. Cofactor Requirements  
   The catalytic activity of MUSK, like most kinases, is dependent on the presence of divalent metal ions that facilitate ATP binding and phosphate transfer. In particular, Mg²⁺ is required as an essential cofactor for its kinase activity. The presence of Mg²⁺ allows proper coordination of the ATP molecule within the active site of the kinase domain, enabling the efficient transfer of the phosphate group to the substrate tyrosine residue. This requirement for Mg²⁺ is a well‐established characteristic shared with other receptor tyrosine kinases (wheeler2015receptortyrosinekinases pages 367-370).
4. Substrate Specificity  
   MUSK exhibits substrate specificity predominantly for tyrosine residues on its target proteins. A notable aspect of its enzymatic function involves autophosphorylation at critical tyrosine residues within its regulatory domains. Key autophosphorylation sites include tyrosine 553 in the juxtamembrane region and tyrosines 750, 754, and 755 within the activation loop of the kinase domain. These phosphorylated residues are essential for full activation of the receptor and for the recruitment of downstream adaptor proteins such as Dok7. Although the intrinsic substrate consensus motif for MUSK has not been fully defined in the literature, the pattern of phosphorylation seen on MUSK itself and on associated proteins implicated in acetylcholine receptor (AChR) clustering suggests that MUSK preferentially targets specific tyrosine residues within proteins that participate in neuromuscular synapse assembly (cheusova2006caseinkinase2dependent pages 1-2, herbst2000thejuxtamembraneregion pages 1-2, cruz2020congenitalmyasthenicsyndrome pages 1-2, cocanougher2024theseverityof pages 9-10).
5. Structure  
   MUSK is organized as a type I transmembrane receptor with a multi‐domain architecture that underpins its biological function. The extracellular region is composed of several immunoglobulin‐like domains and a Frizzled‐like cysteine‐rich domain. The Ig1 domain is critical for receptor homodimerization and for mediating interactions with the co‐receptor LRP4, which is essential for agrin‐induced activation of MUSK (bello2023structuralandbiochemical pages 38-43, cocanougher2024theseverityof pages 1-2). Additional Ig domains contribute to the stabilization of the receptor complex, and the Frizzled‐like domain may participate in binding regulatory molecules potentially associated with Wnt signaling, although its precise function in the context of NMJ formation remains to be fully elucidated (bello2023structuralandbiochemical pages 43-46, hubbard2013structureandactivation pages 2-4). The single transmembrane segment anchors MUSK in the muscle cell membrane, while the intracellular region comprises a short juxtamembrane segment followed by a catalytic tyrosine kinase domain. The juxtamembrane domain contains a highly conserved tyrosine residue (Tyr553) which, upon phosphorylation, serves as a docking site for the adaptor protein Dok7. This is followed by the kinase domain, which adopts the canonical bilobal structure observed in many protein kinases, featuring an N-terminal lobe predominantly composed of β-sheets and a C-terminal lobe housing α-helices such as the C-helix. Within the kinase domain, a flexible activation loop contains critical autophosphorylation sites (Tyr750, Tyr754, Tyr755) required for full enzymatic activation. Structural studies, including high-resolution crystallographic analyses of the extracellular Ig domains, have helped delineate the semi-rigid arrangement of these modules and underscore the importance of the disulfide bonds that stabilize the fold of the Ig1 domain (bello2023structuralandbiochemical pages 38-43, stiegler2006crystalstructureof pages 1-2, herbst2020muskfunctionduring pages 19-21). Unique structural features of MUSK include the juxtaposition of an Ig domain responsible for binding a co-receptor alongside a Frizzled-like domain, a combination not typically found in other receptor tyrosine kinases, and the presence of a C-terminal region that may contain PDZ-binding motifs that contribute to the assembly of synaptic signaling complexes (hubbard2013structureandactivation pages 1-2, cruz2020congenitalmyasthenicsyndrome pages 2-4).
6. Regulation  
   MUSK activity is regulated through a combination of extracellular ligand interactions, receptor dimerization, and a cascade of phosphorylation events. Extracellularly, the binding of neural agrin to the low-density lipoprotein receptor-related protein 4 (LRP4) initiates the activation of MUSK. The agrin–LRP4 complex facilitates the dimerization of MUSK, which in turn triggers autophosphorylation at key tyrosine residues. Phosphorylation of Tyr553 in the juxtamembrane region is of particular importance, as this modification creates a binding site for the adaptor protein Dok7; the recruitment of Dok7 further enhances MUSK autophosphorylation within its kinase domain, especially on residues Tyr750, Tyr754, and Tyr755, thereby stabilizing the active conformation of the receptor (bergamin2010thecytoplasmicadaptor pages 7-8, inoue2009dok7activatesthe pages 1-2, cruz2020congenitalmyasthenicsyndrome pages 7-9). In addition to this primary mechanism, MUSK regulation involves cooperation with other intracellular kinases. Activation of Src family kinases and ABL1 has been implicated in further modulating MUSK activity and promoting the phosphorylation of substrates involved in acetylcholine receptor clustering (cocanougher2024theseverityof pages 5-7, cruz2020congenitalmyasthenicsyndrome pages 11-12). Furthermore, there is evidence that casein kinase 2 phosphorylates serine residues within the kinase insert region of MUSK, a modification that stabilizes acetylcholine receptor aggregates although it does not affect the kinase’s intrinsic tyrosine phosphorylating activity (cheusova2006caseinkinase2dependent pages 1-2). The overall regulation of MUSK involves an intricate network of ligand-induced conformational changes, autophosphorylation events, and subsequent recruitment of downstream effectors that together ensure a tightly controlled activation state essential for proper NMJ assembly and function (herbst2020muskfunctionduring pages 4-7, inoue2009dok7activatesthe pages 1-2).
7. Function  
   MUSK plays a central role in the development and maintenance of the neuromuscular junction. It is predominantly expressed in skeletal muscle and is concentrated at the postsynaptic membrane of the NMJ. Upon activation by neural agrin via its co-receptor LRP4, MUSK initiates a cascade of phosphorylation events that are crucial for the clustering of acetylcholine receptors (AChRs) on the muscle fiber, a process that is essential for efficient neuromuscular transmission (bello2023structuralandbiochemical pages 38-43, cocanougher2024theseverityof pages 1-2). The autophosphorylation of MUSK on specific tyrosine residues triggers downstream signaling pathways that not only result in the reorganization of the actin cytoskeleton, thereby facilitating AChR clustering, but also promote the expression of synapse-specific genes in the subsynaptic nuclei. Additionally, MUSK is involved in presynaptic differentiation through retrograde signaling mechanisms that help coordinate the development of both sides of the synapse (burden2018fundamentalmoleculesand pages 3-5, cruz2020congenitalmyasthenicsyndrome pages 1-2). Key interacting partners in these processes include LRP4, the ligand agrin, the adaptor protein Dok7—which is essential for full MUSK activation—as well as other proteins such as DVL1 and PAK1 that form part of a ternary complex with MUSK to regulate acetylcholine receptor clustering (inoue2009dok7activatesthe pages 1-2, cocanougher2024theseverityof pages 5-7). Moreover, MUSK activity has been linked to the regulation of Rho family GTPases via interactions with FNTA, thereby influencing actin dynamics and contributing to the overall architecture of the NMJ. The precise coordination of these signaling events ensures that synapse formation, maintenance, and plasticity occur in a highly regulated and spatially restricted manner, which is critical for muscle function and efficient neuromuscular transmission (cocanougher2024theseverityof pages 1-2, cruz2020congenitalmyasthenicsyndrome pages 7-9).
8. Other Comments  
   MUSK is of considerable clinical importance because disruptions in its function can lead to severe neuromuscular disorders. Mutations within the MUSK gene that impair receptor autophosphorylation, disrupt interaction with essential adaptor proteins such as Dok7, or interfere with LRP4 binding are causative for congenital myasthenic syndromes; in these cases, patients often display symptoms that include muscle weakness and fatigability, with significant variability in disease severity even among affected individuals (maggi2013markedphenotypicvariability pages 1-3, cruz2020congenitalmyasthenicsyndrome pages 13-13). In addition, autoantibodies directed primarily against MUSK—mainly of the IgG4 subclass—have been implicated in an autoimmune form of myasthenia gravis (MuSK-MG). These autoantibodies disrupt the normal ligand–receptor interactions necessary for NMJ maintenance, rendering conventional therapies such as acetylcholinesterase inhibitors ineffective and necessitating the use of immunosuppressive agents or other targeted treatments (keritam2024aclinicalperspective pages 1-2, pinto2019congenitalvocalcord pages 4-4). Although small-molecule inhibitors specific to MUSK kinase activity have not yet been developed as clinical agents, current research is exploring therapeutic strategies that modulate upstream or downstream signaling events associated with MUSK activation. The continuing effort to develop a more detailed understanding of MUSK’s structure, regulation, and interaction networks is critical for the design of novel treatments that can restore normal neuromuscular function in patients with MUSK-related disorders (cocanougher2024theseverityof pages 10-11, wheeler2015receptortyrosinekinases pages 367-370).

References

1. (bello2023structuralandbiochemical pages 38-43): A DI BELLO. Structural and biochemical characterization of human musk ectodomain using a nanobody library. Unknown journal, 2023.
2. (bello2023structuralandbiochemical pages 43-46): A DI BELLO. Structural and biochemical characterization of human musk ectodomain using a nanobody library. Unknown journal, 2023.
3. (bergamin2010thecytoplasmicadaptor pages 7-8): E. Bergamin, Peter T. Hallock, S. Burden, and S. Hubbard. The cytoplasmic adaptor protein dok7 activates the receptor tyrosine kinase musk via dimerization. Molecular cell, 39 1:100-9, Jul 2010. URL: https://doi.org/10.1016/j.molcel.2010.06.007, doi:10.1016/j.molcel.2010.06.007. This article has 171 citations and is from a highest quality peer-reviewed journal.
4. (burden2018fundamentalmoleculesand pages 13-14): S. Burden, M. Huijbers, and Leonor Remédio. Fundamental molecules and mechanisms for forming and maintaining neuromuscular synapses. International Journal of Molecular Sciences, Feb 2018. URL: https://doi.org/10.3390/ijms19020490, doi:10.3390/ijms19020490. This article has 107 citations and is from a peer-reviewed journal.
5. (burden2018fundamentalmoleculesand pages 3-5): S. Burden, M. Huijbers, and Leonor Remédio. Fundamental molecules and mechanisms for forming and maintaining neuromuscular synapses. International Journal of Molecular Sciences, Feb 2018. URL: https://doi.org/10.3390/ijms19020490, doi:10.3390/ijms19020490. This article has 107 citations and is from a peer-reviewed journal.
6. (cheusova2006caseinkinase2dependent pages 1-2): Tatiana Cheusova, Muhammad Amir Khan, Steffen Wolfgang Schubert, Anne-Claude Gavin, Thierry Buchou, Germaine Jacob, Heinrich Sticht, Jorge Allende, Brigitte Boldyreff, Hans Rudolf Brenner, and Said Hashemolhosseini. Casein kinase 2-dependent serine phosphorylation of musk regulates acetylcholine receptor aggregation at the neuromuscular junction. Genes & Development, 20:1800-1816, Jul 2006. URL: https://doi.org/10.1101/gad.375206, doi:10.1101/gad.375206. This article has 80 citations.
7. (cocanougher2024theseverityof pages 1-2): Benjamin T. Cocanougher, Samuel W. Liu, Ludmila Francescatto, Alexander Behura, Mariele Anneling, David G. Jackson, Kristen L. Deak, C. Hornik, Mai K. ElMallah, Carolyn E. Pizoli, Edward C. Smith, Khoon Ghee Queenie Tan, and Marie T. McDonald. The severity of musk pathogenic variants is predicted by the protein domain they disrupt. Human Genetics and Genomics Advances, Apr 2024. URL: https://doi.org/10.1016/j.xhgg.2024.100288, doi:10.1016/j.xhgg.2024.100288. This article has 1 citations.
8. (cocanougher2024theseverityof pages 10-11): Benjamin T. Cocanougher, Samuel W. Liu, Ludmila Francescatto, Alexander Behura, Mariele Anneling, David G. Jackson, Kristen L. Deak, C. Hornik, Mai K. ElMallah, Carolyn E. Pizoli, Edward C. Smith, Khoon Ghee Queenie Tan, and Marie T. McDonald. The severity of musk pathogenic variants is predicted by the protein domain they disrupt. Human Genetics and Genomics Advances, Apr 2024. URL: https://doi.org/10.1016/j.xhgg.2024.100288, doi:10.1016/j.xhgg.2024.100288. This article has 1 citations.
9. (cocanougher2024theseverityof pages 5-7): Benjamin T. Cocanougher, Samuel W. Liu, Ludmila Francescatto, Alexander Behura, Mariele Anneling, David G. Jackson, Kristen L. Deak, C. Hornik, Mai K. ElMallah, Carolyn E. Pizoli, Edward C. Smith, Khoon Ghee Queenie Tan, and Marie T. McDonald. The severity of musk pathogenic variants is predicted by the protein domain they disrupt. Human Genetics and Genomics Advances, Apr 2024. URL: https://doi.org/10.1016/j.xhgg.2024.100288, doi:10.1016/j.xhgg.2024.100288. This article has 1 citations.
10. (cocanougher2024theseverityof pages 9-10): Benjamin T. Cocanougher, Samuel W. Liu, Ludmila Francescatto, Alexander Behura, Mariele Anneling, David G. Jackson, Kristen L. Deak, C. Hornik, Mai K. ElMallah, Carolyn E. Pizoli, Edward C. Smith, Khoon Ghee Queenie Tan, and Marie T. McDonald. The severity of musk pathogenic variants is predicted by the protein domain they disrupt. Human Genetics and Genomics Advances, Apr 2024. URL: https://doi.org/10.1016/j.xhgg.2024.100288, doi:10.1016/j.xhgg.2024.100288. This article has 1 citations.
11. (cruz2020congenitalmyasthenicsyndrome pages 1-2): Pedro M. Rodríguez Cruz, Judith Cossins, Jonathan Cheung, Susan Maxwell, Sandeep Jayawant, Ruth Herbst, Dominic Waithe, Alexandr P. Kornev, Jacqueline Palace, and David Beeson. Congenital myasthenic syndrome due to mutations in musk suggests that the level of musk phosphorylation is crucial for governing synaptic structure. Human Mutation, 41:619-631, Nov 2020. URL: https://doi.org/10.1002/humu.23949, doi:10.1002/humu.23949. This article has 26 citations and is from a domain leading peer-reviewed journal.
12. (cruz2020congenitalmyasthenicsyndrome pages 11-12): Pedro M. Rodríguez Cruz, Judith Cossins, Jonathan Cheung, Susan Maxwell, Sandeep Jayawant, Ruth Herbst, Dominic Waithe, Alexandr P. Kornev, Jacqueline Palace, and David Beeson. Congenital myasthenic syndrome due to mutations in musk suggests that the level of musk phosphorylation is crucial for governing synaptic structure. Human Mutation, 41:619-631, Nov 2020. URL: https://doi.org/10.1002/humu.23949, doi:10.1002/humu.23949. This article has 26 citations and is from a domain leading peer-reviewed journal.
13. (cruz2020congenitalmyasthenicsyndrome pages 13-13): Pedro M. Rodríguez Cruz, Judith Cossins, Jonathan Cheung, Susan Maxwell, Sandeep Jayawant, Ruth Herbst, Dominic Waithe, Alexandr P. Kornev, Jacqueline Palace, and David Beeson. Congenital myasthenic syndrome due to mutations in musk suggests that the level of musk phosphorylation is crucial for governing synaptic structure. Human Mutation, 41:619-631, Nov 2020. URL: https://doi.org/10.1002/humu.23949, doi:10.1002/humu.23949. This article has 26 citations and is from a domain leading peer-reviewed journal.
14. (cruz2020congenitalmyasthenicsyndrome pages 2-4): Pedro M. Rodríguez Cruz, Judith Cossins, Jonathan Cheung, Susan Maxwell, Sandeep Jayawant, Ruth Herbst, Dominic Waithe, Alexandr P. Kornev, Jacqueline Palace, and David Beeson. Congenital myasthenic syndrome due to mutations in musk suggests that the level of musk phosphorylation is crucial for governing synaptic structure. Human Mutation, 41:619-631, Nov 2020. URL: https://doi.org/10.1002/humu.23949, doi:10.1002/humu.23949. This article has 26 citations and is from a domain leading peer-reviewed journal.
15. (cruz2020congenitalmyasthenicsyndrome pages 7-9): Pedro M. Rodríguez Cruz, Judith Cossins, Jonathan Cheung, Susan Maxwell, Sandeep Jayawant, Ruth Herbst, Dominic Waithe, Alexandr P. Kornev, Jacqueline Palace, and David Beeson. Congenital myasthenic syndrome due to mutations in musk suggests that the level of musk phosphorylation is crucial for governing synaptic structure. Human Mutation, 41:619-631, Nov 2020. URL: https://doi.org/10.1002/humu.23949, doi:10.1002/humu.23949. This article has 26 citations and is from a domain leading peer-reviewed journal.
16. (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 228 citations.
17. (herbst2020muskfunctionduring pages 4-7): R Herbst. Musk function during health and disease. Neuroscience Letters, Dec 2020. URL: https://doi.org/10.1016/j.neulet.2019.134676, doi:10.1016/j.neulet.2019.134676. This article has 49 citations and is from a peer-reviewed journal.
18. (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 62 citations.
19. (hubbard2013structureandactivation pages 2-4): 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 62 citations.
20. (chu…1999xenopusmuscle‐specifickinase pages 1-3): Xenopus muscle‐specific kinase: molecular cloning and prominent expression in neural tissues during early embryonic development
21. (herbst2020muskfunctionduring pages 19-21): R Herbst. Musk function during health and disease. Neuroscience Letters, Dec 2020. URL: https://doi.org/10.1016/j.neulet.2019.134676, doi:10.1016/j.neulet.2019.134676. This article has 49 citations and is from a peer-reviewed journal.
22. (inoue2009dok7activatesthe pages 1-2): Akane Inoue, Kiyoko Setoguchi, Yosuke Matsubara, Kumiko Okada, Nozomi Sato, Yoichiro Iwakura, Osamu Higuchi, and Yuji Yamanashi. Dok-7 activates the muscle receptor kinase musk and shapes synapse formation. Science Signaling, 2:ra7-ra7, Feb 2009. URL: https://doi.org/10.1126/scisignal.2000113, doi:10.1126/scisignal.2000113. This article has 133 citations and is from a domain leading peer-reviewed journal.
23. (keritam2024aclinicalperspective pages 1-2): Omar Keritam, Angela Vincent, Fritz Zimprich, and Hakan Cetin. A clinical perspective on muscle specific kinase antibody positive myasthenia gravis. Frontiers in Immunology, Dec 2024. URL: https://doi.org/10.3389/fimmu.2024.1502480, doi:10.3389/fimmu.2024.1502480. This article has 0 citations and is from a peer-reviewed journal.
24. (maggi2013markedphenotypicvariability pages 1-3): Lorenzo Maggi, R. Brugnoni, V. Scaioli, T. L. Winden, L. Morandi, A. G. Engel, R. Mantegazza, and P. Bernasconi. Marked phenotypic variability in two siblings with congenital myasthenic syndrome due to mutations in musk. Journal of Neurology, 260:2894-2896, Oct 2013. URL: https://doi.org/10.1007/s00415-013-7118-5, doi:10.1007/s00415-013-7118-5. This article has 27 citations and is from a domain leading peer-reviewed journal.
25. (pinto2019congenitalvocalcord pages 4-4): Marcus V. Pinto, Jacqui-Lyn Saw, and Margherita Milone. Congenital vocal cord paralysis and late-onset limb-girdle weakness in musk–congenital myasthenic syndrome. Frontiers in Neurology, Dec 2019. URL: https://doi.org/10.3389/fneur.2019.01300, doi:10.3389/fneur.2019.01300. This article has 14 citations and is from a peer-reviewed journal.
26. (sossin2006tracingtheevolution pages 8-9): Wayne S. Sossin. Tracing the evolution and function of the trk superfamily of receptor tyrosine kinases. Brain, Behavior and Evolution, 68:145-156, Aug 2006. URL: https://doi.org/10.1159/000094084, doi:10.1159/000094084. This article has 38 citations.
27. (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.
28. (wheeler2015receptortyrosinekinases pages 367-370): D. Wheeler and Yosef Yarden. Receptor Tyrosine Kinases: Structure, Functions and Role in Human Disease. Springer New York, Jan 2015. ISBN 9781493920532. URL: https://doi.org/10.1007/978-1-4939-2053-2, doi:10.1007/978-1-4939-2053-2. This article has 52 citations.
29. (zong2013structuralmechanismsof pages 2-4): Yinong Zong and Rongsheng Jin. Structural mechanisms of the agrin–lrp4–musk signaling pathway in neuromuscular junction differentiation. Cellular and Molecular Life Sciences, 70:3077-3088, Nov 2013. URL: https://doi.org/10.1007/s00018-012-1209-9, doi:10.1007/s00018-012-1209-9. This article has 102 citations and is from a domain leading peer-reviewed journal.