1. Phylogeny  
   ULK4 is a member of the Unc-51-like kinase (ULK) family, a group of serine/threonine kinases that can be traced back to eukaryotic ancestors and are evolutionarily related to the yeast autophagy-related kinase Atg1 and the Caenorhabditis elegans UNC-51 protein. Within the ULK family, active kinases such as ULK1–3 and the related STK36 retain key catalytic machinery, whereas ULK4 is distinguished by significant divergence in its catalytic motifs, resulting in its classification as a pseudokinase. This divergence indicates that although ULK4 shares a conserved N-terminal kinase fold with its relatives, its evolutionary history has led to the loss of catalytic residues necessary for classical phosphotransfer, thereby re-purposing its structure for regulatory and scaffolding functions. Comparative analyses have demonstrated that ULK4 is evolutionarily conserved across metazoans, implying that its functions in cellular signaling and neuronal development have been maintained since the last common ancestor of higher eukaryotes (lang2014recurrentdeletionsof pages 2-3, alers2012theincredibleulks pages 3-5, luo2022ulk4inneurodevelopmental pages 1-2). In phylogenetic trees constructed using kinase domain sequences, ULK4 clusters with the other ULK family kinases; however, its branch is more distant from the catalytically active ULK1 and ULK2. Its unique domain architecture—including an N-terminal pseudokinase domain coupled with extended C-terminal HEAT repeats—suggests that following an ancestral gene duplication event, ULK4 underwent functional specialization in the regulation of neuronal signaling pathways and cytoskeletal remodeling (karmacharya2023smallmoleculeinhibitors pages 2-5, luo2022ulk4inneurodevelopmental pages 2-3, mccoy2023ulk4andfusedstk36 pages 1-2). This evolutionary context not only distinguishes ULK4 from its paralogs in terms of biochemical activity but also implies a conserved role in neurodevelopment that has been maintained over evolutionary time.
2. Reaction Catalyzed  
   Canonical serine/threonine kinases catalyze the reaction ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺. Although ULK4 possesses a domain that adopts the classic kinase fold, its biochemical behavior indicates that it is a pseudokinase; that is, it exhibits no or negligible phosphotransferase activity under standard in vitro conditions. In experimental assays employing γ-32P-ATP, ULK4 fails to demonstrate significant catalytic activity despite its ability to bind ATP with high affinity. This lack of detectable enzymatic activity suggests that ULK4 does not efficiently transfer a phosphate group to substrate proteins even though, by sequence and structure, it nominally belongs to the serine/threonine kinase superfamily (khamrui2019highresolutionstructureand pages 1-2, karmacharya2023smallmoleculeinhibitors pages 2-5). Therefore, while the canonical reaction for serine/threonine kinases is maintained in description—ATP + substrate → ADP + phosphorylated substrate—the reaction catalyzed by ULK4 is effectively non-operative in the classical sense, with its biological role instead attributed to its capacity for ATP binding and scaffolding of protein complexes (khamrui2019highresolutionstructureand pages 1-2).
3. Cofactor Requirements  
   Most active serine/threonine kinases require divalent cations, notably Mg²⁺, which coordinate with ATP to facilitate efficient phosphotransfer via stabilization of the nucleotide’s triphosphate moiety. In contrast, ULK4 demonstrates an atypical cofactor requirement in that its high-affinity nucleotide binding occurs in the absence of Mg²⁺. Detailed biochemical studies using fluorescent nucleotide analogs have revealed that ULK4 binds ATP and ADP with micromolar affinity when no Mg²⁺ is present, and the addition of Mg²⁺ actually diminishes this binding affinity (khamrui2019highresolutionstructureand pages 1-2, khamrui2019highresolutionstructureand pages 3-4). This magnesium independence is consistent with its pseudokinase nature and indicates that ULK4, unlike canonical kinases, does not rely on divalent metal ions to orient ATP for phosphotransfer reactions; rather, its ATP binding function likely serves a regulatory purpose unrelated to catalysis (karmacharya2023smallmoleculeinhibitors pages 2-5).
4. Substrate Specificity  
   Active serine/threonine kinases typically recognize specific consensus sequence motifs in their substrates—often characterized by a preference for basic residues such as arginine preceding the phospho-acceptor site. For example, many kinases recognize motifs of the type RxRxxp[ST]. However, ULK4, due to its classification as a pseudokinase with negligible catalytic activity, has not been shown to phosphorylate substrates in the conventional manner, and no consensus substrate motif has been empirically established. Instead, functional evidence points to a role for ULK4 in the remodeling of cytoskeletal components, particularly in the regulation of alpha-tubulin acetylation, which influences neurite branching, elongation, and overall cell motility (hu2022deletionofschizophrenia pages 1-2, lang2014recurrentdeletionsof pages 7-8). Given the absence of robust phosphotransferase activity, any substrate specificity attributed to ULK4 is presumed to be indirect and mediated through its function as a structural scaffold that facilitates the assembly or localization of active kinases and phosphatases. Consequently, although the classical reaction mechanism would predict a substrate specificity profile, ULK4’s functional role in cellular signaling is more consistent with the regulation of substrate accessibility and complex formation rather than with direct catalytic modification of specific peptide sequences (luo2022ulk4inneurodevelopmental pages 1-2, khamrui2019highresolutionstructureand pages 1-2).
5. Structure  
   ULK4 is a large protein with an approximate molecular weight of 142 kDa and displays a domain organization that is distinct among the ULK family members. Its N-terminal region comprises a pseudokinase domain that retains the canonical kinase fold—including an N-terminal lobe and a C-terminal lobe—as observed in high-resolution crystal structures. Despite this conserved architecture, the pseudokinase domain of ULK4 lacks several key catalytic residues that are required for phosphotransfer activity, rendering the domain catalytically inert as confirmed by biochemical assays (khamrui2019highresolutionstructureand pages 1-2, pages 2-3). Structural studies indicate that the ATP-binding pocket is well-formed, allowing ULK4 to bind nucleotides with high affinity, yet the ATP binding occurs in a magnesium-independent manner and does not lead to conventional catalytic activity (khamrui2019highresolutionstructureand pages 1-2, karmacharya2023smallmoleculeinhibitors pages 2-5). The C-terminal portion of ULK4 is characterized by repeated HEAT motifs, which are arrays of alpha-helical repeats known to mediate protein–protein interactions and act as flexible scaffolds for the assembly of multi-protein complexes (karmacharya2023smallmoleculeinhibitors pages 5-7, luo2022ulk4inneurodevelopmental pages 2-3). These HEAT repeats are thought to facilitate interactions with other regulatory proteins, including components of phosphatase complexes and kinases involved in neuronal signaling. Furthermore, structural analyses using crystallography and high-resolution modeling have revealed that while ULK4 maintains key features of the classic kinase fold—such as a defined C-helix and an activation loop—these regions do not undergo the dynamic phosphorylation-dependent conformational changes typical of active kinases (khamrui2019highresolutionstructureand pages 4-5, karmacharya2023smallmoleculeinhibitors pages 12-14). In summary, the unique structural features of ULK4—its pseudokinase domain with an intact yet nonfunctional ATP-binding pocket and its extended HEAT repeat region—underscore its role as a regulatory scaffold rather than as a bona fide enzyme catalyzing phosphorylation reactions (luo2022ulk4inneurodevelopmental pages 4-6, mccoy2023ulk4andfusedstk36 pages 1-2).
6. Regulation  
   The regulation of ULK4 is achieved not through classical activation and inhibition via phosphorylation of its catalytic domain, but rather through mechanisms that involve conformational modulation upon ATP binding and through the assembly of protein complexes that dictate its subcellular localization and function. Although ULK4 is structurally equipped to bind ATP, its designation as a pseudokinase implies that it does not require activation by conventional autophosphorylation or phosphorylation by regulatory kinases (khamrui2019highresolutionstructureand pages 1-2, karmacharya2023smallmoleculeinhibitors pages 2-5). Instead, regulatory control of ULK4 appears to be mediated by its interactions with other signaling molecules and phosphatases. For instance, deletion of ULK4 in conditional knockout mouse models leads to diminished levels of phosphorylated Akt and phosphorylated GSK-3α/β, indicating that ULK4 exerts an indirect regulatory influence on the Akt-GSK-3 signaling pathway (hu2022deletionofschizophrenia pages 1-2). Additional studies have demonstrated that ULK4 can form complexes with major serine/threonine phosphatases such as PP1α and PP2A, implicating these interactions in the fine-tuning of kinase signaling cascades within neurons (luo2022ulk4inneurodevelopmental pages 2-3, lang2014recurrentdeletionsof pages 7-8). Moreover, ULK4’s extended C-terminal HEAT repeat region further contributes to its regulation by mediating scaffolding interactions that ensure the proper assembly and spatial organization of signaling complexes, which is particularly important in the context of neuronal migration, cilia assembly, and cytoskeletal dynamics (mccoy2023ulk4andfusedstk36 pages 11-12, lang2016controlofcortex pages 9-11). Although small molecule inhibitors have been developed that target ULK4’s ATP-binding pocket, these compounds act by modulating its conformational state and interaction capabilities rather than by inhibiting catalytic activity in the classical sense (khamrui2019highresolutionstructureand pages 3-4, karmacharya2023smallmoleculeinhibitors pages 12-14). Collectively, the regulatory mechanisms of ULK4 are orchestrated through a combination of nucleotide-induced conformational adjustments and strategic protein–protein interactions that allow it to function as an essential scaffold in neuronal signaling networks.
7. Function  
   ULK4 plays a pivotal role in neurodevelopment and cellular signaling, with functions that extend to the regulation of cytoskeletal dynamics and neurite outgrowth. In neuronal tissues, ULK4 is critical for processes such as neurite branching, elongation, and cell motility, which are fundamental for proper neuronal connectivity and brain architecture. Studies using conditional knockout mouse models have demonstrated that loss of ULK4 results in cognitive deficits, impaired sensorimotor gating, and reduced spine density on cortical pyramidal neurons, thereby establishing its importance in neuronal circuit formation and function (hu2022deletionofschizophrenia pages 1-2, lang2014recurrentdeletionsof pages 2-3). Further, ULK4 has been implicated in corticogenesis by influencing the proliferation of neural stem cells and the migration of neurons, as evidenced by cortical layer anomalies observed in animal models lacking functional ULK4 (lang2016controlofcortex pages 9-11, luo2022ulk4inneurodevelopmental pages 6-7). One of the key cellular functions attributed to ULK4 is the remodeling of cytoskeletal components, particularly in the regulation of alpha-tubulin acetylation, which is a critical determinant of microtubule stability and neuronal polarity (lang2014recurrentdeletionsof pages 7-8, hu2022deletionofschizophrenia pages 1-2). In addition to its roles in neuronal differentiation and migration, ULK4 is involved in the assembly and maintenance of motile cilia. The interaction between ULK4 and the kinase Fused/STK36, as demonstrated in studies on flagellar and ciliary assembly, underscores its contribution to cilia formation and function, which is essential for proper cerebrospinal fluid flow and may have implications in conditions such as hydrocephalus (mccoy2023ulk4andfusedstk36 pages 11-12, karmacharya2023smallmoleculeinhibitors pages 5-7). The multifaceted functions of ULK4 in neuronal signaling, cytoskeletal dynamics, and ciliary assembly point to its critical role in brain development and neuropsychiatric health, with genetic variations and deletions of the ULK4 gene being associated with an increased risk of schizophrenia and other neurodevelopmental disorders (hu2022deletionofschizophrenia pages 1-2, lang2014recurrentdeletionsof pages 2-3, luo2022ulk4inneurodevelopmental pages 1-2). In summary, ULK4 functions as an essential regulator in the central nervous system by orchestrating structural and signaling events that underpin neurite formation, neuronal migration, and cytoskeletal organization.
8. Other Comments  
   Numerous studies have reported that small molecule compounds are capable of binding to the ATP-binding site of ULK4, even though these compounds do not result in classical kinase inhibition due to ULK4’s pseudokinase status. For example, high-throughput virtual screening and experimental assays have yielded molecules that bind ULK4 in the micromolar range, with some compounds, such as a prodrug known as R788, being evaluated as tool compounds despite limitations related to their phosphate moieties (khamrui2019highresolutionstructureand pages 3-4, karmacharya2023smallmoleculeinhibitors pages 12-14). In addition, genetic studies have highlighted recurrent deletions and copy number variations in ULK4 among patients with schizophrenia and other neurodevelopmental disorders, suggesting that alterations in ULK4 dosage contribute to aberrant cortical development and neuronal signaling (hu2022deletionofschizophrenia pages 1-2, lang2014recurrentdeletionsof pages 2-3). ULK4’s interaction with phosphatases such as PP1α and PP2A, and its involvement in the regulation of prominent signaling pathways—most notably the Akt-GSK-3 cascade—further underscore its potential as a regulator of cellular dynamics in neural systems (luo2022ulk4inneurodevelopmental pages 2-3, lang2014recurrentdeletionsof pages 7-8). Moreover, studies focusing on cortical development have observed that ULK4 modulates the acetylation status of alpha-tubulin, thereby influencing microtubule stability, neuronal polarity, and migration of neural progenitor cells, processes which are integral to forming proper cortical structures (lang2016controlofcortex pages 9-11). Despite these advances in understanding, detailed biochemical characterization regarding ULK4’s substrate specificity, its complete repertoire of protein interaction partners, and the full spectrum of its regulatory post-translational modifications remain incomplete, representing areas for further investigation (karmacharya2023smallmoleculeinhibitors pages 2-5, khamrui2019highresolutionstructureand pages 2-3). Collectively, the available evidence positions ULK4 as a critical non-catalytic regulator within neuronal and ciliary signaling networks and highlights its relevance in neuropsychiatric disorders, thereby making it an attractive target for future therapeutic exploration.
9. References
10. Hu, L., et al. (2022). Deletion of schizophrenia susceptibility gene ULK4 leads to abnormal cognitive behaviors via Akt-GSK-3 signaling pathway in mice. Schizophrenia Bulletin, 48:804-813, May 2022. URL: https://doi.org/10.1093/schbul/sbac040.
11. Karmacharya, U., & Jung, J. (2023). Small molecule inhibitors for unc-51-like autophagy-activating kinase targeting autophagy in cancer. International Journal of Molecular Sciences, Jan 2023. URL: https://doi.org/10.3390/ijms24020953.
12. Khamrui, S., et al. (2019). High-resolution structure and inhibition of the schizophrenia-linked pseudokinase ULK4. Journal of the American Chemical Society, 142:33-37, Dec 2019. URL: https://doi.org/10.1021/jacs.9b10458.
13. Lang, B., et al. (2014). Recurrent deletions of ULK4 in schizophrenia: a novel gene crucial for neuritogenesis and neuronal motility. Journal of Cell Science, Jan 2014. URL: https://doi.org/10.1242/jcs.137604.
14. Luo, S., Zheng, N., & Lang, B. (2022). ULK4 in neurodevelopmental and neuropsychiatric disorders. Frontiers in Cell and Developmental Biology, Apr 2022. URL: https://doi.org/10.3389/fcell.2022.873706.
15. McCoy, C. J., et al. (2023). ULK4 and fused/STK36 interact to mediate assembly of a motile flagellum. Molecular Biology of the Cell, Jun 2023. URL: https://doi.org/10.1091/mbc.e22-06-0222.
16. Alers, S., Löffler, A. S., Wesselborg, S., & Stork, B. (2012). The incredible ULKs. Cell Communication and Signaling, Mar 2012. URL: https://doi.org/10.1186/1478-811x-10-7.
17. Lang, B., et al. (2016). Control of cortex development by ULK4, a rare risk gene for mental disorders including schizophrenia. Scientific Reports, Sep 2016. URL: https://doi.org/10.1038/srep31126.

References

1. (hu2022deletionofschizophrenia pages 1-2): Ling Hu, Bing-Yao Zhou, Cui-Ping Yang, Da-Yun Lu, Yun-Chao Tao, Lin Chen, Lei Zhang, Jun-Hui Su, Ying Huang, Ning-Ning Song, Jia-Yin Chen, Li Zhao, Yi Chen, Chun-Hui He, Yu-Bing Wang, Bing Lang, and Yu-Qiang Ding. Deletion of schizophrenia susceptibility gene ulk4 leads to abnormal cognitive behaviors via akt-gsk-3 signaling pathway in mice. Schizophrenia Bulletin, 48:804-813, May 2022. URL: https://doi.org/10.1093/schbul/sbac040, doi:10.1093/schbul/sbac040. This article has 6 citations and is from a highest quality peer-reviewed journal.
2. (karmacharya2023smallmoleculeinhibitors pages 2-5): Ujjwala Karmacharya and Jongjon Jung. Small molecule inhibitors for unc-51-like autophagy-activating kinase targeting autophagy in cancer. International Journal of Molecular Sciences, Jan 2023. URL: https://doi.org/10.3390/ijms24020953, doi:10.3390/ijms24020953. This article has 19 citations and is from a peer-reviewed journal.
3. (karmacharya2023smallmoleculeinhibitors pages 5-7): Ujjwala Karmacharya and Jongjon Jung. Small molecule inhibitors for unc-51-like autophagy-activating kinase targeting autophagy in cancer. International Journal of Molecular Sciences, Jan 2023. URL: https://doi.org/10.3390/ijms24020953, doi:10.3390/ijms24020953. This article has 19 citations and is from a peer-reviewed journal.
4. (khamrui2019highresolutionstructureand pages 1-2): Susmita Khamrui, Peter M. U. Ung, Cody Secor, Avner Schlessinger, and Michael B. Lazarus. High-resolution structure and inhibition of the schizophrenia-linked pseudokinase ulk4. Journal of the American Chemical Society, 142:33-37, Dec 2019. URL: https://doi.org/10.1021/jacs.9b10458, doi:10.1021/jacs.9b10458. This article has 26 citations and is from a highest quality peer-reviewed journal.
5. (khamrui2019highresolutionstructureand pages 2-3): Susmita Khamrui, Peter M. U. Ung, Cody Secor, Avner Schlessinger, and Michael B. Lazarus. High-resolution structure and inhibition of the schizophrenia-linked pseudokinase ulk4. Journal of the American Chemical Society, 142:33-37, Dec 2019. URL: https://doi.org/10.1021/jacs.9b10458, doi:10.1021/jacs.9b10458. This article has 26 citations and is from a highest quality peer-reviewed journal.
6. (khamrui2019highresolutionstructureand pages 4-5): Susmita Khamrui, Peter M. U. Ung, Cody Secor, Avner Schlessinger, and Michael B. Lazarus. High-resolution structure and inhibition of the schizophrenia-linked pseudokinase ulk4. Journal of the American Chemical Society, 142:33-37, Dec 2019. URL: https://doi.org/10.1021/jacs.9b10458, doi:10.1021/jacs.9b10458. This article has 26 citations and is from a highest quality peer-reviewed journal.
7. (lang2014recurrentdeletionsof pages 2-3): Bing Lang, Jin Pu, Irene Hunter, Min Liu, Cristina Martin-Granados, Thomas J Reilly, Guo-Dong Gao, Zhen-Long Guan, Wei-Dong Li, Yong-Yong Shi, Guang He, Lin He, Hreinn Stefánsson, David St Clair, Douglas H Blackwood, Colin D McCaig, and Sanbing Shen. Recurrent deletions of ulk4 in schizophrenia: a novel gene crucial for neuritogenesis and neuronal motility. Journal of Cell Science, Jan 2014. URL: https://doi.org/10.1242/jcs.137604, doi:10.1242/jcs.137604. This article has 90 citations and is from a domain leading peer-reviewed journal.
8. (lang2014recurrentdeletionsof pages 7-8): Bing Lang, Jin Pu, Irene Hunter, Min Liu, Cristina Martin-Granados, Thomas J Reilly, Guo-Dong Gao, Zhen-Long Guan, Wei-Dong Li, Yong-Yong Shi, Guang He, Lin He, Hreinn Stefánsson, David St Clair, Douglas H Blackwood, Colin D McCaig, and Sanbing Shen. Recurrent deletions of ulk4 in schizophrenia: a novel gene crucial for neuritogenesis and neuronal motility. Journal of Cell Science, Jan 2014. URL: https://doi.org/10.1242/jcs.137604, doi:10.1242/jcs.137604. This article has 90 citations and is from a domain leading peer-reviewed journal.
9. (luo2022ulk4inneurodevelopmental pages 1-2): Shilin Luo, Nanxi Zheng, and Bing Lang. Ulk4 in neurodevelopmental and neuropsychiatric disorders. Frontiers in Cell and Developmental Biology, Apr 2022. URL: https://doi.org/10.3389/fcell.2022.873706, doi:10.3389/fcell.2022.873706. This article has 16 citations and is from a peer-reviewed journal.
10. (luo2022ulk4inneurodevelopmental pages 2-3): Shilin Luo, Nanxi Zheng, and Bing Lang. Ulk4 in neurodevelopmental and neuropsychiatric disorders. Frontiers in Cell and Developmental Biology, Apr 2022. URL: https://doi.org/10.3389/fcell.2022.873706, doi:10.3389/fcell.2022.873706. This article has 16 citations and is from a peer-reviewed journal.
11. (luo2022ulk4inneurodevelopmental pages 4-6): Shilin Luo, Nanxi Zheng, and Bing Lang. Ulk4 in neurodevelopmental and neuropsychiatric disorders. Frontiers in Cell and Developmental Biology, Apr 2022. URL: https://doi.org/10.3389/fcell.2022.873706, doi:10.3389/fcell.2022.873706. This article has 16 citations and is from a peer-reviewed journal.
12. (mccoy2023ulk4andfusedstk36 pages 1-2): Ciaran J. McCoy, Humbeline Paupelin-Vaucelle, Peter Gorilak, Tom Beneke, Vladimir Varga, and Eva Gluenz. Ulk4 and fused/stk36 interact to mediate assembly of a motile flagellum. Molecular Biology of the Cell, Jun 2023. URL: https://doi.org/10.1091/mbc.e22-06-0222, doi:10.1091/mbc.e22-06-0222. This article has 6 citations and is from a domain leading peer-reviewed journal.
13. (mccoy2023ulk4andfusedstk36 pages 11-12): Ciaran J. McCoy, Humbeline Paupelin-Vaucelle, Peter Gorilak, Tom Beneke, Vladimir Varga, and Eva Gluenz. Ulk4 and fused/stk36 interact to mediate assembly of a motile flagellum. Molecular Biology of the Cell, Jun 2023. URL: https://doi.org/10.1091/mbc.e22-06-0222, doi:10.1091/mbc.e22-06-0222. This article has 6 citations and is from a domain leading peer-reviewed journal.
14. (alers2012theincredibleulks pages 3-5): Sebastian Alers, Antje S Löffler, Sebastian Wesselborg, and Björn Stork. The incredible ulks. Cell Communication and Signaling, Mar 2012. URL: https://doi.org/10.1186/1478-811x-10-7, doi:10.1186/1478-811x-10-7. This article has 111 citations and is from a peer-reviewed journal.
15. (karmacharya2023smallmoleculeinhibitors pages 12-14): Ujjwala Karmacharya and Jongjon Jung. Small molecule inhibitors for unc-51-like autophagy-activating kinase targeting autophagy in cancer. International Journal of Molecular Sciences, Jan 2023. URL: https://doi.org/10.3390/ijms24020953, doi:10.3390/ijms24020953. This article has 19 citations and is from a peer-reviewed journal.
16. (khamrui2019highresolutionstructureand pages 3-4): Susmita Khamrui, Peter M. U. Ung, Cody Secor, Avner Schlessinger, and Michael B. Lazarus. High-resolution structure and inhibition of the schizophrenia-linked pseudokinase ulk4. Journal of the American Chemical Society, 142:33-37, Dec 2019. URL: https://doi.org/10.1021/jacs.9b10458, doi:10.1021/jacs.9b10458. This article has 26 citations and is from a highest quality peer-reviewed journal.
17. (lang2016controlofcortex pages 9-11): Bing Lang, Lei Zhang, Guanyu Jiang, Ling Hu, Wei Lan, Lei Zhao, Irene Hunter, Michal Pruski, Ning-Ning Song, Ying Huang, Ling Zhang, David St Clair, Colin D. McCaig, and Yu-Qiang Ding. Control of cortex development by ulk4, a rare risk gene for mental disorders including schizophrenia. Scientific Reports, Sep 2016. URL: https://doi.org/10.1038/srep31126, doi:10.1038/srep31126. This article has 32 citations and is from a poor quality or predatory journal.
18. (luo2022ulk4inneurodevelopmental pages 6-7): Shilin Luo, Nanxi Zheng, and Bing Lang. Ulk4 in neurodevelopmental and neuropsychiatric disorders. Frontiers in Cell and Developmental Biology, Apr 2022. URL: https://doi.org/10.3389/fcell.2022.873706, doi:10.3389/fcell.2022.873706. This article has 16 citations and is from a peer-reviewed journal.