Microtubule actin crosslinking factor 1, a brain tumor oncoprotein (Review)

KALA BONNER and QUINCY A. QUICK

Department of Biological Sciences, Tennessee State University, Nashville, TN 37066, USA

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Abstract. Microtubule actin crosslinking factor 1 (MACF1), is a cytoskeletal protein that functions as a crosslinker between microtubules and actin filaments, with early studies expanding the role of this spectraplakin protein to the central nervous system and Wnt signaling. In the early 2000's, genetic alterations of MACF1 were identified in several cancers suggesting that this cytoskeletal crosslinker was involved in tumor development and progression, while preclinical studies provided evidence that MACF1 is a potential diagnostic and prognostic biomarker and therapeutic target in glioblastomas, a central nervous system cancer derived from astrocytes and neural progenitor stem cells. Furthermore, investigations in glioblastomas demonstrated that genetic inhibitory targeting of this spectraplakin protein alone and in combination with DNA damaging agents had synergistic antitumorigenic effects. The established role of MACF1 in Wnt signaling, a known mechanistic driver of central nervous system development and pro-tumorigenic cell behavior in glioblastomas, provide a premise for addressing the potential of this spectraplakin protein as a novel oncoprotein in cancers with origins in the nervous system. The present review provides a summary of the role and function of MACF1 in the central nervous system, Wnt signaling and cancer development, specifically as an oncoprotein that underlie the transformation and oncogenic properties of glioblastomas.

Contents

Correspondence to: Dr Quincy A. Quick, Department of Biological Sciences, Tennessee State University, 3500 John A. Merritt Boulevard, Nashville, TN 37066, USA
E-mail: qquick1@tnstate.edu

Abbreviation: MACF1, microtubule actin crosslinking factor

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1. Introduction

Microtubule actin crosslinking factor 1 (MACF1) is a spectraplakin protein with a N-terminal actin-binding domain, plakin domain, an EF-hand calcium-binding domain, with a spectrin-repeat rod and C-terminal growth-arrest specific 2-related microtubule-binding domain. These structural domains enable MACF1 to perform its primary function as a crosslinker of microtubules and actin microfilaments (1-4), cytoskeletal filamentous proteins involved in vesicular trafficking, cytoarchitecture, cell division, and cell migration. In addition to its function as a cytoskeletal crosslinker, it is widely established that MACF1 plays a role in Wnt signaling, as a component of the Wnt signaling protein complex (axin1, beta-catenin and glycogen synthase kinase) that activates Wnt transmembrane proteins and subsequently induces Wnt transcriptional targets (5). Because several studies provide instructive and informative presentations of MACF1 structure and function (6-8), the focus in the present review is an overview of its role in the etiology of brain tumors, specifically glioblastomas.

2. The role of MACF1 in the nervous system

Early seminal work by Goryunov *et al* (9) demonstrated that MACF1 has a significant and prominent role in the mammalian nervous system using *in vivo* tissue specific knockout technology. To that end, A Cre-loxP approach was employed to knockout MACF1 in the early stages of mouse nervous system development, which consequently compromised the organizational structure of the cerebral cortex and neuronal axon migration (9), while a more recent study by Ka *et al* (10), showed that MACF1 regulates GABAergic interneuron migration and positioning in the developing mouse brain using a conditional deletion approach. Several confirmatory studies, particularly *in vitro* knockdown and deletion experiments of MACF1, showed that the most important nervous system function of

this spectraplakin protein is its crosslinking capacity during axon outgrowth and migration (11-15). Additionally, clinical nervous system manifestations of MACF1 alterations were previously reported in a study by Dobyns *et al* (16), which described missense variants and in-frame deletions within the growth-arrest specific 2-related microtubule-binding domain that resulted in brain malformations of children. Collectively, these studies corroborate a defined function of MACF1 during neuron outgrowth and axon migration as part of nervous system development (Fig. 1). However, despite robust data that MACF1 contributes to neuronal development and maturation, few investigations have examined its function in glial cells (astrocytes, oligodendrocytes and microglia) and non-neuronal cells that provide support and protection for neurons.

3. Cancer genetic aberrations of MACF1

Several investigations have provided experimental evidence that show various MACF1 genetic abnormalities (Table I). One of the earliest studies implicating MACF1 in cancer was described in 2011; alternative splicing in adenocarcinoma patients was examined using microarray analyses and reverse transcription polymerase chain reaction (17). MACF1 was identified as one of four alternatively spliced transcripts that may contribute to non-small cell lung cancer (NSCLC) tumorigenesis as a consequence of exon alterations (17). In support of studies that evaluated MACF1 exon alterations as an underlying inducer of adenocarcinoma tumorigenesis, whole exome sequencing revealed MACF1 mutations in renal cell carcinomas and endometrial cancer as a genetic driver of tumorigenesis in these cancers (18,19). Furthermore, a recent study by Tian *et al* (2020), identified MACF1 mutations as a correlation of poor prognosis in patients with breast cancer. With respect to genetic alterations of MACF1 in brain tumors, specifically glioblastomas, cancer genome atlas cbioportal (https://www.cbioportal.org/) analyses revealed that 5% of patient samples consisted of mutations or amplifications (21-23).

4. Oncogenic properties and expression of MACF1

MACF1 has been described to play a significant role in cancer development, primarily through its influence on cellular processes such as proliferation, migration and apoptosis. Specifically, in acute myeloid leukemia (AML), MACF1 overexpression was associated with poor overall survival and attributed to the promotion of AML cell proliferation by affecting pro-tumorigenic downstream targets, Runx2 and the PI3K/Akt signaling pathway (24). By contrast, silencing MACF1 in AML cells led to reduced proliferation and provided evidence of this spectraplakin as a therapeutic target for managing this type of leukemia (24). Consistent with these findings, MACF1 expression was also upregulated in serous ovarian cancer and correlated with shorter recurrence-free survival and overall survival (25), while in NSCLC cells, particularly in gefitinib-resistant cells, circ_MACF1 (a circular RNA form of MACF1) regulates drug sensitivity and cellular behavior through its interaction with miR-942-5p and TGFBR2 (26). This axis influences cell proliferation, migration, and invasion while promoting apoptosis and sensitivity to gefitinib, suggesting that targeting circ_MACF1 could overcome resistance to EGFR inhibitors such as gefitinib in NSCLC. Collectively, these investigations provide a premise for the role of MACF1 in the etiology and progression of central nervous system glial-derived tumors. It is also noteworthy that previous investigations of plakin family members, plectin and desmoplakin, have been described as biomarkers for glioblastomas (27-29).

5. MACF1 promotes glial cell transformation

Malignant brain tumors in the central nervous system are arguably the deadliest types of cancers diagnosed, with glioblastomas being the most common, with an average median survival of 12-14 months and a five-year survival rate of ~5% (30,31). A major contributing factor to the poor prognosis of these cancers is their complex genetic heterogeneity that underlies their pathological origin, evolution and therapeutic resistance. Identification of novel mediators of disease transformation, progression and therapeutic evasion are critical to advancing strategies for the clinical management and treatment of these cancers. It is widely established that the evolution of glioblastomas from astrocytes and neural progenitor stem cells are a consequence of genetic mutations, deletions and amplifications in phosphatase and tensin homolog, neurofibromin1, p53, epidermal growth factor receptor and platelet-derived growth factor receptor (32-35). Genetic alterations in these oncogenes and tumor suppressors that contribute to glioblastoma initiation and progression are supported by knockout and genetically engineered mice models (36,37).

Although aberrant genetic abnormalities of receptor tyrosine kinases, phosphatases and transcription factors have been attributed to glioblastoma development, cytoskeletal proteins such as nestin, vimentin and alpha-actinin have also been identified as contributors to the inception of these tumors based largely on expression analyses (38-40). The best characterized of these, nestin, an intermediate filament expressed in neural progenitor cells, has long been recognized as a contributing oncogenic element in glioblastomas. Experimentally, nestin positive neural stem cells have been demonstrated to give rise to gliomas in murine models when transduced with EGFRvIII (39). Paralleling expression patterns of nestin and the previously mentioned cytoskeletal proteins, Afghani *et al* (41), also observed that MACF1 expression was absent in normal brain tissue and low-grade gliomas (oligodendrogliomas and medulloblastomas) but displayed significant expression in glioblastomas, which have high recurrence and mortality rates. These data suggested that MACF1 is a potential oncoprotein and therapeutic target in high-grade astrocyte derived gliomas.

Despite the observation that MACF1 was expressed at high levels in glioblastomas and that negatively regulating its function impaired glioblastoma cell proliferation and migration, the role of this spectraplakin protein as a tumorigenic driver in cancer and glioblastomas specifically, has not been investigated. However, a preliminary assessment of MACF1 tumor transformation properties in normal astrocytes, one of the two cell types, along with neural progenitor stem cells, considered the cellular origins of glioblastomas was conducted to evaluate whether MACF1 perpetuates tumorigenic characteristics. To that end, unpublished data of MACF1

Table I. MACF1 genetic abnormalities. Genetic mutations and amplifications of MACF1 have been found in several solid cancers.

First author, year	Cancer type	Results	(Refs.)
Misquitta-Ali *et al*, 2011	Non-small cell lung cancer	Alternative transcript splicing	(17)
Arai *et al*, 2014	Renal cell carcinoma	Mutations	(18)
Chang *et al*, 2017	Endometrial cancer	Mutations	(19)
Tian *et al*, 2022	Breast cancer	Mutations	(20)
Cerami *et al*, 2012; Gao *et al*, 2013; de Bruijn *et al*, 2023	Glioblastomas	Mutations, amplifications	(21-23)

MACF1, microtubule actin crosslinking factor.

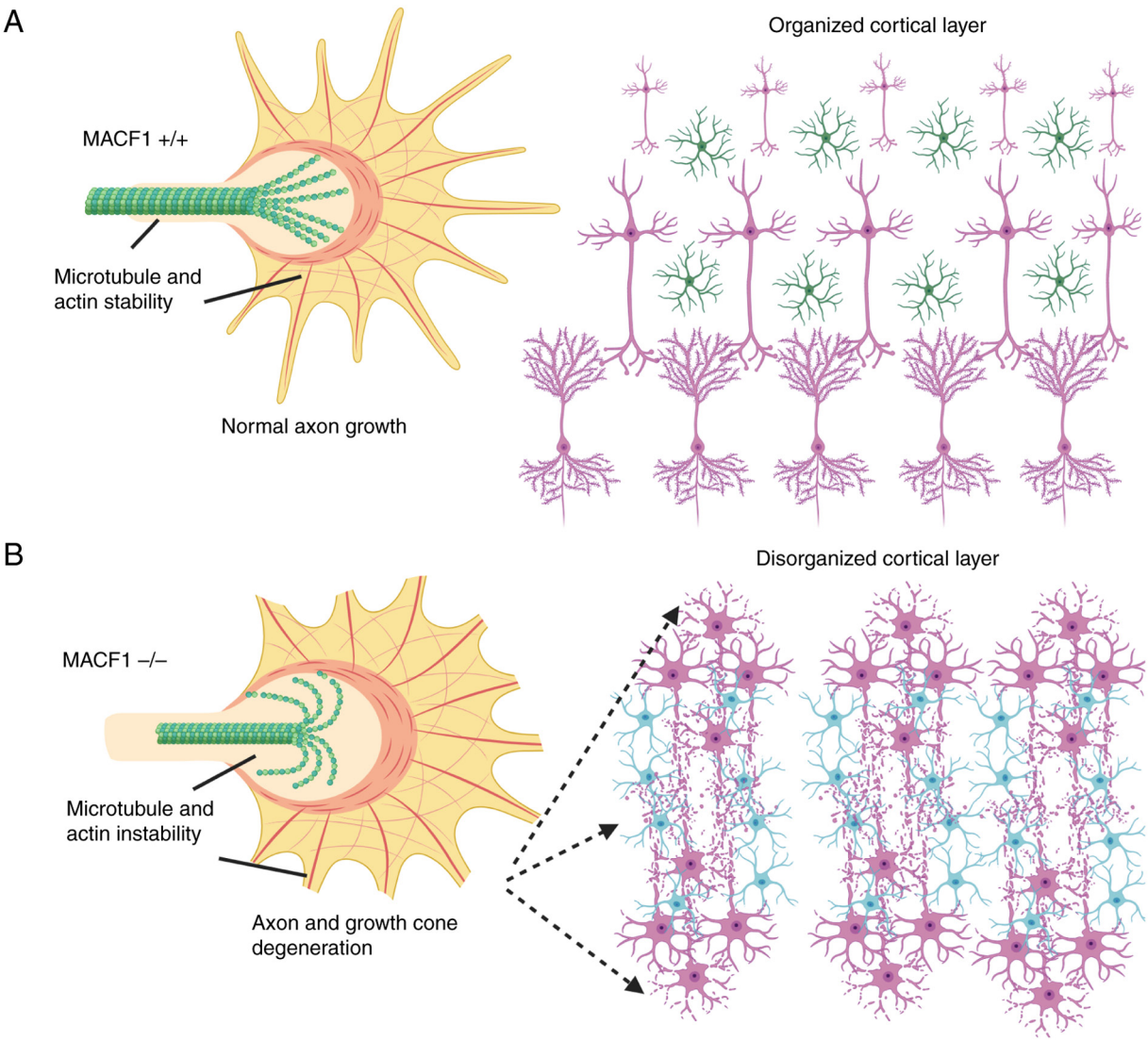

Figure 1. MACF1 supports axon growth, nervous system development and cortex organization. (A) Wild-type MACF1 maintains axon and growth cone extension via crosslinking stabilization of microtubules and actin filaments that supports cellular organization of cortical layers in the cerebral cortex of the brain. (B) Deletion of MACF1 disrupts crosslinking stabilization and interaction of microtubules and actin filaments leading to disorganization of cerebral cortex cortical layers. (purple-pyramidal neurons; green-stellate neurons). The figure was created using bioRender (https://www.biorender.com/). MACF1, microtubule actin crosslinking factor.

overexpression studies performed in normal astrocytes, previously demonstrated to express low MACF1 protein levels, displayed significant increases in cell viability and anchorage independent growth (42-44), indicators of the transformed

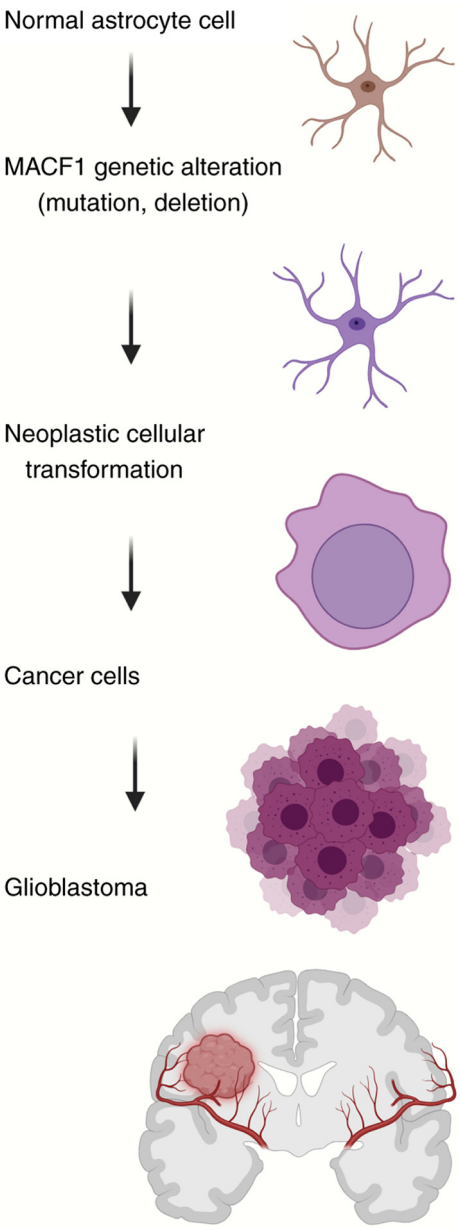

Figure 2. MACF1 promotes proliferative growth, transformation and cell migration. Schematic of MACF1 genetic alterations leading to astrocyte transformation and glioblastoma development. The figure was created using bioRender (https://www.biorender.com/). MACF1, microtubule actin cross-linking factor.

phenotype in normal astrocyte cells (Fig. 2). These cellular responses are consistent with the aforementioned oncogenic role of cytoskeletal nestin in glioblastoma formation.

In addition to primary tumor development, secondary glioblastomas and disease progression as manifested by tumor recurrence resulting from normal tissue invasion is a collateral oncogenic process, also derived from genetic abnormalities as aforementioned, that leads to poor disease management and high mortality rates. Further support of the pro-tumorigenic role of MACF1 in glioblastomas, specifically as it relates to disease recurrence, was also demonstrated in unpublished experimental studies (42-44), which showed that MACF1 overexpression increased astrocyte cell migration, a prerequisite cell behavior of metastatic invasion. Taken together, these cellular biological data (42-44) provide evidence that spectraplakin protein is causally involved in primary and secondary glioblastoma tumorigenesis and expands the notion that MACF1 contributes to tumor development due to mutations and alternative splicing events identified in endometrial cancer, renal cell carcinomas and lung cancers, respectively (17-19).

6. Wnt-MACF1-mTOR signaling

As previously discussed, early investigations have established that MACF1 plays a mechanistic role in Wnt-mediated signaling. Specifically, MACF1 downregulation was demonstrated to reduce nuclear β-catenin and transcriptional activation of Wnt responsive genes (5). More importantly, aberrant regulation of Wnt signaling is also known to contribute to tumor proliferation and migratory invasion in malignant brain tumors (45-48), providing a correlative association that the onco-tumorigenic impact of MACF1 is related to its interaction with the Wnt signaling pathway (Fig. 3), a well-characterized mechanistic mediator of tumor cell survival and proliferation. As it pertains to central nervous system-derived cancers such as glioblastomas, the most direct evidence for a mechanistic role of MACF1 intracellular signaling in these tumors was provided by studies from Afghani *et al* (41), which showed that downregulation of MACF1 reduced Axin and phospho-β-catenin protein levels in glioblastoma cells (41). Furthermore, studies by Bonner *et al* (49) in irradiated glioblastoma cells revealed that genetic silencing of MACF1 reduced the expression of ribosomal protein s6, a downstream effector target of mTORC1, and consequently sensitized these astrocyte-derived cancer cells to radiation (49). This is particularly significant given the established roles of both the Wnt signaling pathway and PI3K-Akt-mTOR signaling axis as contributors in glioblastoma progression (Fig. 3), invasion and therapeutic resistance (50-53).

More importantly, when MACF1 is genetically silenced, Wnt signaling mediators and mTOR effector proteins are functionally impaired (Fig. 3). Given the breadth of these pro-tumorigenic signaling pathways in several cancers and glioblastomas in particular, a number of investigations have examined small molecule inhibitors targeting these pathways in glioblastomas (54,55). Although signaling functions of MACF1 have been predominantly associated with positive regulation of the Wnt signaling pathway, additional studies in AML, a blood and bone marrow cancer have provided additional insights on intracellular signaling roles of MACF1. Specifically, silencing MACF1 function in AML cells was found to reduce runt-related transcription factor Runx2 expression and inactivated phosphatidyl inositol 3 kinase signaling (24). Furthermore, co-immunoprecipitation experiments in AML cells provided evidence that MACF1 interacts with leucine-rich repeat-containing protein 1 (56), while osteogenesis studies revealed that MACF1 positively regulates the TCF4/miR-335-5p signaling pathway, consequently influencing bone formation (57). Collectively, these studies provide evidence that extend the mechanistic function of MACF1 beyond Wnt pathway.

Collectively, this suggests that MACF1 is a contributor to treatment resistance of glioblastomas by acting as a signaling mediator in divergent intracellular signaling cascades.

Table II. Therapeutic targeting of MACF1. Singular negative genetic inhibitory targeting of MACF1 and combinatorial silencing with clinical therapeutic treatment strategies promote anti-tumorigenic responses.

First author, year	Cancer type	Results	(Refs.)
Afghani *et al*, 2017	Glioblastomas	Inhibition of MACF1 impaired glioblastoma progression in patient derived xenograft cell lines	(41)
Kaur *et al*, 2013	Glioblastomas	Silencing MACF1sensitized glioblastoma cells to DNA damaging agents	(48)
Wang *et al*, 2020	Melanoma	Targeted MACF1 inhibition prevents metastasis	(58)

MACF1, microtubule actin crosslinking factor.

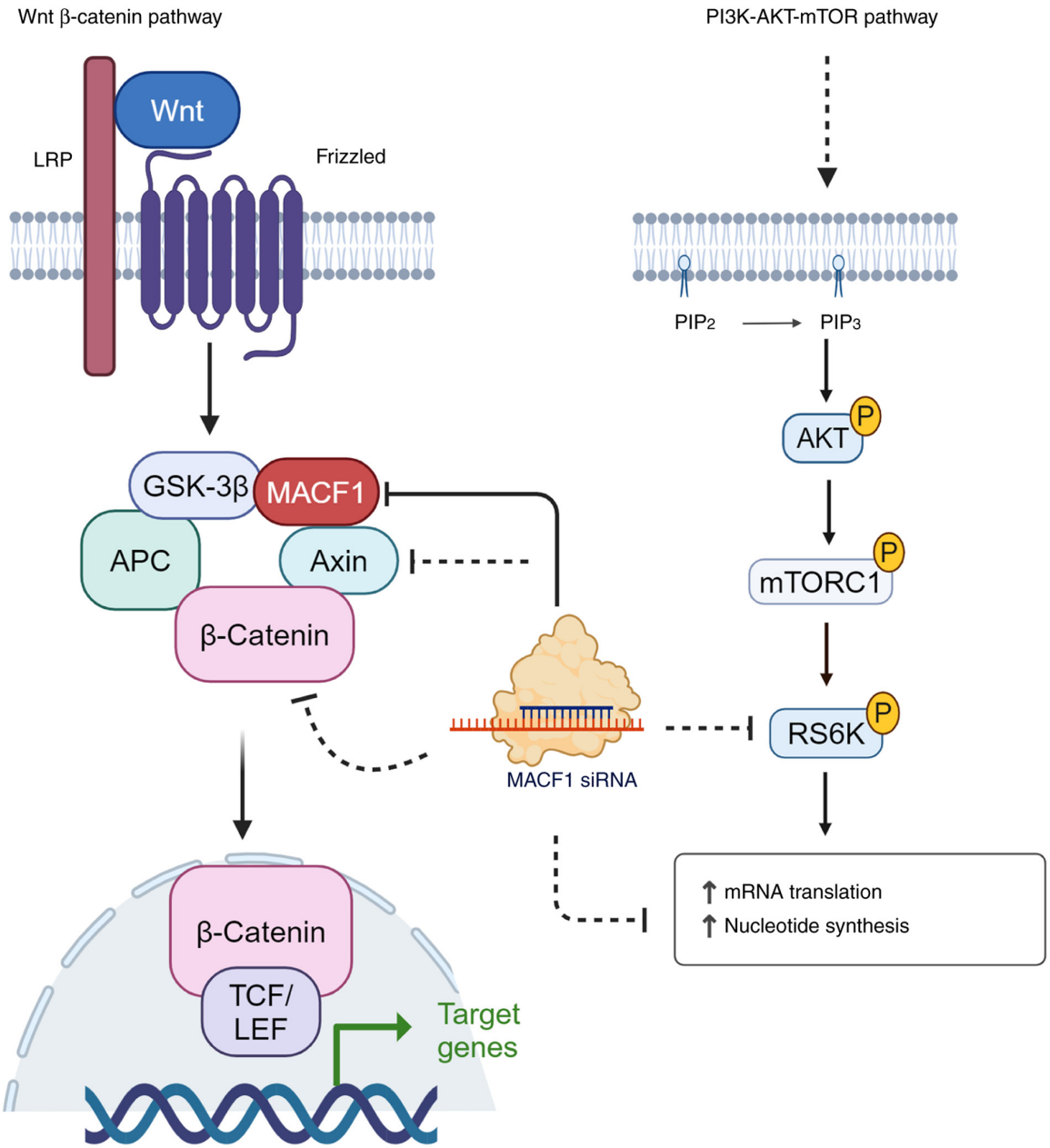

Figure 3. MACF1 is an effector mediator of Wnt and mTOR signaling. MACF1 has been described as a component of the Wnt signaling complex (GSK3β, axin, APC and beta-catenin) and assists with the translocation of these signaling mediators to the LRP receptor and activation of this signaling cascade. Subsequently, beta-catenin is released to facilitate its transcriptional activation function via interaction with TCF/LCF. Suppression of MACF1 has been demonstrated to reduce axin, beta-catenin,and s6-ribosomal protein expression levels and attributed to reducing glioblastoma cell proliferation and migration. The figure was created using bioRender (https://www.biorender.com/). MACF1, microtubule actin crosslinking factor; GSK-3, glycogen synthase kinase-3; APC, adenomatous polyposis coli; LRP, low-density lipoprotein receptor-related protein; TCF/LEF, T cell factor, lymphocyte enhancer factor-1.

However, despite the absence of MACF1 in normal human astrocytes and high expression levels in high-grade astrocytomas (19), as well as the onco-transformation properties of this spectraplakin protein in glial cells, small pharmacological inhibitory molecules targeting this cytoskeletal cross-linker have not yet been identified. Because MACF1 crosslinks microtubules and actin-filaments have prevalent biophysical roles in mitotic tumor cell division and migration, developing pharmacological agents that impair MACF1 provides a singular therapeutic target that disrupts tumor cell behaviors that lead to glioblastoma progression and therapeutic evasion.

7. MACF1 as a cancer therapeutic target

Although the aforementioned experimental investigations provided evidence that genetic alterations of MACF1 were prevalent in several cancers, the role of MACF1 in cancer cell biology and as a neoplastic target had remained unexamined. To that end, studies by Afghani *et al* (41) and Bonner *et al* (49), were the first to investigate MACF1 as a cancer therapeutic target and demonstrated that inhibiting the functional expression of MACF1 alone and in combination with radiation and the clinically used DNA damaging agent, temozolomide, had antitumorigenic effects on glioblastomas (Table II), astrocyte-derived central nervous system tumors (57,58). Additionally, findings in glioblastomas along with those by Wang *et al* (58), revealed that negative regulation of MACF1 impaired glioblastoma cell migration and melanoma metastasis by decreasing the epithelial to mesenchymal transition (Table II) and thus provided evidence of the functional role of MACF1 in metastatic invasion (57,58).

To date, therapeutic agents that directly target MACF1 are not yet available. Given MACF1's role in cellular processes such as intracellular signaling and cell migration, which are often dysregulated in cancer, warrants the development and evaluation of anticancer drugs that target this cytoskeletal protein. Further rationale to support the feasibility of developing such drugs includes the role of MACF1 in cytoskeleton dynamics for maintaining cell shape, polarity and motility, which are important characteristics of cancer cell invasion and metastasis. It is also noteworthy that because of MACF1's role in Wnt signaling, which is often dysregulated in several cancers, inhibiting the function of this plakin protein represents a novel neoplastic target. However, a caveat to the druggability of MACF1 is its large size of ~600 kDa and the numerous structural domains that it contains. Additionally, engineering molecules that target such a large protein as well as bioavailability challenges posed by the blood brain barrier to access astrocytic glioblastomas, provide unique challenges.

8. Conclusion

The development of cancers are a consequence of combinatorial genetic factors and their expressed products that underlie intra- and inter-tumor heterogeneity. MACF1 is a potential novel tumorigenic protein that may contribute to the clinical etiology and progression of astrocyte-derived cancers such as glioblastomas that reside in the central nervous system, specifically the human brain, by perpetuating glial cell proliferation and invasion. The investigation of MACF1 in cancer biology, specifically glioblastomas, as a novel oncoprotein that contributes to the etiology and progression of these central nervous system-derived tumors warrants continued investigation. To further establish the pro-tumorigenic role of MACF1 in the evolution of brain tumors, it is essential to perform oncogenic analyses of MACF1 in more translational applicable model systems with diverse genetic backgrounds, such as orthotopic patient-derived xenograft brain tumor models. The utility of these model systems would provide further insight and perspective of MACF1 in the context of oncogenes that drive a plethora of intracellular signaling mechanisms and regulate tumorigenic cell behaviors such as the PI3K signaling pathway, one of the most prevalent in the perpetuation of tumorigenesis, and in the absence of tumor suppressors during oncogenic transformation. Additionally, pursuing the development of chemotherapeutic agents that target MACF1 will broaden clinical approaches beyond therapeutic agents such as vinca alkaloids that inhibit microtubules used to treat this disease.

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KB and QQ conceptualized and developed the review framework and wrote the manuscript. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hu L, Xiao Y, Xiong Z, Zhao F, Yin C, Zhang Y, Su P, Li D, Chen Z, Ma X, *et al*: MACF1, versatility in tissue-specific function and in human disease. Semin Cell Dev Biol 69: 3-8, 2017.
2. Applewhite DA, Grode KD, Duncan MC and Rogers SL: The actin-microtubule cross-linking activity of Drosophila Short stop is regulated by intramolecular inhibition. Mol Biol Cell 24: 2885-2893, 2013.
3. Goryunov D and Liem RK: Microtubule-Actin cross-linking factor 1: Domains, interaction partners, and tissue-specific functions. Methods Enzymol 569: 331-353, 2016.

4. Cusseddu R, Robert A and Côté JF: Strength through unity: The power of the mega-scaffold MACF1. Front Cell Dev Biol 9: 641727, 2021.
5. Yin C, Zhang Y, Hu L, Tian Y, Chen Z, Li D, Zhao F, Su P, Ma X, Zhang G, *et al*: Mechanical unloading reduces microtubule actin crosslinking factor 1 expression to inhibit β-catenin signaling and osteoblast proliferation. J Cell Physiol 233: 5405-5419, 2018.
6. Bouameur JE, Favre B and Borradori L: Plakins, a versatile family of cytolinkers: Roles in skin integrity and in human diseases. J Invest Dermatol 134: 885-894, 2014.
7. Hu L, Su P, Li R, Yin C, Zhang Y, Shang P, Yang T and Qian A: Isoforms, structures, and functions of versatile spectraplakin MACF1. BMB Rep 49: 37-44, 2016.
8. Quick QA: Microtubule-Actin crosslinking factor 1 and plakins as therapeutic drug targets. Int J Mol Sci 19: 368, 2018.
9. Goryunov D, He CZ, Lin CS, Leung CL and Liem RK: Nervous-tissue-specific elimination of microtubule-actin cross-linking factor 1a results in multiple developmental defects in the mouse brain. Mol Cell Neurosci 44: 1-14, 2010.
10. Ka M, Moffat JJ and Kim WY: MACF1 controls migration and positioning of cortical GABAergic interneurons in mice. Cereb Cortex 27: 5525-5538, 2017.
11. Qu Y, Alves-Silva J, Gupta K, Hahn I, Parkin J, Sánchez-Soriano N and Prokop A: Re-evaluating the actin-dependence of spectraplakin functions during axon growth and maintenance. Dev Neurobiol 82: 288-307, 2022.
12. Alves-Silva J, Sánchez-Soriano N, Beaven R, Klein M, Parkin J, Millard TH, Bellen HJ, Venken KJ, Ballestrem C, Kammerer RA and Prokop A: Spectraplakins promote microtubule-mediated axonal growth by functioning as structural microtubule-associated proteins and EB1-dependent +TIPs (tip interacting proteins). J Neurosci 32: 9143-9158, 2012.
13. Ka M and Kim WY: Microtubule-Actin crosslinking factor 1 is required for dendritic arborization and axon outgrowth in the developing brain. Mol Neurobiol 53: 6018-6032, 2016.
14. Ka M, Jung EM, Mueller U and Kim WY: MACF1 regulates the migration of pyramidal neurons via microtubule dynamics and GSK-3 signaling. Dev Biol 395: 4-18, 2014.
15. Moffat JJ, Ka M, Jung EM, Smith AL and Kim WY: The role of MACF1 in nervous system development and maintenance. Semin Cell Dev Biol 69: 9-17, 2017.
16. Dobyns WB, Aldinger KA, Ishak GE, Mirzaa GM, Timms AE, Grout ME, Dremmen MHG, Schot R, Vandervore L, van Slegtenhorst MA, *et al*: MACF1 mutations encoding highly conserved zinc-binding residues of the GAR domain cause defects in neuronal migration and axon guidance. Am J Hum Genet 103: 1009-1021, 2018.
17. Misquitta-Ali CM, Cheng E, O'Hanlon D, Liu N, McGlade CJ, Tsao MS and Blencowe BJ: Global profiling and molecular characterization of alternative splicing events misregulated in lung cancer. Mol Cell Biol 31: 138-150, 2011.
18. Arai E, Sakamoto H, Ichikawa H, Totsuka H, Chiku S, Gotoh M, Mori T, Nakatani T, Ohnami S, Nakagawa T, *et al*: Multilayer-omics analysis of renal cell carcinoma, including the whole exome, methylome and transcriptome. Int J Cancer 135: 1330-1342, 2014.
19. Chang YS, Huang HD, Yeh KT and Chang JG: Identification of novel mutations in endometrial cancer patients by whole-exome sequencing. Int J Oncol 50: 1778-1784, 2017.
20. Tian Y, Zhu K, Li Y, Ren Z and Wang J: MACF1 mutations predict poor prognosis: A novel potential therapeutic target for breast cancer. Am J Transl Res 14: 7670-7688, 2022.
21. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, *et al*: The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. Cancer Discov 2: 401-404, 2012.
22. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, *et al*: Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 6: pl1, 2013.
23. de Bruijn I, Kundra R, Mastrogiacomo B, Tran TN, Sikina L, Mazor T, Li X, Ochoa A, Zhao G, Lai B, *et al*: Analysis and visualization of longitudinal genomic and clinical data from the AACR project GENIE biopharma collaborative in cBioPortal. Cancer Res 83: 3861-3867, 2023.
24. Wang P, Zhang J, Zhang H and Zhang F: The role of MACF1 on acute myeloid leukemia cell proliferation is involved in Runx2-targeted PI3K/Akt signaling. Mol Cell Biochem 478: 433-441, 2023.
25. Liu L, Hu K, Zeng Z, Xu C, Lv J, Lin Z and Wen B: Expression and clinical significance of microtubule-actin cross-linking factor 1 in serous ovarian cancer. Recent Pat Anticancer Drug Discov 16: 66-72, 2021.
26. Fan D, Yang Y and Zhang W: A novel circ_MACF1/miR-942-5p/TGFBR2 axis regulates the functional behaviors and drug sensitivity in gefitinib-resistant non-small cell lung cancer cells. BMC Pulm Med 22: 27, 2022.
27. Žugec M, Furlani B, Castañon MJ, Rituper B, Fischer I, Broggi G, Caltabiano R, Barbagallo GMV, Di Rosa M, Tibullo D, *et al*: Plectin plays a role in the migration and volume regulation of astrocytes: A potential biomarker of glioblastoma. J Biomed Sci 31: 14, 2024.
28. Kubelt C, Hattermann K, Sebens S, Mehdorn HM and Held-Feindt J: Epithelial-to-mesenchymal transition in paired human primary and recurrent glioblastomas. Int J Oncol 46: 2515-2525, 2015.
29. Žugec M, Furlani B, Castañon MJ, Rituper B, Fischer I, Broggi G, Caltabiano R, Barbagallo GMV, Di Rosa M, Tibullo D, *et al*: Plectin plays a role in the migration and volume regulation of astrocytes: A potential biomarker of glioblastoma. J Biomed Sci 31: 14, 2024.
30. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol 21 (Suppl 5): v1-v100, 2019.
31. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. Neuro Oncol 25 (12 Suppl 2): iv1-iv99, 2023.
32. Zhang P, Xia Q, Liu L, Li S and Dong L: Current opinion on molecular characterization for GBM classification in guiding clinical diagnosis, prognosis, and therapy. Front Mol Biosci 7: 562798, 2020.
33. Georgescu MM: Translation into clinical practice of the G1-g7 molecular subgroup classification of glioblastoma: Comprehensive demographic and molecular pathway profiling. Cancers (Basel) 16: 361, 2024.
34. Lazzarini E, Silvestris DA, Benvenuto G, Osti D, Fattore L, Paterra R, Finocchiaro G, Malatesta P, Daga A, Gallotti AL, *et al*: Genome-wide profiling of patient-derived glioblastoma stem-like cells reveals recurrent genetic and transcriptomic signatures associated with brain tumors. J Neurooncol 163: 47-59, 2023.
35. Ludwig K and Kornblum HI: Molecular markers in glioma. J Neurooncol 134: 505-512, 2017.
36. Robertson FL, Marqués-Torrejón MA, Morrison GM and Pollard SM: Experimental models and tools to tackle glioblastoma. Dis Model Mech 12: dmm040386, 2019.
37. Miyai M, Tomita H, Soeda A, Yano H, Iwama T and Hara A: Current trends in mouse models of glioblastoma. J Neurooncol 135: 423-432, 2017.
38. Ciechomska IA, Wojnicki K, Wojtas B, Szadkowska P, Poleszak K, Kaza B, Jaskula K, Dawidczyk W, Czepko R, Banach M, *et al*: Exploring novel therapeutic opportunities for glioblastoma using patient-derived cell cultures. Cancers (Basel) 15: 1562, 2023.
39. Chen Z, Herting CJ, Ross JL, Gabanic B, Vallcorba MP, Szulzewsky F, Wojciechowicz ML, Cimino PJ, Ezhilarasan R, Sulman EP, *et al*: Genetic driver mutations introduced in identical cell-of-origin in murine glioblastoma reveal distinct immune landscapes but similar response to checkpoint blockade. Glia 68: 2148-2166, 2020.
40. Quick Q and Skalli O: Alpha-actinin 1 and alpha-actinin 4: Contrasting roles in the survival, motility, and RhoA signaling of astrocytoma cells. Exp Cell Res 316: 1137-1147, 2010.
41. Afghani N, Mehta T, Wang J, Tang N, Skalli O and Quick QA: Microtubule actin cross-linking factor 1, a novel target in glioblastoma. Int J Oncol 50: 310-316, 2017.
42. Quick Q and Bonner K: Immunoblot, cell viability, and transformation bar graphs. 2023 https://doi.org/10.6084/m9.figshare.24391903 (unpublished data).
43. Quick Q and Bonner K: Cell motility bar graph and images. 2023 https://doi.org/10.6084/m9.figshare.24392593 (unpublished data)
44. Quick Q and Bonner K: Methods. 2023 https://doi.org/10.6084/m9.figshare.24393145 (unpublished data).
45. Li GF, Cheng YY, Li BJ, Zhang C, Zhang XX, Su J, Wang C, Chang L, Zhang DZ, Tan CL and Wang N: miR-375 inhibits the proliferation and invasion of glioblastoma by regulating Wnt5a. Neoplasma 66: 350-356, 2019.

46. Precilla DS, Kuduvalli SS, Purushothaman M, Marimuthu P, Muralidharan AR and Anitha TS: Wnt/β-catenin antagonists: Exploring new avenues to trigger old drugs in alleviating glioblastoma multiforme. Curr Mol Pharmacol 15: 338-360, 2022.
47. De Robertis A, Valensin S, Rossi M, Tunici P, Verani M, De Rosa A, Giordano C, Varrone M, Nencini A, Pratelli C, *et al*: Identification and characterization of a small-molecule inhibitor of Wnt signaling in glioblastoma cells. Mol Cancer Ther 12: 1180-1189, 2013.
48. Kaur N, Chettiar S, Rathod S, Rath P, Muzumdar D, Shaikh ML and Shiras A: Wnt3a mediated activation of Wnt/β-catenin signaling promotes tumor progression in glioblastoma. Mol Cell Neurosci 54: 44-57, 2013.
49. Bonner K, Borlay D, Kutten O and Quick QA: Inhibition of the spectraplakin protein microtubule actin crosslinking factor 1 sensitizes glioblastomas to radiation. Brain Tumor Res Treat 8: 43-52, 2020.
50. Langhans J, Schneele L, Trenkler N, von Bandemer H, Nonnenmacher L, Karpel-Massler G, Siegelin MD, Zhou S, Halatsch ME, Debatin KM and Westhoff MA: The effects of PI3K-mediated signaling on glioblastoma cell behaviour. Oncogenesis 6: 398, 2017.
51. Li X, Wu C, Chen N, Gu H, Yen A, Cao L, Wang E and Wang L: PI3K/Akt/mTOR signaling pathway and targeted therapy for glioblastoma. Oncotarget 7: 33440-33450, 2016.
52. Suwala AK, Koch K, Rios DH, Aretz P, Uhlmann C, Ogorek I, Felsberg J, Reifenberger G, Köhrer K, Deenen R, *et al*: Inhibition of Wnt/beta-catenin signaling downregulates expression of aldehyde dehydrogenase isoform 3A1 (ALDH3A1) to reduce resistance against temozolomide in glioblastoma in vitro. Oncotarget 9: 22703-22716, 2018.
53. Von Achenbach C, Weller M, Kaulich K, Gramatzki D, Zacher A, Fabbro D, Reifenberger G and Szabó E: Synergistic growth inhibition mediated by dual PI3K/mTOR pathway targeting and genetic or direct pharmacological AKT inhibition in human glioblastoma models. J Neurochem 153: 510-524, 2020.
54. Salphati L, Alicke B, Heffron TP, Shahidi-Latham S, Nishimura M, Cao T, Carano RA, Cheong J, Greve J, Koeppen H, *et al*: Brain distribution and efficacy of the brain penetrant PI3K inhibitor GDC-0084 in orthotopic mouse models of human glioblastoma. Drug Metab Dispos 44: 1881-1889, 2016.
55. Guo T, Wu C, Zhang J, Yu J, Li G, Jiang H, Zhang X, Yu R and Liu X: Dual blockade of EGFR and PI3K signaling pathways offers a therapeutic strategy for glioblastoma. Cell Commun Signal 21: 363, 2023.
56. Wang Y, Tong H, Wang J, Hu L and Huang Z: LRRC1 knockdown downregulates MACF1 to inhibit the malignant progression of acute myeloid leukemia by inactivating β-catenin/c-Myc signaling. J Mol Histol 55: 37-50, 2024.
57. Zhang K, Qiu W, Li H, Li J, Wang P, Chen Z, Lin X and Qian A: MACF1 overexpression in BMSCs alleviates senile osteoporosis in mice through TCF4/miR-335-5p signaling pathway. J Orthop Translat 39: 177-190, 2023.
58. Wang X, Jian X, Dou J, Wei Z and Zhao F: Decreasing microtubule actin cross-linking factor 1 inhibits melanoma metastasis by decreasing epithelial to mesenchymal transition. Cancer Manag Res 12: 663-673, 2020.