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Microtubule actin cross-linking factor 1, a novel potential target in cancer

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Cancer is a polygenic disease characterized by uncontrolled growth of normal body cells, deregulation of the cell cycle as well as resistance to apoptosis. The spectraplakin protein microtubule actin cross-linking factor 1 (MACF1) plays an essential function in various cellular processes, including cell proliferation, migration, signaling transduction and embryo development. MACF1 is also involved in processes such as metastatic invasion in which cytoskeleton organization is a critical element that contributes to tumor progression in various human cancers. Aberrant expression of MACF1 initiates the tumor cell proliferation, and migration and metastasis in numerous cancers, such as breast cancer, colon cancer, lung cancer and glioblastoma. In this review, we summarized the current knowledge of MACF1 and its critical role in different human cancers. This will be helpful for researchers to investigate the novel functional role of MACF1 in human cancers and as a potential target to enhance the efficacy of therapeutic treatment modalities.

A cytoskeleton is a highly organized network of filaments, which is composed of microfilaments (F-actin), microtubules (MT) and intermediate filaments (IF). Recently, various studies have suggested that particular crosslinking proteins synchronize and act together with the diverse functions of cytoskeleton.(1) Cytoskeletal reorganization is a matter of critical importance in the development of the phenotype of invasive cancer cells. Through their roles in cell mechanics, intracellular trafficking and signaling, cytoskeleton proteins take part in all central events leading to tumor cell migration.(2)

Microtubule actin cross-linking factor (MACF1), also known as actin crosslinking family 7 (ACF7), macrophin and trabeculin-α, is a widely expressed critical spectraplakin.(3) MACF1 plays an essential role in coordination of cell migration, cell proliferation and maintenance of tissue integrity in the presence of F-actin and microtubules. Moreover, MACF1 mediates signal transduction, which is essential for embryo development.(4) MACF1 also plays a critical role in brain development through regulating the migration as well as differentiation of pyramidal neurons in the mammalian brain.(5) The role of MACF1 in signaling pathway suggests that MACF1 is involved in cancer development.

In this review, based on the molecular characteristics of MACF1, we summarized the recent advances of its physiological and pathological roles in various cancers, such as brain tumor, breast cancer, lung cancer and colon cancer. This article will inform the future research and help researchers to further study the role of MACF1 in cancer progression.

Feature of Microtubule Actin Cross-Linking Factor 1

Gene, structure and isoform of microtubule actin cross-linking factor 1. Microtubule actin cross-linking factor 1, belonging to the cytoskeletal linker protein family with a molecular weight of approximately 600 kD, was first discovered by Byers *et al.*,

in the effort to screen for additional members of the actin crosslinker superfamily.[4] Consequently, murine ACF7 was fully characterized[6] and its cDNA encoding a protein with a molecular weight 608-kD was cloned.[7] The name of ACF7 became "microtubule actin cross-linking factor 1" (MACF1) because ACF7 is closely associated with actin and MT. In addition, human cDNA was cloned independently by two groups and named macrophin and trabeculin-α, respectively.[8,9]

MACF1 is encoded by *MACF1* gene, which is positioned on human chromosomes 1p34.3 and mouse chromosome 4.[4] Human *MACF1* constitutes at least 110 exons and spans over 402 kb. Genomic organization of human *MACF1* confirms that *MACF1* and *ACF7* genes are identical.[10] *MACF1* gene is a mixture of genes that shares the characteristics of both plakin and spectrins/dystrophins.[7,10] The gene sequence of *MACF1* is identical to both plakin and spectrin. *MACF1* constitutes multiple domains, such as ABD and plakin domain at the N-terminus and microtubules binding domain (MTBD) at the C-terminus. The fusion structure of *MACF1* reveals that it is correlated with the short spot (shot) gene in *Drosophila* and the vab-10 gene in *Caenorhabditis elegans*.

Microtubule actin cross-linking factor 1 potentially differs from other members of the plakin family due to a unique rod domain consisting of spectrin repeats (SR), which make up the usual plakin domain. Growth arrest-specific protein 2 related (GAR) domain located at the C-terminus binds to and stabilizes MT.[11] The C-terminal repeats of MACF1 posses complex with end-binding protein 1 (EB1) .[12]

Alternative splicing and promoter usage in MACF1 results in various isoforms like dystonin/BPAG1. The first three MACF1/ACF7 isoforms that constitute identical 3′ and 5′ sequences have been identified by Bernier *et al.*[13] ACF-1 and ACF-2 isoforms have similar actin-binding domains but slightly differ in their 5′ UTR. The third isoform of MACF1/ACF7 consists of common 5′ UTR and the longer N-terminal domain. Consequently, Gong *et al.*[10] cloned the fourth isoform of MACF1/ACF7, called MACF1-4, that lacks ABD but contains plakin repeats at the N-terminus. Moreover, another alternative splicing in MACF1 results in a gigantic protein with molecular weight 800 kD, identified and named as MACF1b.[14] To distinguish it, the original isoform is renamed as MACF1a. Based on the differences of N-terminal domain, the name of first three isoforms (ACF7-1, ACF7-2 and ACF7-3) are modified as MACF1a1, MACF1a2 and MACF1a3.[14] Goryunov *et al.*[15] discovered a novel isoform, MACF1c, while studying the role of MACF1 in the nervous system.

MACF1c is indistinguishable from MACF1a because it lacks ABD at N-terminal. Sun *et al.*[9] determined that the sequence similarity of amino acids encoding a polypeptide between human MACF1 and MACF2 was 68%. Transcripts of MACF1 and MACF2 have different chromosomal location and nucleotide sequence based on the UniGene database. Moreover, human MACF1 and MACF2 are two discrete protein products of two diverse genes.[9] Hence, approximately six isoforms of MACF1, including MACF1a1, MACF1a2, MACF1a3, MACF1-4, MACF1b and MACF1c, have been identified (Table 1).[3]

Tissue distribution of microtubule actin cross-linking factor 1. Microtubule actin cross-linking factor 1 has been reported to be broadly expressed in different tissues. Initially Bernier *et al.* found that the transcripts of MACF1 were widely present in postnatal mouse tissues, such as skin, skeletal muscle, heart, lung, liver, stomach, kidney, spleen, brain and spinal cord tissues. The expression of MACF1 isoforms occurred from high to lower level in various tissues, including lung, brain, spinal cord, cardiac/skeletal muscle and skin tissues.[6] Bernier *et al.*[13] also verified that the transcripts of MACF1 were expressed in muscle, neural and lung tissues during embryonic development. Through IHC (MACF1 antibody, abcam, 1:200), we recently detected that MACF1 broadly expressed in mouse and human bone tissues (Fig. 1a,b).

Table 1. Similarities and differences of MACF1 isoforms

Isoforms	Similarities	Differences	Tissue distribution
MACF1a1	Plakin, spectrin repeats, EF hand and GAR	N-terminal ABD (CH1 and CH2), unique 5′ UTR	Skin, kidney and stomach
MACF1a2		N-terminal (CH1 and CH2) different 5′ UTR as compared with MACF1a1	Brain, spinal cord, lung, kidney, heart and skeletal muscles
MACF1a3		Unique 5′ UTR region, longer N-terminal sequence	Brain, spinal cords, skin, lung and kidney
MACF1-4		Plectin repeats, lack of N-terminal ABD (CH)	Heart, lung, placenta and pituitary gland
MACF1b		ABD (CH1, CH2), Containing extra plakin repeat	Lung, brain, spinal cord, cardiac/skeletal muscle and skin
MACF1c		Lack of N-terminal ABD (CH)	Broadly expressed in nervous system

MACF1, microtubule actin cross-linking factor 1.

The isoforms of MACF1 have been shown to distribute in various tissues.[8,9,12] MACF1a1 was highly expressed in skin, kidney and stomach tissues. Moreover, the mRNA of MACF1a1 was identified in embryos 7.5–10.5 days.[4] The expression of MACF1a2 was observed in brain, spinal cord, lung, kidney, heart and skeletal muscles tissues, while its mRNA was detected in embryos at day 10.5.[4] MACF1a3 was highly expressed in brain and spinal cord tissues, and was moderately expressed in the skin, lung and kidney tissues.[13] MACF1b transcript was present in all tissues, as well as throughout the development stage for mouse embryos.[14] MACF1 transcript was broadly distributed in human tissues, such as skeletal muscle, heart and pancreas, and in glands, such as salivary, mammary, adrenal, thyroid and pituitary glands.[8,9,12] MACF1a2 isoform was also expressed in the brain, heart, liver, pancreas, lung and kidney tissues,[8] while MACF1-4 isoform was strongly expressed in the heart, lung, placenta and pituitary gland tissues (Table 1).[10]

Physiological Role of Microtubule Actin Cross-Linking Factor 1

Role of microtubule actin cross-linking factor 1 in cell migration. Microtubule actin cross-linking factor 1 and other plakins are classified as members of the multifunctional cytoskeletal protein family and play crucial roles in cell proliferation, migration, cell signaling, tissue veracity and preservation, as

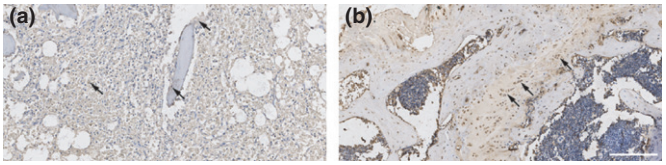

Fig. 1. Microtubule actin cross-linking factor 1 (MACF1) immunohistochemical staining in mouse (a) and human (b) bone tissues. (a) 4-month-old male C57BL6 mouse femur and (b) 75-year-old male femur trabecula bone. Scale bar: 200 μm.

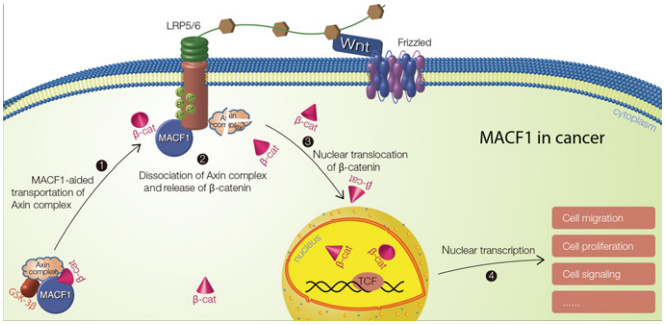

Fig. 2. Microtubule actin cross-linking factor 1 (MACF1) is involved in Wnt/β-catenin signal pathways and associated with the Axin complex, including Axin, β-catenin, GSK-3β and APC to regulate cell function.

well as axonal expansion.[16,17] The cellular movement is highly complicated and involves organized processes that focus on both actin and its binding proteins. Feng *et al.*[18] show that MACF1, HMGB1 and annexinA2 proteins were upregulated in HepG2 cells treated with hepatitis B virus × protein (HBx). The upregulation of these proteins were mainly involved in cell migration and cytoskeleton association.

However, lack of ACF7/MACF1 or aberration in GSK3β activity results in perturbations in cell migration and proliferation of the noticeable bulge stem cells/progeny produced from hair follicles.[19] Wu *et al.*[19] show that ACF7 deficiency led to a reduction in the activity of cell migration. Interestingly, deficiency of ACF7/MACF1 disturbed the targeting of the microtubules along with F-actin to focal adhesions (FA), stabilized FA-actin frameworks and inhibited epidermal migration. The essential mechanism indicates that both F-actin binding domains and an inherent actin-regulated ATPase domain in ACF7/MACF1 are critical for the direction of cell migration. In the case of stem cells, MACF1 also sustains directional cell migration, which is responsible for establishing homeostasis and wound healing.[19] Moreover, conditional aberration of ACF7/MACF1 in follicular stem cells results in the disturbance of MT networks, cell polarity, efficiency and insistency of migration.[20] MACF1 also occurs in neurons to regulate cell migration along with various partners such as ErbB2 receptor and ELMO.[21,22]

Role of microtubule actin cross-linking factor 1 in cell proliferation. Microtubule actin cross-linking factor 1 is associated with the regulation of cell differentiation and proliferation. Our previous studies showed that MACF1 knockdown distorted the cell morphology, discontinued the allocation of MT and F-actin, restrained cell proliferation and inhibited the cell cycles at S phase.[23,24] Wu *et al.* conclude that a lack of ACF7 could not completely reduce cell proliferation or mitosis deficiency in epidermal or endodermal cells.[19,20,25] MACF1 plays a crucial role both in cell cycle and Wnt receptor signaling transduction.[26] The calponin homology (CH) domain of MACF1 plays an essential role in regulating the activity of actin cytoskeleton, which maintains cell shape and movement of the intracellular molecule.[27]

Role of microtubule actin cross-linking factor 1 in cell signaling. Microtubule actin cross-linking factor 1 has been reported to be involved in Wnt/β-catenin signal pathways and has a close association with the Axin complex, including Axin, β-catenin, GSK-3β and APC (Fig. 2).[26] Chen *et al.*[26] found that MACF1 plays crucial roles in the movement of the Axin complex to cell membrane, where interaction of MACF1 and co-receptor LRP5/6 occurs. MACF1 deficiency restrains the translocation of the Axin complex, which results in the disruption of the Wnt-signaling pathways. MACF1 exhibits a phosphorylation site for GSK-3β[19] and also regulates GSK-3 signaling pathway.[28,29] These conclusions confirm the role of MACF1 in cell signaling and vesicular transport. In the case of Axonal vesicle transportation, MACF1 plays a critical role in translocation of vesicles between the *Trans*-Golgi network and Kif5A. Loss of MACF1 function results in incompetency of vesicles that circulates to the cell periphery.[30] During initial step of autophagy, the relationship of MACF1 with *Trans*-Golgi protein p230 stimulates the movement of mAtg9 between the *Trans*-Golgi network and peripheral phagophores.[31]

Pathological Characteristic of Microtubule Actin Cross-Linking Factor 1 in Human Cancer

Role of microtubule actin cross-linking factor 1 in brain tumor. Glioblastoma (GBM) is the most prevalent type of malignant primary brain tumor which posses surgical resection, radiation, chemotherapy and exhibits a survival rate of 14–16 months from the date of diagnosis.[32] The prevalence of GBM is high in the USA and approximately 45% of all gliomas show 5% of survival rate.[33] Aberrantly expressed factors that may be genetic, such as mutation, amplifications and deletions, are associated with low survival rates of brain tumor.[34–39]

Cytoskeletal linker proteins play crucial roles in tumor cell motility, invasion and proliferation.[40] Afghani *et al.*[41] investigated the role of MACF1 in glioblastoma and concluded that MACF1 acted as a latent diagnostic and prognostic indicator of GBM. Downregulation of MACF1 with the interference of a short sequence of RNA inhibited the migration and proliferation of glioblastoma cells. Genetic mutation and lack of MACF1 results in the block of cell cycle progression, which is associated with reduced proliferation and migration.[20,24] Knockdown of MACF1 reduced the translocation of β-catenin into the nucleus, which led to inhibited Wnt signaling pathways, and, ultimately, inhibited β-catenin-dependent transcriptional activation of certain genes in P19 and Rat-1 cells.[26,41] In addition, suppression of MACF1 results in the downregulation of Wnt signaling mediators, including Axin1 and β-catenin, and leads to the inhibition of proliferation and migration of glioblastoma cells.[41] In glioblastoma cells, the isoform-specific silencing of α-actinin targets to various cellular consequences, providing the prospective that differential expression of MACF1 isoforms might inhibit glioblastoma cell behavior (Table 2).[42]

Role of microtubule actin cross-linking factor 1 in breast cancer. Breast cancer is the most frequently diagnosed cancer among women and is the leading cause of cancer death in women worldwide.[43] Generally, breast cancer accounts for 23% of all cancer cases.[44] Aberrant expression of Her2/ErbB2/Neu

Table 2. Roles of MACF1 in various cancers

Various cancers	Roles of MACF1	Mechanism
Brain tumor	Promotes the migration and proliferation of glioblastoma cells	Wnt signaling pathways
Breast cancer	ErB2 receptor tyrosine kinase enhances and stabilizes MT outgrowth, which targeting of MACF1/ACF7 to plasma membrane	Suppression of GSK3 by induction of ErB2
Colon cancer	Maintains cytoskeleton framework, controls interstitial proliferation, colon paracellular permeability, columnar epithelial cell arrangement and expression of TJP	Cellular mobility and upholding of cellular morphology
Lung cancer	Involved in metastasis and migration, contributes in the activating factors of lung adenocarcinoma metastasis	Actin remodeling, angio-genesis and Wnt/Notch signaling

MACF1, microtubule actin cross-linking factor 1; MT, microtubules; TJP, tight junction proteins.

receptor is identified in approximately 20%–25% of breast carcinoma patients and is correlated with a poor prognosis.[45] ErB2 is mostly involved in tumor cell metastasis, invasion and motility.

In a comprehensive mutational study, MACF1 is recognized as a gene responsible for breast cancer.[46] The localization of MACF1 targeting to plasma membrane occurs through membrane-binding APC, which is necessary for the stabilization and capturing of MT.[22] MT contribute to the establishment and maintenance of cell orientation, regulation of focal adhesion turnover at the cell front, and cell detachment at the cell back.[47] It was reported that the regulation of MT outgrowth to the cell cortex was enhanced by ErB2 receptor tyrosine kinase through a complex including Memo, the formin mDia1 and the GTPase RhoA. Receptor tyrosine kinase ErB2 is mainly involved in stimulating the motility of breast cancer cells. Due to activation of ErB2, breast cancer cells form extensive protrusions, which are occupied by outgrowing MT.[21] Zaoui *et al.*[21] report that the activity of glycogen synthase kinase-3 (GSK3) was suppressed by induction of ErB2, which is mediated by Memo and mDia1. Memo and mDia1 are necessary for stabilization and capturing of MT as well as targeting of MACF1/ACF7 to the plasma membrane of breast cancer cells.[21] Moreover, GSK3β plays a crucial role in the migration of breast carcinoma cells and stimulates tyrosine kinase receptor ErbB2 (Table 2).[21,48]

Role of microtubule actin cross-linking factor 1 in lung cancer. Lung cancer is one of the most prevalent type of malignant tumor that posse's mortality ratios approximately 1.3 million of deaths annually.[49] The life span of 15% of lung cancer patients is <5 years.[13] Adenocarcinoma is the most common type of lung cancer, not only in smokers but also in nonsmokers.[50] The most prevalent tumor-associated changes occur in transcripts of different genes, such as MACF1, vascular endothelial growth factor A (VEGFA), amyloid beta (A4) precursor protein (APP) and *Drosophila melanogaster* NUMB genes, which mainly function in angiogenesis, actin cytoskeleton remodeling and Wnt/Notch signaling. MACF1 is not closely linked with cancer, but its function has been recognized in Wnt signaling pathway, having various mediators that are involved in tumorigenesis.[51]

MACF1/ACF7 plays an essential role in the development of muscle, neuron and lung. Before birth, MACF1/ACF7 is upregulated in alveolar cells of the lung.[13] MACF1b isoform is strongly expressed in the lung tissue as well as closely linked with the Golgi complex.[14] Lin *et al.*[14] conclude that the plakin repeats of MACF1b were essential to maintain the structure and function of the Golgi complex in lung cells. Bidkhori *et al.* report that MACF1, MYBBP1A, MYO10 and ATP6V1C1 were upregulated in lung adenocarcinoma and concluded that these genes played a critical role in the metastasis of lung adenocarcinoma.[52,53] Moreover MACF1, MYBBP1A, MYO10 and ATP6V1C1 in the merged-module are involved in cell metastasis and migration. The overexpression of these genes may contribute as an activating factor of lung adenocarcinoma metastasis.[52] While MACF1 has not been directly implicated in cancer, it has been reported to function in the Wnt signaling pathway, of which various components have been linked to tumorigenesis.[54] Increased inclusion of the alternative exon in MACF1 transcripts in lung adenocarcinoma tissues may contribute to altered Wnt signaling in cancers.[55] Changes in MACF1 result in the inhibition of Wnt signaling pathway due to the reduced level of β-catenin in the nucleus and depletion of TCF/β-catenin transcription activation that may lead to lung adenocarcinoma development. Somatic mutation of MACF1 can also contribute in the Wnt/β-catenin-related carcinogenetic pathways (Table 2).

Role of microtubule actin cross-linking factor 1 in colon cancer. The physiological role of the intestinal wall is to regulate the discriminatory channel from the gut lumens, such as the movement of only small molecules or ions.[12] Previous studies have concluded that tight junction proteins (TJP) regulate intestinal permeability.[7] Moreover, alteration in intestinal permeability might result in changes in cytoskeletal networks.[9] Madara *et al.* conclude that disruption of F-actin in the T84 colon cancer cell line gave rise to the enhancement of paracellular permeability.[9,56] MT are critically involved in the cellular mobility and maintaining of cellular morphology.[5]

Microtubules and microfilaments are associated with formation of the dynamic cytoskeleton, that specifies cellular mobility and cell shape.[57] ACF7 plays a crucial role in regulating the cytoskeleton dynamics. Kodama *et al.*[58] conclude that ACF7 plays a critical role in the association of MT-microfilament dynamics. ACF7 helps in maintaining cytoskeleton frameworks by either closely linking to MT or establishing an association among MT and microfilaments. Liang *et al.*[59] report that ACF7 regulates cytoskeleton dynamics to alter mucosal epithelial arrangement and colonic paracellular permeability. Liang *et al.*[59] observed the disrupted arrangement of epithelial cells in ACF7-deficient colonic mucosa and concluded that dysregulation of the cytoskeleton framework resulted in the modification of colonic paracellular permeability. Lack of ACF7 gave rise to considerable interstitial proliferation as well as columnar epithelial cell rearrangement.

Moreover, ACF7 changes the epithelial framework of the mucosal paracellular permeability of the colon and regulates the expression of TJP (Table 2).[59]

Conclusion and Future Prospective

In this review, we summarized the features of MACF1, including the physiological role of MACF1 and the pathological role of MACF1 in various cancers. MACF1 comprises different isoforms, such as MACF1a1, MACF1a2, MACF1a3, MACF1-4, MACF1b and MACF1c, and is broadly expressed in brain, spinal cord, lung, kidney, heart, bone and skeletal muscles tissues. MACF1 plays a crucial role in cell proliferation, migration and cell signaling. MACF1 is also closely associated with cancer development, including breast cancer, colon cancer, lung cancer and glioblastoma.

Microtubule actin cross-linking factor 1 has been earmarked for further research, and a broad range of functional roles have already been attributed in the progression of various human cancers. However, the absolute abundance and variety of MACF1 pose a challenge for its classification and understanding its role in cell cycle regulation. A greater understanding of the MACF1-to-cell signaling relationship (i.e. how and which molecules determine a cell signaling pathway) will be required to initiated tumor progression (Fig. 2). How can MACF1 dissociate from the β-Catanin, Axin and GSK3-β complexes? How can MACF1 regulate the wnt signaling pathway that enhances the proliferation of oncogenes? What is the epigenetic relationship of MACF1 isoforms with cancer? What is the exact role of MACF1 in cancer initiation and progression? What is the relationship between MACF1 and cell cycle regulatory genes in various human cancers? This could ultimately permits the functional assignation and validation of MACF1 isoforms on the basis of structure and might be hugely informative in the development of MACF1 as a novel target in different human cancers. Given its enormous potential, MACF1 has begun to produce substantial interest in the development and progression of treatments for human cancers.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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