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The role of MACF1 in nervous system development and maintenance

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Abstract

Microtubule-actin crosslinking factor 1 (MACF1), also known as actin crosslinking factor 7 (ACF7), is essential for proper modulation of actin and microtubule cytoskeletal networks. Most MACF1 isoforms are expressed broadly in the body, but some are exclusively found in the nervous system. Consequentially, MACF1 is integrally involved in multiple neural processes during development and in adulthood, including neurite outgrowth and neuronal migration. Furthermore, MACF1 participates in several signaling pathways, including the Wnt/β-catenin and GSK-3 signaling pathways, which regulate key cellular processes, such as proliferation and cell migration. Genetic mutation or dysregulation of the *MACF1* gene has been associated with neurodevelopmental and neurodegenerative diseases, specifically schizophrenia and Parkinson's disease. MACF1 may also play a part in neuromuscular disorders and have a neuroprotective role in the optic nerve. In this review, the authors seek to synthesize recent findings relating to the roles of MACF1 within the nervous system and explore potential novel functions of MACF1 not yet examined.

Keywords

MACF1; ACF7; neuron; brain; nervous system; development; dendrite; axon; neurite; neuron migration; proliferation

1. Introduction

Microtubule-actin crosslinking factor 1 (MACF1), also widely known as actin crosslinking factor 7 (ACF7), is a member of the spectraplakin family of cytoskeletal crosslinking proteins. Spectraplakins are large proteins distinguished by their ability to bind to different cytoskeletal networks. There are only two known mammalian spectraplakins, MACF1/ACF7

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Competing interests

None

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and bullous pemphigoid antigen 1 (BPAG1)/dystonin, and this family of proteins is evolutionarily conserved in most multicellular organisms [1]. MACF1 was originally identified as an actin-crosslinking protein in 1995 [2]. MACF1 belongs to a subset of microtubule plus-end tracking proteins (+TIPs), functioning at the microtubule plus-end to coordinate microtubule and F-actin interactions at the plasma membrane [3]. The most widely researched function of MACF1 is in regulation of cytoskeletal proteins, specifically F-actin and microtubules [4]. Microtubules, the actin cytoskeleton and their interacting components are involved in many polarized cellular processes including cell shape, cell division, intracellular transport, adhesion, and cell migration [5–8]. MACF1 interacts with microtubules and F-actin via distinct microtubule and actin-binding domains to regulate the polarization of cells and coordination of cellular movements [1, 4, 9]. MACF1 stabilizes the downstream cytoskeleton structure by either directly binding to microtubules or forming links between microtubules and F-actin [10], and plays an important role in cell migration via its regulation of Golgi polarization [11, 12]. This large and complex protein, however, is involved in a wide range of cellular signaling networks and processes, including Wnt/β-catenin signaling, cell migration, proliferation, survival and autophagy [13–18]. MACF1 has recently received increased attention due to its broad expression in the nervous system, more specifically, in the brain [15, 19, 20]. *MACF1* mutations have been linked to neurological diseases including Parkinson's disease (PD), autism spectrum disorder (ASD), and schizophrenia [21–23]. On a related note, several contemporary studies from our group and others have found that MACF1 is essential for proper neural progenitor proliferation, neuronal migration and neurite development [15, 16, 20, 24, 25].

In this review, we provide a brief overview of the MACF1 protein and its known functions and interactions, followed by an in-depth analysis of the roles of MACF1 in nervous system development and function. We also seek to highlight current research questions and potential explanations relating to MACF1 and its neuronal activities and related disorders.

2. Isotype structure and expression

MACF1 is expressed in multiple tissues throughout the body and has various isoforms with distinctive structures. MACF1 is a large protein of ~600 kD [2] and its primary function is cross-linking microtubules and F-actin microfilaments. MACF1 is encoded by the *MACF1* gene, which is located on the human chromosome 1p32 and on chromosome 4 in mice [2, 26, 27], and is a unique hybrid of dystrophin/spectrin and plakin genetic domains [4, 27]. The MACF1 actin-binding domain (ABD) is located at the N-terminus and is composed of either one or two calponin homology domains, CH1 and CH2, respectively [4, 28–31]. Furthermore, the MACF1 ABD is conserved within the spectrin superfamily [4, 30]. Adjacent to the ABD in the N-terminus, all MACF1 isoforms possess a plakin domain stemming from spectrin repeats [4, 9, 28, 32], which can be observed throughout the plakin superfamily [33]. Separating the functionally distinct N- and C-terminal domains, each MACF1 protein exhibits 23 flexible, α-helical spectrin repeats in one domain [1, 4, 33–35]. At the C-terminus of MACF1, two calcium-binding EF-hand motifs can be found [9], followed by a spectraplakin-specific Gas2-related protein (GAR) domain responsible for microtubule binding and stabilization (Figure 1A) [4, 9, 33].

There are six identified murine MACF1 isoforms [36]. The first three isoforms to be discovered are currently known as MACF1a1, MACF1a2 and MACF1a3 [26, 37]. They possess identical 3′ RNA sequences, but display significant variation in the 5′ region leading to distinct protein N-termini [26]. MACF1a1 and MACF1a2 are both broadly expressed, although MACF1a1 is more predominantly found in the kidney, stomach and skin [19, 26, 37]. MACF1a2 is detected at higher levels in the lung and central nervous system [19, 26, 37, 38]. MACF1a3 expression is mainly restricted to the brain and spinal cord [19, 26]. In 2001, a fourth MACF1 isoform, MACF1-4, was discovered, with heightened expression levels in the placenta, pituitary gland, heart and lung. MACF1-4 is unique in that it lacks an ABD and instead expresses a series of plectin repeats at its N terminus [27]. Successively, a further, exceptionally-large MACF1 isoform, MACF1b, was found to be expressed throughout the body. It contains additional plakin repeats between its N-terminal plakin domain and its spectrin repeat domain [37]. The most recent MACF1 isoform to be isolated, MACF1c, is thought to only be expressed in the nervous system. It is structurally similar to the MACF1a isoforms, but lacks an ABD at its N-terminus [15]. A recent, brief review from Hu et al. provides a summary of all MACF1 isotypes and their functions [36].

In mice, MACF1 is broadly expressed throughout the developing brain. MACF1 protein can be detected in somas and neurites of cortical neurons [20]. During early brain development, MACF1 levels are highest in the ventricular zone and upper cortical areas near the marginal zone of the developing cerebral cortex [20]. As neurodevelopment progresses, MACF1 expression in the ventricular zone gradually decreases while MACF1 levels in the cortical plate steadily increase, following the established pattern of radial neuronal migration [20]. Additionally, MACF1 expression in postmitotic neurons is mainly restricted to the marginal zone at early stages of brain development, but transitions into the cortical plate by embryonic day 15.5 (E15.5) [20], indicating that MACF1 may participate in neuronal migration and differentiation.

3. Cellular signaling associated with MACF1

Beyond its role crosslinking cytoskeletal proteins, MACF1 is actively involved in multiple signaling cascades. In 2006, Chen and colleagues published that *Macf1* knockout (*Macf1*$^{-/-}$) mice do not survive beyond gastrulation, as evidenced by a failure to develop a primitive streak, node or axial mesoderm. Interestingly, they also found that knockout of *BPAG1*, a closely related plakin protein, had strikingly different effects (mice survived until weaning), indicating a unique role for MACF1 in regulation of embryonic development [13]. They further noted that the developmental defects present in *Macf1*$^{-/-}$ embryos mirror those seen in *Wnt3*$^{-/-}$ and *LRP5/6* double-knockout mice [13, 39, 40], indicating a potential role for MACF1 in the Wnt/β-catenin signaling pathway. Consequently, they demonstrated that MACF1 interacts with the β-catenin destruction complex in the cell, binding directly to Axin using the MACF1-spectrin repeat 0 (SR0) domain. The SR0 domain is defined as the region between the MACF1 plakin domain and the first spectrin repeat [41]. They also illustrated that either knockdown of MACF1 or overexpression of the MACF1 deletion fragment of SR0 successfully inhibits Wnt/β-catenin signaling by preventing Axin translocation to the cell membrane (Figure 1B) [13]. It was further shown that MACF1 interacts directly with Wnt co-receptors LRP5/6 at the cell membrane via its SR0 domain.

Interestingly, it was later shown that MACF1 is directly phosphorylated by GSK-3 at its C-terminal microtubule-binding domain in skin stem cells, effectively preventing MACF1-microtubule interactions and nullifying microtubule polarization along actin focal-adhesion networks [42]. We have demonstrated that MACF1 and GSK-3 physically bind to one another and that MACF1 is phosphorylated in a GSK-3-dependent manner in the developing brain [20], similar to what was seen in skin stem cells [42]. It is unclear, however, whether the GSK-3 and MACF1 interaction is part of the Wnt destruction complex or downstream of growth factor signaling. While Wnt signaling utilizes a protein-protein interaction mechanism to control GSK-3, growth factors regulate a different pool of GSK-3 in the cell by phosphorylation at serine 21 (α) and 9 (β). Both signaling pathways are thought to be insulated. Wu and colleagues have shown that phosphorylation-refractile constructs of GSK-3 modulate MACF1 phosphorylation and activity in skin cells [42]. Thus, at least a part of MACF1 regulation by GSK-3 appears to be induced by growth factor signaling. In a breast carcinoma model, it was found that MACF1 is involved in microtubule stabilization via an ErbB2 receptor tyrosine kinase signaling pathway. Heregulin β activates ErbB2, which leads to the phosphorylation and inhibition of GSK-3 through the Memo-RhoA-mDial pathway. Inhibition of GSK-3 kinase activity blocks the phosphorylation of two other cytoskeletal regulators, adenomatous polyposis coli (APC) and cytoplasmic linker-associated protein 2 (CLASP2), and their subsequent translocation to the cell membrane. MACF1 is recruited to the membrane by APC, but not CLASP2, where it regulates microtubule dynamics [43].

Additionally, MACF1 plays a role in DOCK 180-ELMO-Rac signaling in cell protrusion/lamellipodium extension during cell migration. In this system, ELMO recruits MACF1 to sites of emerging protrusions, where MACF1 orchestrates microtubule capture and stabilization [44]. Following stimulation by integrin, Elmo and MACF1 colocalize at the cell membrane [36, 44]. MACF1 then organizes the cytoskeleton to extend stable membrane protrusions [44].

MACF1 is also integrally involved in some forms of vesicular trafficking, specifically relating to axonal vesicle transport [45] and autophagy [14]. MACF1 can act as a Rab21 effector. The complex of Rab21, Kif5A, GolginA4, and MACF1 acts together to transport TI-VAMP from the Golgi to neurite tips along microtubule [45]. In autophagy, MACF1 and its binding partner, the *trans*-Golgi protein p230, are responsible for trafficking of mAtg9 from the *trans*-Golgi network to the cell surface, a necessary step in phagophore formation. MACF1 knockdown impairs mAtg9 transport and blocks early steps in autophagy in a state of amino acid starvation [14].

4. MACF1 in cell proliferation

Cell proliferation is the process that results in an increased number of cells. During cell division, microtubule and actin interactions regulate spindle positioning and cytokinesis. Abnormal microtubules and actin cytoskeleton dynamics cause cytokinesis defects, thus altering cell proliferation [46–48]. In osteoblast cells, MACF1 knockdown inhibits cell proliferation and induces S phase cell cycle arrest [49]. Additionally, the microtubule organizing center (MTOC) fails to form in proximity to the condensed α-tubulin fibers

surrounding the nucleus in osteoblasts [49]. These observations indicate dysregulated cytokinesis following MACF1 knockdown [46–48, 50]. Wu and colleagues, however, have observed no significant deficit in cell proliferation in epidermal or endodermal cells in the absence of MACF1 expression [42, 51]. This cell type-specific function of MACF1 could be explained by unknown unique MACF1 protein-protein interactions in osteoblast cells or by additional proteins fulfilling the same functional role as MACF1 in epidermal and endodermal cells during cytokinesis [49, 50]. Taken together, these findings may provide insight into the role of MACF1 in the proliferation of neural progenitor cells.

In dividing neural progenitor cells, proper positioning of the centrosome, the main MTOC, is necessary for cell proliferation [52]. Neurons originate from a limited number of neural progenitor cells during embryonic development [53]. Neural progenitors can either self-renew (symmetric division) or undergo the process of neurogenesis, in which one daughter remains a neural progenitor cell and the other undergoes sequential differentiations toward becoming a neuron (asymmetric division) [53–58]. This process takes place in the ventricular zone (VZ) or subventricular zone (SVZ) of the developing cerebral cortex for most excitatory pyramidal neural progenitors and in the VZ or SVZ of the medial ganglionic eminence (MGE) for most inhibitory interneuron progenitors [53–55, 57, 58]. Throughout the process of neurogenesis, a significant reorganization of cellular components is required before mitosis can take place. Following the completion of S phase, the nucleus must migrate before apical mitosis can be undergone in a process known as interkinetic nuclear migration, which requires the interplay of the actin and microtubule cytoskeletons [59–61]. Initially, neural progenitors and/or stem cells divide symmetrically along a vertical axis before asymmetrical division along a horizontal axis can begin [55, 61, 62]. The plane of neural progenitor division is highly regulated by the cytoskeleton, specifically the orientation of mitotic spindles [61, 63, 64], thus microtubules and their regulatory proteins are crucial to proper proliferation and cell division throughout neural progenitor proliferation [53, 61, 64, 65]. During mitosis, microtubule assembly and disassembly at the plus- and minus-ends is required for proper separation of chromosomes and cytokinesis [66–69]. +TIPs crucially regulate microtubule dynamics during cell division and must be maintained at proper levels [66, 70], as abnormal microtubule stabilization can suppress microtubule dynamics, preventing cell division and resulting in apoptosis [70, 71]. Like other +TIPs, MACF1 is localized to microtubule plus-ends and physically interacts with several other +TIPs, including EB1, APC and CLASP [13, 72], and regulates centrosome movement [20]. All of this circumstantial evidence suggests the importance of MACF1 in neural cell proliferation. However, its function in this process is still unclear.

Examining a *Macf1* conditional knockout mouse model (*Macf1* cko), in which *Macf1* expression is eliminated in the developing nervous system, Goryunov and colleagues observed extensive heterotopia, or distinct disorganization of neural layers, in the cortex and hippocampus of *Macf1* cko mice [15]. The majority of early-born cortical neurons were found in their proper, deep layers, whereas neurons with a late-born phenotype appeared to be mixed in with the deep-layer neurons and not in their typical outer cortical layers [15]. Heterotopia is often attributed to neuronal migration impediments but can also be caused by defective neuronal proliferation. It is unclear whether the layer positioning defects in *Macf1*

cko mice are due to a reduced neuronal migration rate, aberrant migratory guidance, or defective neuronal proliferation [15].

5. MACF1 in neuronal and non-neuronal cell migration

Cell migration is a fundamental cellular process and is essential for embryonic development, tissue repair and regeneration, and tumor metastasis [73]. Cell migration begins with various extracellular cues such as chemokines and signals from the extracellular matrix that lead to the polarization and the extension of protrusions in the direction of movement [74]. Migrating cells must acquire a polarized, asymmetric morphology and develop a single leading edge with one filopodia [75]. During the migration process, cells actively reorganize the actin cytoskeleton and microtubules [73]. MACF1 directly interacts with other +TIPs, such as the EB1 protein, to recruit cell polarity and signaling molecules to microtubule tips [76]. MACF1 also interacts with CLASP2, another +TIP protein, and regulates CLASP localization. CLASP2 is involved in microtubule stabilization and is required for efficient, persistent motility [77]. It was recently discovered that MACF1 also directly interacts with the ELMO protein (engulfment and cell motility protein), as mentioned above. ELMO1 recruits MACF1 to the cell membrane, where MACF1 regulates microtubule capture and stabilization of cellular protrusions [44].

In *MACF1* null cells, many microtubules exhibit irregular trajectories and are more sensitive to depolymerizing agents. Moreover, loss of MACF1 causes defective polarization of stable microtubules in epidermal cells, and a lack of coordinated migration in response to wounding [10]. In migrating skin stem cells, GSK-3β phosphorylates the microtubule-binding domain of MACF1, resulting in the dissociation of MACF1 from microtubules. Thus, phosphorylation of MACF1 is necessary for microtubule growth and for skin stem cell migration [42]. Moreover, it was recently suggested that the FAK/Src kinase phosphorylation of MACF1 is essential for its binding to F-actin and coordination of cytoskeletal dynamics at focal adhesions. The effects of MACF1 phosphorylation in focal adhesion dynamics and cell motility have been clearly observed in epithelial cells [78]. In motile fibroblasts, MACF1 regulates cortical CLASP localization, allowing microtubule stabilization and promoting directionally persistent motility [77]. In breast carcinoma cells, the ErbB2 receptor controls microtubule capture by recruiting MACF1 to the plasma membrane, where MACF1 contributes to microtubule guidance and capture in migrating cells [43]. miR-34a regulates cytoskeletal proteins such as MACF1, LMNA, GFAP, ALDH2 and LOC100129335, and transfection of miR-34a into carcinoma cells causes inhibition of cell migration and invasion [79].

During brain development, neurons migrate from their place of birth to a specified final destination (Figure 2). Excitatory pyramidal neurons migrate from the cortical ventricular zone into the cortical plate along radial glial processes in a pattern known as radial migration (Figure 2A) [80–83]. Later-born pyramidal neurons migrate outwards beyond earlier-born neurons, resulting in more superficially-positioned late-born neurons in mature brains. Inhibitory interneurons (GABAergic neurons) begin migration in the medial ganglionic eminence of the ventral telencephalon and tangentially migrate into the dorsal telencephalon before changing course and radially entering the cortical plate (Figure 2B) [84–86].

Neuronal migration and positioning are critical steps for establishing functional neural circuitry in the developing brain. Therefore, abnormal neuronal migration during development causes brain malformations, which have been linked to a variety of neurodevelopmental and neuropsychiatric diseases such as ASD, attention deficit hyperactivity disorder (ADHD), intellectual disability, and schizophrenia [87–90]. Neuronal migration is a dynamic process, which requires persistent reconstruction of the cytoskeleton. In this context microtubules and microtubule-related proteins, including MACF1, play important roles in the regulation of neuronal migration during brain development [91–93]. We and others have reported that MACF1 is highly expressed in the nervous system and developing brain [4, 20]. *Macf1* conditional knockout brains using a nestin-cre driver display partially-mixed upper- and deeper-layer neurons in the cerebral cortex [15]. The expression pattern of MACF1 and the heterotopic cortical phenotype in *Macf1/nestin-cre* conditional knockout mice strongly suggest a role for MACF1 in neuronal migration. Indeed, our study shows that neuron-specific *Macf1* deletion using a Nex-cre driver or *in utero* electroporation of the Dcx-cre-iGFP construct suppresses the radial migration of cortical pyramidal neurons, resulting in aberrant positioning of excitatory pyramidal neurons in the cortical layers [20]. During radial neuron migration, MACF1 regulates leading process morphogenesis and dynamics. *Macf1*-deleted neurons develop short and unstable leading processes resulting in unidirectional and slow radial neuron migration. Also, *Macf1*-deleted pyramidal neurons exhibit microtubule destabilization and static centrosomes [20]. Centrosomes show dynamic back-and-forth movements along the leading process to pull the soma during normal neuron migration. However, centrosomes in *Macf1*-deleted neurons have little movement and remain close to the cell body, resulting in the creation of insufficient tension for somal translocation. Thus, MACF1-mediated regulation of microtubule stability and centrosome movement contributes to radial neuron migration in the developing brain. Consistent with migrating skin stem cells, GSK-3-mediated phosphorylation is an important mechanism for the MACF1 function in neuronal migration [20, 42]. In addition to the role of MACF1 in radial migration, we have recently shown that MACF1 is also a key molecule in tangential neuron migration [16]. MACF1 is highly expressed in the tangential migratory stream [16]. *Macf1* deletion in interneuron progenitors and progeny using Nkx2.1-cre or Dlx5/6-cre lines results in abnormal migration and defective positioning of GABAergic inhibitory interneurons in the mouse cerebral cortex and hippocampus [16]. *Macf1*-deleted GABAergic interneurons show slower speed and aberrant orientation of movement during migration. Importantly, MACF1 regulates the transition of migration direction from a tangential to a radial route during cortical development [16]. *Macf1*-deleted interneurons develop abnormal leading processes and disrupted microtubule stability and severing [16]. Overall, MACF1 is an essential regulator of cell migration via its management of microtubule and actin cytoskeleton dynamics.

6. MACF1 in neurite development

Neurite outgrowth is an essential event in neural development, which involves coordinated changes between the actin cytoskeleton and the microtubule network [94, 95]. This process is regulated by various proteins that manipulate the cytoskeletal network by various means [96, 97]. Recent studies indicate that MACF1 plays a vital role in neurite outgrowth.

MACF1 controls the extension and differentiation of neurites in *Drosophila* neurons [25]. Knockdown of *MACF1* decreases axon outgrowth, a process dependent on its F-actin- and microtubule-binding domains in *Drosophila* neuronal cultures [25]. We have recently provided evidence that supports the MACF1 function in mouse neurite growth in vivo [24]. Using an *in utero* electroporation method and conditional knockout mouse lines to generate temporal and spatial *Macf1* deletion, we have knocked out or down *Macf1* in developing cortical and hippocampal pyramidal neurons. We have found that MACF1 deletion decreases dendrite growth and branching in mouse pyramidal neurons. Accordingly, *Macf1*-deleted neurons show reduced density and abnormal morphology of dendritic spines. *Macf1*-deleted spines appear long and thin with short spine heads and necks [24]. The cellular cytoskeletal network is critical in dendritic spine morphogenesis, a process which is regulated by a complex network of signaling molecules [98–100]. Dendritic spine morphology is dependent on the amount and structure of F-actin within neurons [101, 102]. MACF1 interacts with F-actin to regulate cell polarization [4, 9]. Loss of MACF1 also impairs the elongation of callosal axons in the brain. MACF1 is thought to regulate neurite development via GSK-3 signaling in the brain (Figure 3). As described above, knockdown of the MACF1 protein inhibits Wnt signaling, which is mediated by GSK-3 [13]. GSK-3 is a master-regulator of the cellular cytoskeletal network, neural progenitor regulation and neurite growth [103–106]. Over-expression of a constitutively-active GSK-3β (ca-GSK-3β) construct reduces the number and length of dendrites. However, co-expression of MACF1 S:A (phosphorylation-refractile form) rescues the inhibitory effects of ca-GSK-3β [24], suggesting that GSK-3-mediated phosphorylation is an important mechanism for the MACF1 function in neurite development. Future studies will be needed to expand our understanding of MACF1 as to regulatory mechanisms and cellular signaling pathways in neurite development.

7. Neural diseases and MACF1

MACF1 gene mutations have been associated with neuromuscular diseases. Mutations in cytoskeletal genes, such as *dystonin*, *dystrophin*, and *plectin* result in myopathic consequences, thus suggesting MACF1 may have similar muscular phenotypes [17]. In a family with novel neuromuscular conditions including diminished motor skills, lax muscles, and occasional hypotonia, the *Macf1* gene product is found at low levels due to a chromosome modification in one gene locus. This novel myopathy is termed “spectraplakinopathy type I,” based on MACF1 belonging to the spectraplakin protein family [17]. Ultrastructural changes and altered motility are accompanied in muscle tissues of affected individuals [17].

MACF1 mutations have been shown to contribute to psychological disorders. Two schizophrenia risk genes, *disrupted in schizophrenia 1* (*DISC1*) and *dysbindin* (*DTNBP1*), are associated with cognitive deficits in schizophrenics [107]. DISC1 and DTNBP1 are important molecules in many aspects of neural development including neural progenitor proliferation and neurogenesis, neurite outgrowth, neuronal migration, and synaptic differentiation [108–112]. Several instances of synaptic pathology have been reported in individuals diagnosed with schizophrenia [113]. Both proteins form a similar network of protein-protein interactions, and the profiles of proteins that they interact with suggest

similar functions in cytoskeletal stability and organization, intracellular transport, and cell cycle progression [114]. Camargo and colleagues have shown that MACF1 is one of the proteins involved in critical interactions with both DISC1 and DTNBP1. They suggest that DISC1 and DTNBP1 may play a converging role in affecting synapse structure and function by disrupting intracellular transport and cytoskeletal stability via interactions with MACF1, contributing to cognitive deficits in schizophrenics [114]. Furthermore, schizophrenia and ASD may share underlying pathology, as suggested by shared risk genes [22]. For example, rare mutations in genes that are functional in the synapse have been identified in ASD and schizophrenia cases [23]. Several novel loss-of-function variants overlap in both cases, including those coding for proteins involved in protein-protein interactions with DISC1, such as MACF1 [23]. These results suggest that mutations in multiple genes involved in synapse formation, including *Macf1*, are a risk factor for both ASD and schizophrenia.

Several neurodegenerative disorders show evidence of cytoskeletal collapse. In particular, a hallmark of Parkinson's Disease (PD) is degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta [21]. It has been observed that both genetic and neurotoxic causes of PD may target the cytoskeleton, and resulting cytoskeletal disorganization and dysregulation may be a mechanistic cause of PD [115]. Two lines of evidence suggest that MACF1 is involved in the pathogenesis of PD. First, *Macf1* knockout inhibits Wnt signaling, which is important in the development of dopamine neurons. Second, *MACF1* mRNA levels in DA neurons of PD patients are significantly lower than in controls [116]. Thus, reduced MACF1 levels leading to dysregulation of the cytoskeleton may cause vulnerability of DA neurons to neurodegeneration. More directly, *MACF1* has been shown to be a risk gene for PD [21]. MACF1 is a downstream target of PD biochemical pathways, and has been found to be significantly associated with PD in 713 families studied. In addition, knockdown of the *Macf1* orthologue *Vab-10* in *C. elegans* results in selective loss of DA neurons [21]. These results suggest that MACF1 may contribute to genetic etiology of PD, and may be a mechanistic cause.

Optic nerve injury is another neurological condition in which MACF1 has been implicated. Retinal ganglion cells (RGCs) are the final neuronal output of the retina, receiving visual signals from amacrine and bipolar cells and transmitting them to the brain via the optic nerve [18]. Degeneration of RGCs and their axons in the optic nerve leads to vision loss in multiple optic neuropathies, including glaucoma most commonly. The work of Munemasa and colleagues shows strong Nell2 and MACF1 expression in RGCs [18]. Nell2 has a strong neuroprotective function, increasing survival of neurons in the hippocampus and cerebral cortex. After an optic nerve injury, Nell2 interacts with MACF1 to promote survival of RGCs [18].

8. Concluding remarks

In this review, we have summarized and synthesized much of the current research regarding MACF1 in nervous system development and maintenance. MACF1 is a large protein with multiple distinct isoforms, expressed at varying levels throughout the body. The MACF1 protein is involved in important signaling pathways and plays roles in many cellular processes. Genetic mutations of *Macf1* or deficits in MACF1 protein function have far

reaching effects in nervous system development and activity. Specifically, MACF1's interactions with cytoskeletal proteins and other cytoskeletal regulators are required for proper polarity, proliferation, migration and neurite outgrowth in neurons and neural progenitors. Beyond these established roles, MACF1 has also been shown to participate in the Wnt/β-catenin signaling pathway, as well as several other pathways related to cellular processes such as vesicular transport and autophagy. Despite increased understanding of MACF1 and its functions in the nervous system, there are still many questions to be answered and opportunities for further research. For example, although several studies have implicated *MACF1* mutations as a risk factor for neural disorders including psychiatric and neurodegenerative diseases, relatively few studies have examined how *MACF1* genetic abnormalities relate to the pathology of these conditions on a mechanistic or disease-specific level. Additionally, due to MACF1's broad roles in nervous system regulation, is it possible to modulate MACF1 expression or activity in a specific setting related to neurological symptoms? On a more basic level, although recent studies have offered a role of MACF1 in neurite outgrowth and the formation and/or pruning of dendritic spines during development, detailed regulatory mechanisms of MACF1 in these neural processes remain to be studied.

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List of Abbreviations

MACF1	microtubule-actin crosslinking factor 1
ACF7	actin crosslinking factor 7
BPAG1	bullous pemphigoid antigen 1
PD	Parkinson's disease
ASD	autism spectrum disorder
ABD	actin-binding domain
CH1	calponin homology domain 1
CH2	calponin homology domain 2
GAR	Gas2-related protein
LRP5/6	low-density lipoprotein receptor-related protein 5/6
GSK3	glycogen synthase kinase 3
APC	adenomatous polyposis coli
CLASP2	cytoplasmic linker-associated protein 2

MTOC	microtubule organizing center
VZ	ventricular zone
SVZ	subventricular zone
MGE	medial ganglionic eminence
ELMO	engulfment and cell motility protein
VAMP	vesicle-associated membrane protein
LMNA	Lamin A/C
GFAP	glial fibrillary acidic protein
ALDH2	aldehyde dehydrogenase 2
ADHD	attention deficit hyperactivity disorder
DA	dopaminergic
Vab-10	variable abnormal morphology 10
DISC1	disrupted in schizophrenia 1
DTNBP1	dysbindin
RGC	retinal ganglion cell
Nell2	neural EGFL-like 2

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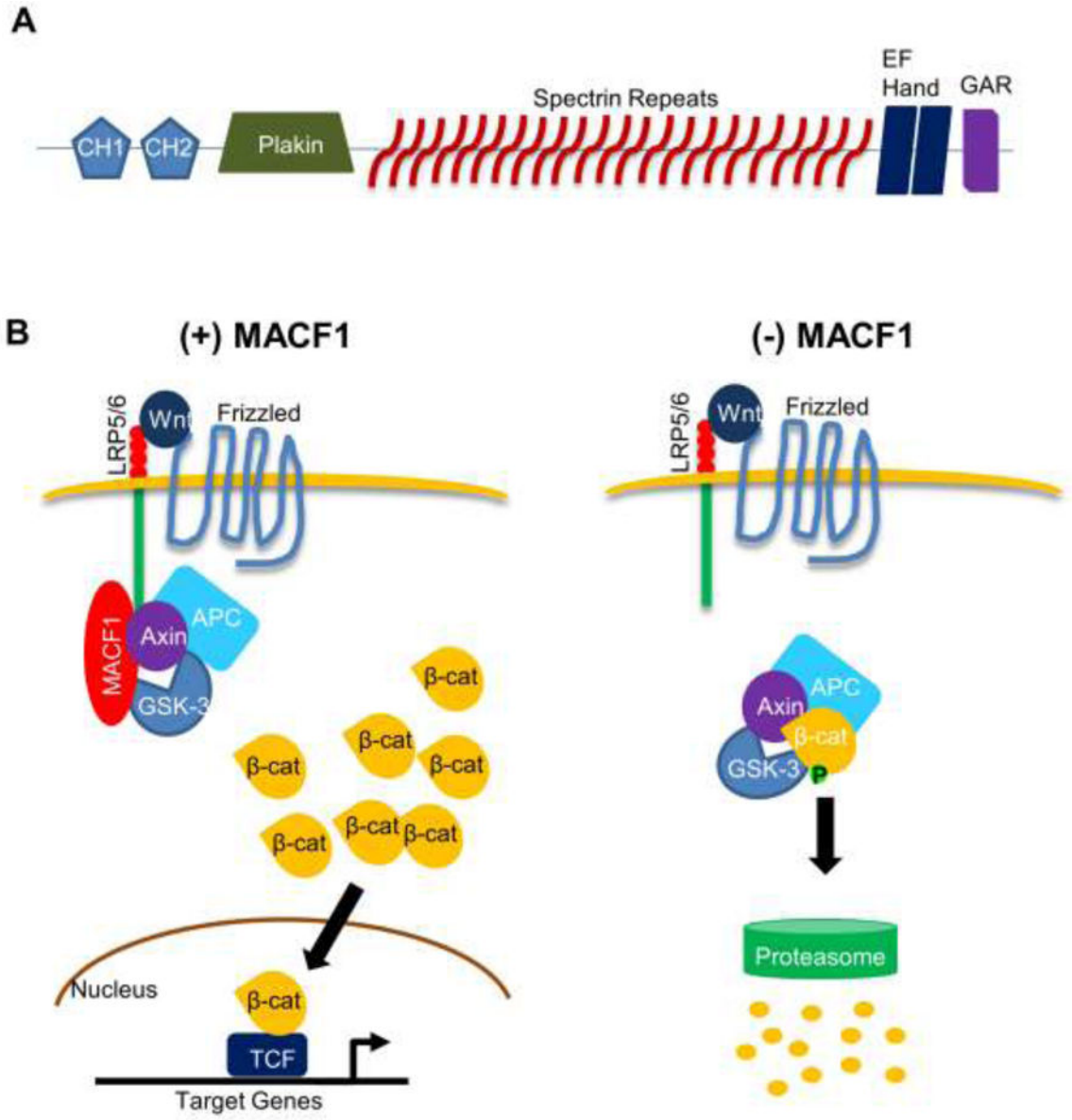

Figure 1. MACF1 structure and role in the Wnt/β-catenin signaling

(A) General protein structure of MACF1. The five functional domains found in most MACF1 isotypes are shown: the actin-binding domain (ABD) comprised of CH1 and CH2 fragments, a plakin domain, 23 α-helical spectrin repeats, two EF hand motifs, and a GAR domain at the C-terminus. CH1: calponin homology domain 1. CH2: calponin homology domain 2. GAR: Gas2-related domain. **(B)** MACF1 knockdown inhibits Wnt/β-catenin signaling. Upon Wnt binding to the receptor, MACF1 translocates axin and associated molecules to the cell membrane, allowing accumulation of β-catenin in the cytosol. Some β-catenin proteins enter the nucleus to turn on target gene expression. In the absence of MACF1, Axin is unable to translocate to the cell membrane and facilitate formation of the destruction complex containing β-catenin, resulting in proteasome-mediated β-catenin

degradation. LRP5/6: low-density lipoprotein receptor-related protein 5/6. GSK-3: glycogen synthase kinase-3. APC: adenomatous polyposis coli.

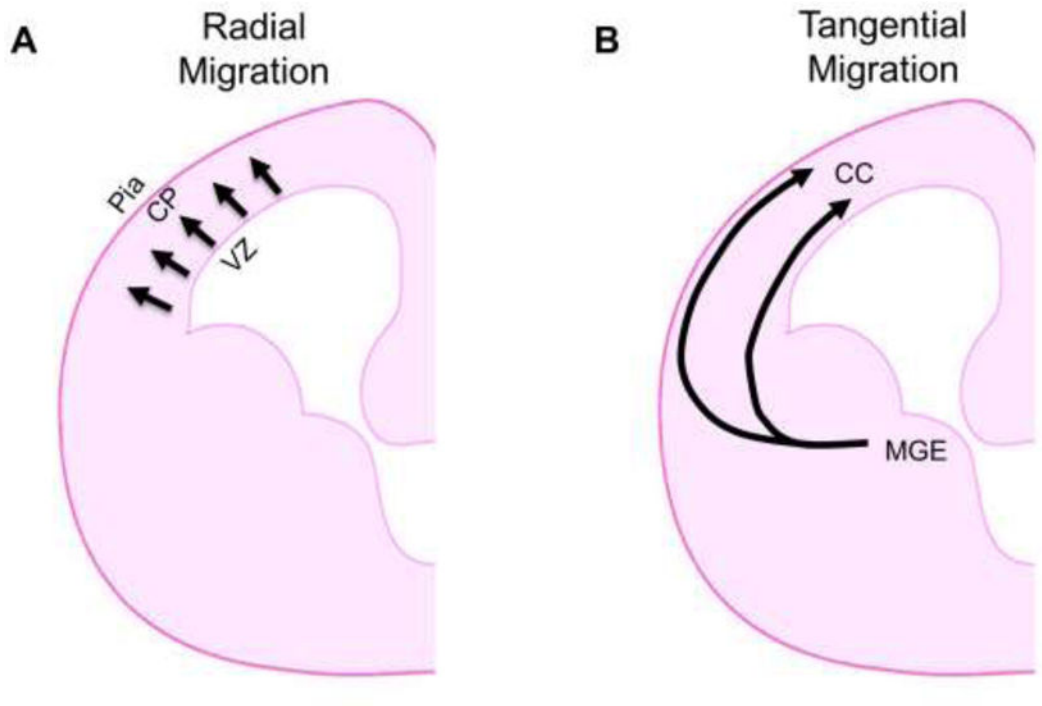

Figure 2. Modes of neuronal migration in the developing brain

(A) Radial migration. Excitatory pyramidal projection neurons migrate outward from the ventricular zone of the cerebral cortex toward the cortical plate during brain development. CP: cortical plate. VZ: ventricular zone. **(B)** Tangential migration. Inhibitory interneurons migrate tangentially from the medial ganglionic eminence (MGE) in the ventral brain to the cerebral cortex, where they undergo further movements until they reach their final cortical destinations. CC: cerebral cortex.

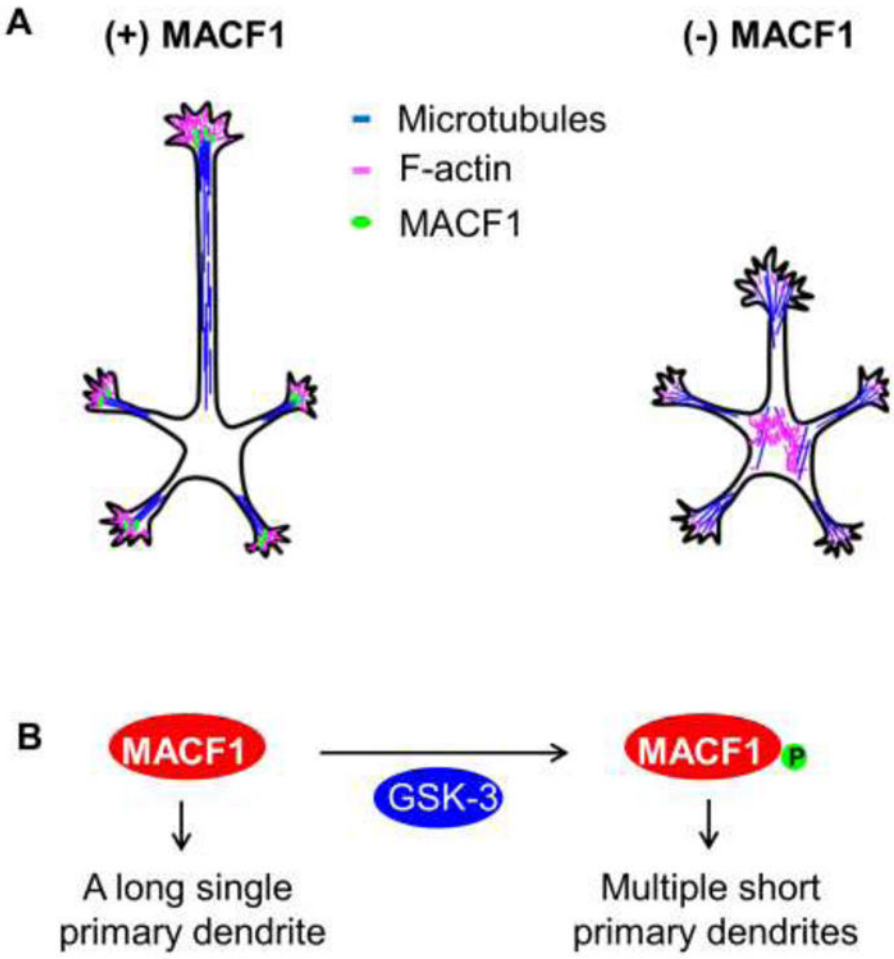

Figure 3. MACF1 in neurite outgrowth

(A) MACF1 regulation of neurite outgrowth. MACF1 localizes near the distal ends of growing axons and dendrites, where it stabilizes microtubule bundles and leads to the assembly of polymerized actin. In the absence of MACF1, microtubules and actin are disorganized and unstable at the neurite tip and scattered in the cytosol. **(B)** GSK-3 regulates the activity of MACF1 in dendrite outgrowth and arborization. When MACF1 is phosphorylated by GSK-3, it results in multiple short primary dendrites. When MACF1 remains unphosphorylated, neurons extend a single long primary dendrite.