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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.

Contents

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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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 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 (Fig. 1**A**) [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 (Fig. 1**B**) [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