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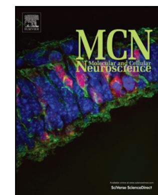

New waves in dendritic spine actin cytoskeleton: From branches and bundles to rings, from actin binding proteins to post-translational modifications

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ABSTRACT

Dendritic spines are small actin-rich protrusions from neuronal dendrites that form the postsynaptic part of most excitatory synapses. Changes in the number or strength of synapses are physiological mechanisms behind learning. The growth and maturation of dendritic spines and the activity-induced changes to their morphology are all based on changes to the actin cytoskeleton. In this review, we will discuss the regulation of the actin cytoskeleton in dendritic spine formation and maturation, as well as in synaptic strengthening. Concerning spine formation, we will focus on spine initiation, which has received less attention in the literature. We will also examine the recently revealed regulation of the actin cytoskeleton through post-translational modifications of actin monomers, in addition to the conventional regulation of actin via actin-binding proteins.

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Contents

1. Introduction . . . 0
2. Dendritic spine morphogenesis . . . 0
   2.1. Filopodia initiation . . . 0
   2.2. Filopodia elongation . . . 0
   2.3. Dendritic spine head enlargement . . . 0
   2.4. Actin dynamics in dendritic spines . . . 0
   2.5. Activity-dependent actin remodeling in dendritic spines . . . 0
3. Actin phosphorylation regulates actin dynamics in dendritic spines . . . 0
   3.1. Actin post-translational modifications . . . 0
   3.2. Actin phosphorylation in the regulation of neuronal maturation . . . 0
   3.3. Actin phosphorylation in the regulation of LTP induction . . . 0
4. Final words . . . 0
   4.1. Dendritic spine initiation in development and learning . . . 0
   4.2. Novel actin structures revealed by super-resolution microscopy . . . 0
   4.3. Post-translational modifications of actin . . . 0
Acknowledgments . . . 0
References . . . 0

1. Introduction

Certain neuron types, such as pyramidal neurons in the hippocampus or cortex, as well as Purkinje cells of the cerebellum, contain small bulbous structures on dendrites called dendritic spines. A single rat hippocampal pyramidal neuron has around 12,000 µm of dendrites and around 30,000 dendritic spines (Megías et al., 2001). The majority of excitatory synapses in the central nervous system localize on dendritic spines (Bourne and Harris, 2008). During normal human development, spine density first increases, peaks prior to adolescence, then declines during adolescence before reaching a stable level in adulthood

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(Huttenlocher and Dabholkar, 1997). Even in adulthood, spines are not always stable, as 5–10% of all spines change daily—with some spines completely eliminated and others formed *de novo* (Holtmaat et al., 2005; Sajo et al., 2016).

Excitatory synapses are strengthened through high-frequency activation to induce long-term-potentiation (LTP) and weakened through low-frequency stimulation to induce long-term-depression (LTD). Spine size and morphology correlate with these changes to synaptic strength (Yuste and Bonhoeffer, 2001). Through the addition or removal, and strengthening or weakening of excitatory and inhibitory synapses, the brain modulates its function and acquires new skills (Holtmaat and Svoboda, 2009; Kasai et al., 2010; Hofer and Bonhoeffer, 2010). The current view is that "learning dendrites" will acquire new spines, thus enhancing neuronal excitation. At the same time, the number of inhibitory synapses within the same area will decrease, further enhancing excitation. Conversely, at other dendrites in the same cell, the number of spines will decrease and the number of inhibitory boutons will increase, thus decreasing excitation (Chen et al., 2015). In addition to excitatory neurons, inhibitory neurons also play important roles in learning and memory, possibly through exerting their effects on excitatory neurons (Zhang et al., 2011; Poort et al., 2015).

The actin cytoskeleton is a structural element underlying the proper morphology of dendritic spines (Hotulainen and Hoogenraad, 2010). Actin filaments are polar structures constantly growing at the barbed(+)-ends and shrinking at the pointed(−)-ends (Blanchoin et al., 2014). A plethora of actin binding proteins controls the initiation, growth and maturation of spines by mediating changes to the actin cytoskeleton (Hotulainen and Hoogenraad, 2010). Actin binding proteins can be regulated by controlling their transcription and subsequent expression levels or by regulating their localization and activity in a better-defined time and space. During learning, changes in the cytoskeleton are under strict spatiotemporal control and can occur rapidly in single spines. Until recently, it was thought that this control was solely regulated by actin-binding proteins, but new evidence shows that this regulation is complemented by the post-translational modification of actin monomers (Terman and Kashina, 2013; Bertling et al., 2016).

2. Dendritic spine morphogenesis

During early brain development, neurons migrate to their target areas and start to make connections with other neurons. Dendrites elongate and dendritic trees establish their arborizations, while axons grow through the tissue towards their target areas by following chemical cues. By the end of the perinatal period, all rudimentary neural networks are complete (Stiles and Jernigan, 2010). The early postnatal period is characterized by the rapid development of excitatory synapses. This process is initiated by a burst of filopodia formation from dendritic shafts and followed by a massive production of connections throughout all brain regions (Huttenlocher and Dabholkar, 1997). Newly made filopodia repeatedly make contacts with axons. Local dendritic calcium influxes occur at these contact sites and the frequency of these local calcium transients is known to be higher at the sites that become stabilized (Lohmann and Bonhoeffer, 2008). Selected contacts grow into mature spines and synapses. This wiring is fine-tuned by the constant deletion of inappropriate or unnecessary contacts. Almost half of the connections emerging during the early postnatal period are lost during adolescence in order to optimize the network (Huttenlocher and Dabholkar, 1997; Penzes et al., 2011). Mature dendritic spines are known for their mushroom-like shape. This characteristic structure helps to compartmentalize post-synaptic proteins, such as receptors, into the large spine head (Noguchi et al., 2005). Dendritic spines are known to be very dynamic structures, constantly growing, shrinking and morphing. Average spine length varies between 0.2 and 2 μm, while head width lies between 0.5 and 1 μm and neck width between 100 and 200 nm (Harris and Stevens, 1989; Tønnesen et al., 2014).

2.1. Filopodia initiation

Controlled filopodia initiation seems to be crucial for achieving and maintaining optimal spine density, and the dysregulation of this process is thus likely to cause aberrant spine density and dysfunctional neuronal circuits (Carlson et al., 2011; Saarikangas et al., 2015). Current literature supports two types of spine initiation mechanisms: one that seems to be activity-independent and another that is induced by neuronal activity (Carlson et al., 2011; Saarikangas et al., 2015; Hamilton et al., 2012; Oh et al., 2016).

Based on our studies, missing-in-metastasis (MIM/Mtss1, hereon referred to as MIM) induces spine initiation throughout dendrites, suggesting that there is no specific local external signal to induce spine protrusions. New filopodia appear and disappear quickly in MIM-expressing primary hippocampal neurons at 14 days-*in vitro* (DIV14). On the contrary, using DIV5-12 organotypic brain slices prepared from P5-7 rats, Zito and colleagues showed that new spines appear upon glutamate uncaging, supporting the hypothesis of a locally regulated and activity-induced spine initiation mechanism (Hamilton et al., 2012). This study also showed that efficient initiation required proteasome, NMDA receptor and CaMKII activity. Zito's group further showed that elevated neural activity leads to rapid degradation of the dendritic RhoA guanine nucleotide exchange factor, Ephexin5 (Hamilton et al., 2017). Ephexin5 has been shown to inhibit synapse formation (Margolis et al., 2010), leading to the idea that activity-induced proteasome activity induces the degradation of Ephexin-5, which then allows new synapses to form through the subsequent reduction of RhoA activity. Surprisingly, Ephexin5 accumulates in the dendritic shaft prior to new spine outgrowth, suggesting that it may promote spine initiation (Fig. 1). Moreover, a reduced Ephexin5 level inhibits new spine outgrowth in response to both global enhancement of neural activity and local stimulation through glutamate uncaging (Hamilton et al., 2017). Ephexin5 contains a pleckstrin homology domain, which could localize it to initiation sites through binding to phosphoinositides. One explanation to reconcile these seemingly contradictory results is that Ephexin5 may enhance filopodia initiation but inhibit spine head growth and synapse formation. Interestingly, GABA uncaging also induces the initiation of new spines in young neurons, as seen in organotypic slices at an equivalent age (EP) 3–4, but not in more mature neurons (EP14–18) (Oh et al., 2016) (Fig. 1). Thus, early depolarizing GABA action appears to promote local synaptogenesis during early brain development (Oh et al., 2016). In activity-independent spine initiation, the Inverse-Bin-Amphiphysin-Rvs (I-BAR) domain-containing protein, MIM, initiates new dendritic spine protrusions by locally curving the dendritic membrane (Fig. 1). This membrane curvature forms a so-called proto-protrusion. Our studies have demonstrated that actin filament polymerization is not required for the initial formation of the protrusion, but for the elongation of the proto-protrusion to push filopodia out from the dendrite (Saarikangas et al., 2015). I-BAR domain-containing proteins are a subclass of the BAR-domain protein superfamily, which is a collection of proteins that bind to and promote different membrane curvatures. Generally, Fes/CIP4 homology-BAR (F-BAR) proteins positively curve the membrane to induce invagination and promote endocytosis, whereas I-BAR proteins form negative curvature on membranes to induce an outgrowth from the cell body and produce filopodia (Kessels and Qualmann, 2015).

There are currently 5 known I-BAR containing proteins, Irsp53, IRTKS, BAIAPL2, MIM and ABBA (Kessels and Qualmann, 2015). Of those, IRTKS and BAIAPL2 seem to have very weak expression in the CNS (Millard et al., 2007; Allen Brain Atlas) and ABBA does not appear to be expressed in neurons at all (Saarikangas et al., 2008). Irsp53 is expressed in neurons where it affects dendritic spine density (Kang et al., 2016), but does not localize to dendritic spine initiation sites. Thus, of the I-BAR proteins, it is likely that MIM is the only one involved in spine initiation. Nevertheless, some F-BAR domains can function like the I-BAR domain of MIM, thus inducing filopodia formation in cells.

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