Actin and Actin-Binding Proteins: Masters of Dendritic Spine Formation, Morphology, and Function

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Abstract: Dendritic spines are actin-rich protrusions that comprise the postsynaptic sites of synapses and receive the majority of excitatory synaptic inputs in the central nervous system. These structures are central to cognitive processes, and alterations in their number, size, and morphology are associated with many neurological disorders. Although the actin cytoskeleton is thought to govern spine formation, morphology, and synaptic functions, we are only beginning to understand how modulation of actin reorganization by actin-binding proteins (ABPs) contributes to the function of dendritic spines and synapses. In this review, we discuss what is currently known about the role of ABPs in regulating the formation, morphology, motility, and plasticity of dendritic spines and synapses.

INTRODUCTION

Neurons are highly specialized cells that communicate through sophisticated structures, known as synapses, which consist of presynaptic axonal terminals and postsynaptic dendrites. Most of the excitatory synaptic input in the central nervous system (CNS) take place on dendritic spines, which are actin-rich structures that protrude from dendritic shafts [1]. Dendritic spines are small structures with a volume ranging from 0.01 μm^3 to 1 μm^3 and generally consist of a bulbous head and a thin neck [2,3]. The morphology of spines can change from filopodia-like protrusions to more mature thin, stubby, or mushroom-shaped structures, depending on the developmental stage or upon neuronal activity [4]. Alterations in spine density, morphology, and maturation strongly correlate with neuronal disorders, such as mental retardation, Fragile-X syndrome, Down's syndrome, Alzheimer's disease, and epilepsy, pointing to the central role of these structures in cognitive function [5-9]. The formation and plasticity of dendritic spines and synapses are attributed to the reorganization of the actin cytoskeleton (also see other reviews in this journal volume). Recently, several genes that were mutated in patients with nonsyndromic mental retardation were found to encode actin-regulatory proteins [10,11], which further indicates a critical role for these proteins in modulating spine function.

Given the physiological significance of actin regulation in spine and synapse formation and plasticity, it is important to understand how ABPs work together to regulate actin reorganization in dendritic spines. Here we review our current understanding of how individual ABPs modulate spine development in order to provide an overall picture of the intricate regulation of the actin cytoskeleton. We will limit our discussion to the postsynaptic terminal of excitatory synapses. We will begin with a general introduction of actin dynamics and how the actin cytoskeleton is modulated by ABPs before addressing the role of these proteins in spine dynamics. In order to provide a clear, concise review, we will focus only on a subset of spine proteins that contribute to actin dynamics and affect spine development, morphology, or function. For discussion of other key synaptic proteins and their role in these processes, we refer the reader to other reviews both within this volume and elsewhere [12-15].

REGULATION OF ACTIN DYNAMICS

Actin exists in two states in the cell: as globular or monomeric actin (G-actin) and as filamentous actin (F-actin), which results from the polymerization of G-actin. Monomeric G-actin can be associated with either ATP or ADP along with a Mg^{++} ion; however, ATP-bound actin has a higher efficiency than ADP-actin in F-actin assembly. Actin assembly is also determined by the available amount of unpolymerized G-actin and the G-actin critical concentration (Cc), which is discussed in greater detail in several excellent reviews [16,17]. The assembly of actin filaments occurs through three sequential steps: nucleation, which is a rate-limiting step, elongation, and ultimately steady state where there is no net change in the amount of F-actin. At steady state, F-actin exhibits net polymerization at a fast growing end (the barbed or plus end) and simultaneous depolymerization at a slow growing end (the pointed or minus end), resulting in continuous actin turnover in filaments. Actin polymerization is initiated by the formation of nucleation seeds, composed of G-actin trimers. These structures are unstable under physiological conditions unless they are stabilized by the binding of certain ABPs, such as the actin-related protein 2/3 (Arp2/3) complex [18]. ABPs serve additional roles in regulating actin dynamics and are responsible for promoting actin polymerization and depolymerization (Fig. **1**). Depolymerization can be carried out by ABPs with severing activity, including cofilin and gelsolin, which break down actin filaments into smaller pieces and thus, provide G-actin reservoirs for further actin assembly and reorganization.

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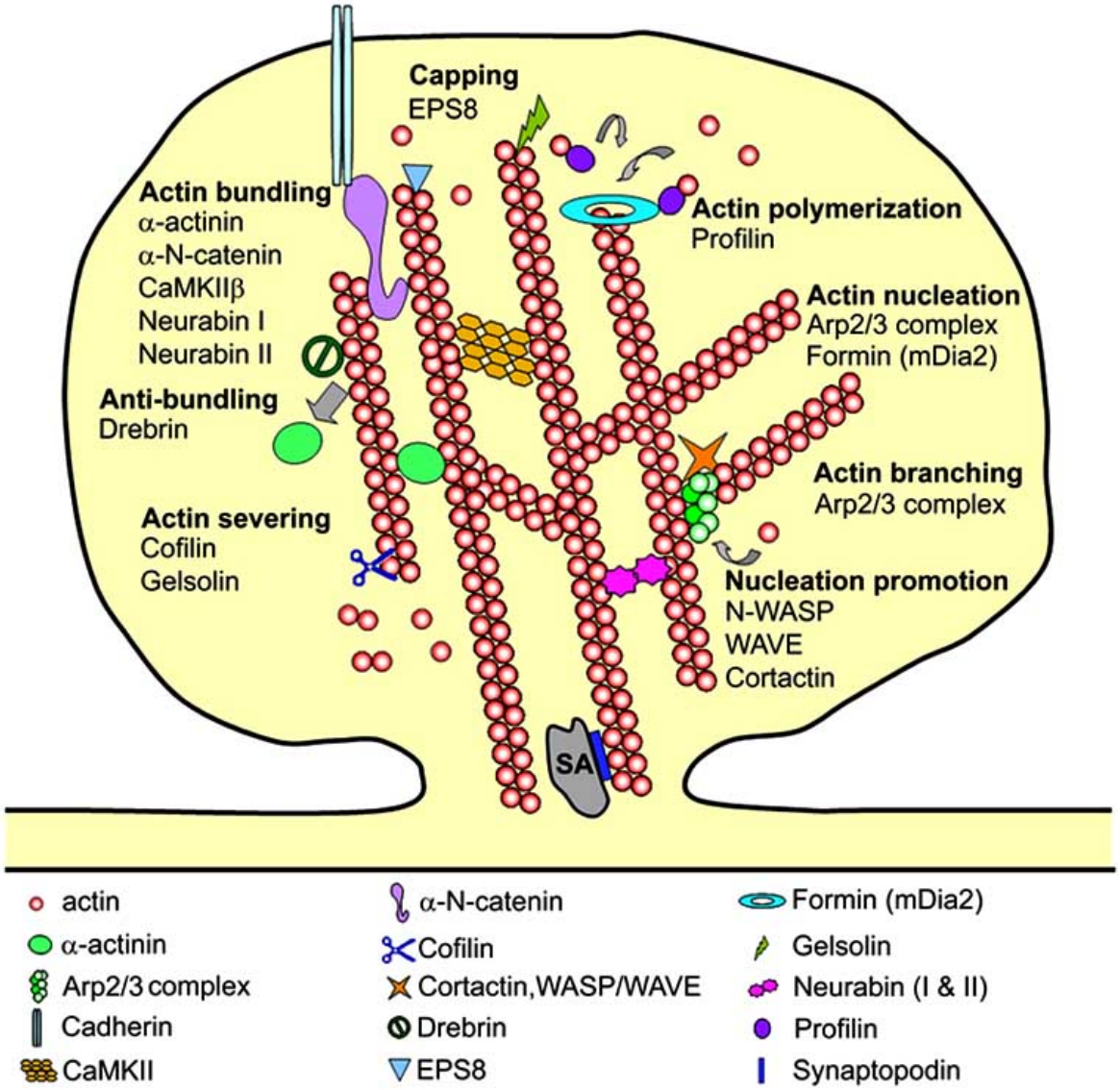

Fig. (1). Schematic diagram of actin-binding proteins in dendritic spines. Dendritic spines are enriched in actin, which is organized into branched and unbranched filaments. Reorganization and turnover of actin filaments are modulated by actin-binding proteins, which regulate spine and synaptic function as discussed in the text. The actin-binding proteins shown here regulate actin capping, polymerization, nucleation, branching, severing, and bundling. SA = spine apparatus.

Other groups of ABPs do not affect the exchange of G-actin and F-actin directly, but instead, stabilize F-actin by binding to the barbed or pointed ends of actin filaments and preventing the addition or loss of G-actin from these sites. Finally, some ABPs, such as α-actinin, are able to modulate the structure of the actin cytoskeleton by bundling or crosslinking actin filaments. ABPs cooperate with each other through these diverse mechanisms to regulate actin-based cellular events and shape actin-rich structures.

ORGANIZATION AND FUNCTION OF THE ACTIN CYTOSKELETON IN DENDRITIC SPINES

Studies from electron microscopy first demonstrated the ultrastructure of actin in dendritic spines as a combination of a branched lattice network and straight crosslinked filaments [19,20]. A subsequent study using fluorescently-labeled actin unexpectedly showed that dendritic spines are highly motile structures with constantly changing morphologies [21]. The dynamic nature of actin in spines was further shown with fluorescence recovery after photobleaching (FRAP), indicating that 85% of actin is highly dynamic and its turnover is modulated by neuronal activity [22]. More recently, a study using photoactivatable β-actin indicated that three distinct actin populations exist in spines, and the subspine localization and spine size determine the kinetics of actin turnover [23]. Under basal conditions, a dynamic F-actin pool is restricted to the tips of spines; however, a stable pool resides at the base of spine heads. Upon glutamate uncaging, which increases synaptic strength, a more kinetically stable F-actin pool is formed and mediates the expansion of spines, indicating neuronal activity can regulate actin dynamics and modulate spine function [23].

Pharmacological approaches to perturb actin dynamics were used to reveal a functional role for actin in spines. The

application of latrunculin A, which facilitates actin depolymerization, alters the number and localization of glutamate receptors [24]. This treatment also disrupts the localization of some ABPs to spines, including drebrin and α-actinin, as well as the signaling molecule calcium-calmodulin-dependent protein kinase II α (CaMKIIα) [25]. Interestingly, actin depolymerization appears to have differential effects on postsynaptic scaffolding proteins. Synaptic localization is altered in the scaffolding proteins guanylate kinase-associated protein (GKAP), Shank, Homer 1c, but no effect is observed on another scaffolding protein, postsynaptic density protein 95 (PSD95) [26]. These studies suggest that the actin cytoskeleton can tether neurotransmitter receptors, signaling molecules, and scaffolding proteins into a spatially confined area, which allows spines to modulate their shape, motility, and function. Indeed, latrunculin A treatment inhibits spine motility and delays synaptic development [21,27], indicating that actin dynamics endow spines with a high degree of plasticity.

THE INTERPLAY BETWEEN ACTIN REMODELING AND SYNAPTIC PLASTICITY

In response to neuronal activity, the strength of synaptic transmission can be persistently changed; this phenomenon is called synaptic plasticity [28]. Synaptic plasticity is the cellular basis of learning and memory and is exemplified by two well characterized models: long-term potentiation (LTP) and long-term depression (LTD), which enhances and decreases synaptic transmission, respectively [29]. Several protocols have been developed to induce these two forms of plasticity, and the most common approach is to apply high frequency stimulation to induce LTP and low frequency stimulation to produce LTD [30]. In most cases, the expression and maintenance of LTP and LTD are controlled by glutamate receptors [30].

Glutamate receptors are the major mediators of excitatory synaptic transmission in the CNS and are activated upon binding to the neurotransmitter glutamate, which is released from presynaptic terminals [31]. For the most part, synaptic transmission takes place through two types of glutamate receptors: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type receptor and N-methyl-D-asparate (NMDA)-type receptor. Stimulation of NMDA-type glutamate receptors (NMDARs) allows influx of calcium ions and transduces electrical information into biochemical signals. This includes activation of protein kinases (e.g. CaMKII, protein kinase A (PKA), or protein kinase C (PKC)) and phosphatases (e.g. protein phosphatase 1 (PP1), calcineurin or PP2B) that in turn regulate the phosphorylation and trafficking of AMPA-type glutamate receptors (AMPARs) to the plasma membrane [28,32,33]. Alterations in the activation of NMDAR and surface expression of AMPAR determine the changes in synaptic strength. During LTP, higher numbers of AMPAR are present on synaptic membranes, which potentiate synaptic trasnsmission. In contrast, LTD involves the removal of AMPAR, leading to a reduction in ion conductance and synaptic transmission. Intriguingly, LTP and LTD expression are synonymous with spine expansion and shrinkage, respectively, linking the regulation of underlying actin dynamics and reorganization to synaptic plasticity.

SYNAPTIC PLASTICITY MODULATES ACTIN TURNOVER

When LTP is induced in the hippocampus, the amount of F-actin as well as several ABPs, including drebrin A and synaptopodin, is increased while the activity of the actin depolymerization factor ADF/cofilin is decreased [34,35]. In addition, a fluorescence resonance energy transfer (FRET)-based approach, which can be used to monitor actin dynamics, shows a close relationship among synaptic activity, spine size, and F-actin/G-actin ratios in spines [36]. In this study, short bursts of electrical inputs were applied to hippocampal slices to induce LTP, which resulted in a higher F-actin/G-actin ratio followed by the enlargement of spine heads. Conversely, induction of LTD promoted the depolymerization of actin, resulting in spine head shrinkage [36]. Thus, this intriguing data suggest that actin turnover is linked to changes in synaptic strength.

THE ACTIN CYTOSKELETON MODULATES SPINE MORPHOGENESIS AND SYNAPTIC PLASTICITY

Two possible mechanisms as to how actin regulates synaptic plasticity have been proposed: (i) the actin cytoskeleton may serve as a scaffold for the retention of glutamate receptors in the postsynaptic density; and (ii) the actin cytoskeleton provides a path for short distance protein trafficking in spines, which is required for synaptic transmission. These mechanisms were first proposed when bath application of the actin depolymerization agent latrunculin B to hippocampal slices resulted in the reduction of AMPAR-mediated basal synaptic transmission and LTP [37]. Subsequent studies also found that actin depolymerizing agents affect the maintenance of the early and late stages of LTP [34,38]. This raises the question as to how actin polymerization affects synaptic transmission. Synaptic transmission is primarily controlled by AMPARs, which move between synapses and extrasynaptic sites [32,33]. It is generally believed that surface expression of AMPAR is regulated by passive diffusion and active endocytosis/exocytosis [39-43]. Importantly, trafficking of AMPAR is conducted by myosin motors, which carry AMPAR-containing endosomes along actin tracks [44-48]. In this way, the polymerization and depolymerization of the actin cytoskeleton can modulate the incorporation and internalization of AMPAR, thereby altering synaptic efficacy [49].

ACTIN-BINDING PROTEINS AND SPINE DEVELOPMENT, MORPHOLOGY, AND FUNCTION

Actin Nucleation: Arp2/3, WASP/WAVE, Cortactin, and Formin

Arp2/3 complex

Following activation, the Arp2/3 complex, which consists of seven subunits, including Arp2, Arp3, and five other actin-related proteins, mediates the formation of new actin filaments at fixed angles to existing filaments to form a branched actin network [50,51]. Arp2/3-mediated branching provides a mechanism for expanding the actin network and is thought to be involved in generating cell protrusions [52]. Since dendritic spines consist of branched actin filaments, this raised an intriguing question as to the role of the Arp2/3 complex in regulating spine dynamics. Several subunits of the Arp2/3 complex, including Arp2 and Arp3, are concen-

trated in dendritic spines, suggesting a functional role for the Arp2/3 complex in spine function [53-56]. Consistent with this, knockdown of Arp2/3 complex proteins causes a reduction in the number of spines without significantly decreasing the density of filopodia-like protrusions [56,57] (Table **1**). The Arp2/3 complex is most likely not essential for the initial extension of dendritic filopodia-like protrusions, but instead is critical for enlargement and maturation of the spine head. Moreover, expression of protein interacting with C kinase1 (PICK1), which is involved in AMPAR endocytosis, inhibits Arp2/3-mediated actin polymerization and causes NMDA-mediated GluR2 endocytosis in spines [58]. This suggests a role for the Arp2/3 complex in regulating AMPAR trafficking.

Table 1. The Role of Actin-Binding Proteins in Actin Regulation and Spine and Synaptic Function

Actin-binding Protein	Actin Regulation	Spine Density	Spine Morphology	Synaptic Strength and Plasticity	References
α-actinin 2	Bundling	Overexpression: reduced spine density and increased number of filopodia-like protrusions	Overexpression: longer filopodia-like protrusions and thinner, elongated spines	Not determined	[117, 123]
Arp2/3 complex	Branching, nucleation	Knockdown (Arp3, p34): reduced spine density Knockdown (p34): fewer mature spines	Knockdown (p34): longer dendritic protrusions	Not determined	[56,57]
CaMKIIβ	Bundling	Knockdown: reduced number of mature dendritic spines	Knockdown: longer spines and smaller heads	Not determined	[149]
α-N-catenin	Bundling	Overexpression: increased spine density	Knockdown: longer, immature spines with enhanced motility; many spines showed unusually dynamic deformation of their heads	Not determined	[169]
Cofilin	Depolymerization, severing	Knockdown: decreased number of thin spines	Knockdown: longer dendritic protrusions Dominant negative: decreased length of spines Constitutively active: longer spines with smaller heads Dominant negative peptide: less spine shrinkage during LTD Constitutively active peptide: more spine shrinkage during LTD	Dominant negative peptide: blockage of NMDAR-mediated, but not AMPAR-mediated LTD Constitutively active peptide: retain LTD expression	[57,107,108]
Cortactin	Nucleation-promoting factor	Knockdown: reduced spine density	Overexpression: longer spines	Not determined	[78]
Drebrin	Anti-bundling	Overexpression: destabilization of dendritic spines Knockdown: fewer filopodia-like protrusions, more mature spines Antisense-based knockdown: reduced spine density	Overexpression: longer, wider protrusions and longer spines Knockdown: larger spine heads Spine containing endogenous drebrin: larger spine heads	Overexpression: no effect on spontaneous synaptic transmission, but stronger and increased miniature synaptic transmission	[186-188,192-194]
EPS8	Caps barbed ends to stabilize F-actin	Not determined	Not determined	Knockout: altered NMDA currents of basal synaptic transmission	[174]
Formin (mDia2)	Nucleation	Knockdown: fewer filopodia-like protrusions and thin spines, but an increase in the number of stubby spines	Knockdown: spines with irregular morphology	Not determined	[57]
Gelsolin	Anti-bundling, capping, severing	Not determined	Not determined	Knockdown: no effect on miniature synaptic transmission	[22]

Table 1. contd…

Actin-binding Protein	Actin Regulation	Spine Density	Spine Morphology	Synaptic Strength and Plasticity	References
N-WASP	Nucleation-promoting factor	Overexpression: increased spine density Knockdown: reduced spine density	Dominant negative: longer, thinner protrusions compared with control neurons	Not determined	[56,71]
Neurabin I	Bundling	Overexpression: more filopodia-like protrusions in younger neurons Overexpression of F-actin binding domain (ABD) of Nrb I: increased density of filopodia-like protrusions and spines with smaller heads	Overexpression ABD: longer spines and filopodia-like protrusions	Overexpression ABD: less miniature synaptic transmission Knockout: reduced LTP, but no effect on LTD Overexpression: inhibited LTP and enhanced LTD Overexpression ABD deletion mutant: increased LTP and reduced LTD	[153-158]
Neurabin II/Spinophilin	Bundling	Overexpression: no significant effect on density of filopodia-like protrusions Knockout: increased spine density in young neurons	Overexpression: longer filopodia-like protrusions	Knockout: reduced LTD, but no effect on LTP	[155,161,162]
Profilin II	Polymerization	Not determined	Not determined	Knockout: no effect on LTP or LTD	[94]
Synaptopodin	Bundling	Not determined	Spines containing endogenous synaptopodin: larger spine heads, but same spine length	Knockout: reduced LTP	[129,133]
WAVE 1	Nucleation-promoting factor	Knockout: reduced spine density and fewer mature spines; increased number of filopodia-like protrusions	Not determined	Knockout: increased LTP and reduced LTD	[72,74]

WAVE/WASP and Cortactin

The Arp2/3 complex is primarily activated by Wiskott Aldrich syndrome protein (WASP) family members and cortactin [59-61]. The WASP family includes WASP, neural WASP (N-WASP), and WASP family verprolin-homologous protein (WAVE)1-3 [62-65]. WASP and N-WASP exist in an autoinhibited conformation, which can be relieved by the binding of phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), activated Cdc42, or adaptor proteins [61,66,67]. WAVE proteins, on the other hand, do not adopt an autoinhibitory conformation, but remain inactive while in a complex with regulatory proteins [68,69]. The WAVE proteins can be released or reactivated by adaptor proteins or the Rho family GTPase Rac1 even though WAVE proteins do not possess a GTPase binding domain [68,70]. Among the WASP family members, N-WASP, WAVE1, and WAVE3 are highly expressed in the brain, and at least two of these proteins have been shown to modulate spine formation [65]. N-WASP localizes to spines and functional synapses where it regulates the development of these structures via its upstream activator, Cdc42, and its downstream effector, the Arp2/3 complex [56,71]. Several studies have also indicated a role for WAVE1 in regulating spine morphogenesis. Striatal neurons from WAVE1 knockout mice display more protrusions but fewer mature spines [72]. This phenotype is recapitulated in cultured hippocampal neurons and can be rescued by a WAVE1 mutant that is unphosphorylatable at serine 310, suggesting an effect for WAVE1 on spine development [72,73]. WAVE1 phosphorylation reduces Arp2/3-mediated actin polymerization and can be modulated by Cdk5 and cAMP, which are important for brain development and synaptic plasticity [72]. This work suggests the altered synaptic plasticity and behavioral abnormalities in WAVE1 knockout mice are due to aberrant actin dynamics [74]. In addition, WAVE1 expression can also affect depolarization-induced mitochondrial translocation into dendritic spines [75]. Since mitochondria provide ATP for many cellular processes, it is possible that WAVE1-mediated mitochondrial mislocalization may affect protein trafficking during synaptic plasticity events.

Compared with WASP family proteins, cortactin is a less potent activator of the Arp2/3 complex because it binds to F-actin, but not to monomeric actin [76]. However, cortactin can enhance WASP-mediated Arp2/3 activation, and binding to WASP-interacting protein (WIP) can enhance the effects of cortactin on Arp2/3 activation [77]. In dendritic spines, the localization of cortactin appears to be highly controlled by neuronal activity. Under basal conditions, cortactin is shown to target to spine heads via its N-terminal region, which contains Arp2/3- and F-actin binding domains [78,79]. Activation of NMDAR causes cortactin to translocate from spines to the dendritic shaft, whereas brain-derived neurotrophic factor (BDNF) induces the localization of cortactin to postsynaptic sites, suggesting a role for this protein in regulating synaptic plasticity [78,80]. Knockdown of cortactin using an siRNA approach results in a significant decrease in the number of spines while overexpression pro-

motes spine elongation [78]. Collectively, these studies point to a functional role for cortactin in the activity-dependent modulation of spine formation. More recently, cortactin has been shown to associate with the microtubule plus-end binding protein EB3, and this interaction appears to be required for EB3-mediated spine expansion [81]. These intriguing results raise the possibility that the cortactin-EB3 interaction can serve as a link between microtubules and the actin cytoskeleton in dendritic spines [81].

Formin

Besides the Arp2/3 complex-related signaling pathways, formins have also been shown to modulate actin nucleation [82-85]. Formin proteins contain a conserved formin homology 2 (FH2) domain, which is required for actin nucleation, and a FH1 domain that assists actin filament assembly via an interaction with profilin [82,83]. Unlike Arp2/3 complex-mediated actin nucleation, formins generate unbranched actin filaments due to their ability to associate with barbed ends and modulate actin elongation [82,83]. Formins, like the Arp2/3 complex, exist in an autoinhibitory conformation, which for most formin family members can be released by the binding of Rho GTPases [86]. Given their essential role in actin nucleation, it is not surprising that mammalian *diaphanous*-related formin2 (mDia2) has been found to regulate spine formation [57]. In this study, activated mDia2 promotes the formation of filopodial protrusions, but the Arp2/3 complex is required for spine head expansion and maturation [57]. Since spines contain both branched and unbranched actin filaments, it is tempting to speculate that formins also play a role in regulating synaptic plasticity.

Polymerization/Depolymerization: Profilin, Gelsolin and Cofilin

Actin polymerization requires the constant addition of G-actin monomers to growing filaments, and ABPs, such as profilin, help supply G-actin to the plus end of actin filaments. However, to maintain actin dynamics and actin-based processes, unlimited actin polymerization cannot occur and must be counterbalanced by depolymerization of existing actin filaments. ABPs, such as gelsolin and cofilin, are critical for this process.

Profilin

As discussed earlier, G-actin can bind to either ADP or ATP and be incorporated into actin filaments; however, ATP-bound actin has a higher efficiency of assembly into filaments [87]. Profilin can induce actin polymerization by catalyzing the exchange of ADP for ATP on G-actin and by promoting the addition of actin monomers to the growing end of filaments [88-90]. Neurons have two types of profilin, profilin I, which is ubiquitously expressed, and brain-specific profilin II [91]. By expressing fluorescently-tagged profilin II in cultured hippocampal neurons, Ackermann *et al.* found that it is targeted to spine heads in response to electrical stimulation and NMDAR activation [92]. Moreover, profilin II-induced enrichment at spine heads appears to be accompanied by the stabilization of spine morphology, suggesting a functional role for this protein in synaptic plasticity [92]. A behavioral study further supports this idea by showing the translocation of profilin into spines in the lateral amygdala under fear-inducing conditions [93]. Surprisingly, profilin II knockout mice do not express any defects in LTP/LTD; however, possible compensatory functions of profilin I cannot be ruled out since profilin I also localizes to spines [94,95].

Gelsolin

Gelsolin is named for its ability to activate the gel to solution (gel-sol) transformation of actin filaments [96]. Among the ABPs, gelsolin has the most potent actin severing activity, which is regulated by calcium [97]. The severing effect ultimately increases the amount of available barbed ends when gelsolin is uncapped from F-actin. Conversely, its severing function and association with actin can be inhibited by a local increase in PI(4,5)P2 [98]. The role of gelsolin in dendritic spines is not well understood; however, it does not appear to influence actin turnover under basal conditions, but it may be required for NMDAR-mediated actin stabilization during LTD by providing more barbed ends for additional actin polymerization [22].

Cofilin

Cofilin belongs to the ADF/cofilin family, and it regulates actin dynamics through several different mechanisms [99]. At the pointed ends of actin filaments, cofilin may enhance actin depolymerization and may sequester G-actin in the ADP-form [100,101]. In addition, cofilin can sever actin filaments and thus create more available barbed ends [102]. Moreover, the binding of cofilin to F-actin causes a structural change in actin filaments, which alters the selection of ABPs that can bind [103]. These activities of cofilin are negatively regulated by its phosphorylation at serine 3 [104,105]. In neurons, cofilin localizes within the postsynaptic density of dendritic spines [106]. Under basal conditions, cofilin knockdown reduces actin turnover, which appears to be necessary to maintain spine length and morphology [57]. In addition, cofilin inactivation is important for spine development and morphology since expression of an inactive cofilin mutant results in shorter protrusions and more mature spines, suggesting that the severing activity of cofilin impedes spine maturation [107]. Synaptic plasticity is shown to regulate cofilin activity, and cofilin, in turn, is able to modulate actin dynamics to control spine expansion during LTP and spine shrinkage during LTD [34,108-111]. The importance of cofilin in synaptic plasticity is also supported by studies of LIM kinases, which are upstream regulators of cofilin. In mice, knockout of LIM kinase 1, which is highly expressed in the brain, results in altered spine morphology, enhanced LTP, and impaired spatial learning [112,113]. This can most likely be attributed to a reduction in cofilin phosphorylation and an increase in its severing activity. In contrast, LIM kinase 2 knockout mice do not exhibit obvious differences to wild-type mice in cofilin phosphorylation and synaptic transmission [110].

Actin Reorganization: α-Actinin, Synaptopodin, CaMKIIβ, Neurabins, α-N-catenin, EPS8, and Drebrin

ABPs may also affect spine function via modulation of actin organization. Indeed, some ABPs regulate spine development and synaptic plasticity by remodeling actin filaments without necessarily affecting the kinetics of actin polymerization. In this section, we will discuss ABPs that modulate

reorganization of the actin cytoskeleton and how they regulate the function of dendritic spines and synapses.

α-Actinin

α-Actinin belongs to the spectrin/dystrophin family of proteins and serves to crosslink actin filaments [114,115]. The α-actinin family consists of four members and among them only α-actinin 3 is not expressed in the brain [54,116]. α-Actinin localizes to the postsynaptic density of excitatory synapses [116]. Exogenous expression of α-actinin 2 in hippocampal neurons increases the length and density of dendritic protrusions and promotes faster motility of these structures [117]. Intriguingly, α-actinin 2 interacts and influences the function of several proteins related to synaptic strength, including NMDAR, CaMKII, and spine associated *Rap* GTPase GAP (SPAR). It is believed that α-actinin 2 links NMDAR (NR1 and NR2B) to the actin cytoskeleton and modulates their channel gating [116,118]. The opening of NMDAR is highly controlled by the intracellular calcium concentration; when the level of calcium increases, the probability that NMDAR channels will open is decreased by the binding of activated calmodulin [119]. However, this reduced activation by calmodulin can be abrogated by the presence of α-actinin through its ability to compete with calmodulin for binding to NMDAR [118,120]. In addition, α-actinin 2 also competes with calcium/calmodulin for binding to CaMKII and hence negatively modulates CaMKII activity [121,122]. Since both α-actinin 2 and CaMKII are enriched at the postsynaptic density in spines, a higher local calcium concentration may be required to induce CaMKII activation [121]. More recently, α-actinin is shown to interact with SPAR and increase the elongation of dendritic spines while SPAR induces the enlargement of spine heads [123]. The actin bundling activity of α-actinin can be regulated by other molecules, such as synaptopodin, which is thought to be important in dendritic spines [124,125].

Synaptopodin

Synaptopodin is an actin-associated protein that is thought to regulate actin bundling through its interaction with α-actinin [124,125]. Synaptopodin accumulates in dendritic spines where it is closely associated with the spine apparatus, which is a distinct organelle, consisting of smooth ER and electron-dense plates located in the neck of most mature spines [126-128]. Although the function of the spine apparatus is still largely unknown, it may serve as a reservoir for calcium and a regulator of glutamate receptor trafficking [127]. Synaptopodin knockout mice lack a spine apparatus, which indicates an essential role for synaptopodin in the formation of this structure [129]. Electron microscopy shows that actin filaments are in close contact with the spine apparatus and serve as a link between this compartment and the postsynaptic density [130]. The localization of synaptopodin to the spine apparatus suggests that it can connect actin filaments to the spine apparatus although the functional significance of this is currently unknown [131].

During LTP, the expression of synaptopodin is increased both at a transcriptional and translational level; however, when synaptopodin is knocked out, LTP is reduced [129,132]. In addition, synaptopodin knockout mice exhibit impaired spatial learning. Another more recent report indicates a strong correlation between synaptopodin expression and calcium storage during LTP [133]. In this study, synaptopodin knockdown reduces spine size, LTP responses, and the expression of ryanodine receptors in spines. Ryanodine receptors localize to smooth ER and are responsible for intracellular calcium release [134]. In synaptopodin knockdown neurons, agonist-driven ryanodine receptor activation failed to induce LTP expression and GFP-GluR1 accumulation into spines, suggesting that synaptopodin controls synaptic transmission by regulating calcium release from the spine apparatus.

CaMKII

CaMKII is one of the most abundant serine/threonine kinases expressed in neurons where it is highly concentrated in the postsynaptic density [135,136]. It is well known for its role in regulating synaptic plasticity as well as memory and can modulate plasticity through phosphorylation of NMDARs and AMPARs [137-142]. CaMKII forms homo- or hetero- oligomers of 12 subunits and consists of α, β, γ, δ families [143]. The major isoforms in neurons are α and β family members [144]. These two isoforms have similar domain organization, and their activation is regulated by calcium/calmodulin binding and autophosphorylation despite slight differences in calmodulin binding affinities [145]. While only CaMKIIβ appears to directly associate with actin filaments, CaMKIIα can bind to α-actinin to regulate actin dynamics and organization [122,145-147]. CaMKIIβ binding to F-actin is dependent on its activation, but not on its kinase activity [148,149]. The role of CaMKIIβ in regulating postsynaptic actin may be due to its ability to bundle F-actin since it has been shown to promote the formation of mature spines by crosslinking actin filaments and reducing actin turnover [148,149].

Neurabins

Neurabin I (Nrb I) and neurabin II (Nrb II)/spinophilin are two related proteins that contain similar domain structures, including an F-actin-binding domain, a PDZ domain, and a coiled-coil domain, which mediates homo- and heterodimerization [150]. While Nrb I is exclusively expressed in the brain, Nrb II/spinophilin is found in numerous mammalian tissues [151,152]. In neurons, these two molecules have been reported to localize to dendritic spines where they bind to PP1, but appear to have distinct functions [152-155].

Nrb I through its F-actin binding domain regulates spine morphology by increasing the length of filopodia-like protrusions and spines [156]. The interaction of Nrb I with PP1 appears to be important for the maturation of spines and modulation of surface expression of AMPAR (GluR1) as well as synaptic transmission [157]. In the hippocampus, exogenous expression of Nrb I enhances LTD but inhibits LTP; however, the opposite effects on synaptic plasticity are observed when Nrb I fails to bind to PP1, suggesting PP1 may not be properly targeted to spines if this association is altered [153]. Interestingly, Nrb I knockout mice exhibit a reduction in LTP, GluR1 phosphorylation, and contextual fear memory, but an increase in basal synaptic transmission and unaltered LTD [158]. These knockout phenotypes are also shown at corticostriatal synapses with altered dopamine-modulated AMPAR activity, reduced LTP, and normal LTD [155]. It is possible that Nrb I knockout leads to pre-

saturation of synaptic responses and thus, impairs LTP since LTP can be rescued via pre-conditioning with LTD [158].

Nrb II/spinophilin is enriched in dendritic spines and ectopic expression of this protein induces elongation of filopodia-like protrusions in hippocampal neurons [159-161]. Nrb II/spinophilin knockout mice exhibit reduced LTD due to altered glutamatergic transmission; however, these mice possess normal LTP as well as enhanced resistance to kainate-induced seizures and neuronal degeneration [161,162]. A behavioral study supports the impaired synaptic plasticity in Nrb II/spinophilin knockouts by showing defects in learning-conditioned taste aversion [163].

These phenotypes from Nrb I and Nrb II/spinophilin knockout mice raise a couple of intriguing questions. First, how are actin dynamics at the cellular level modulated by Nrb II/spinophilin during synaptic plasticity? LTP and LTD induction are believed to be modulated by protein phosphatases and protein kinases, including PKA, CaMKII, Cdk5, and extracellular signal-regulated kinase (ERK) [32]. Interestingly, Nrb I can be phosphorylated by PKA, and Nrb II/spinophilin has been shown to be phosphorylated by all the above mentioned kinases. In most cases, phosphorylation of Nrb II/spinophilin reduces its capacity to bind and crosslink F-actin [154,161,164,165]. Thus, phosphorylation of both neurabin proteins is likely to affect spine structure via reorganization of actin. Second, how do Nrb I and Nrb II/spinophilin coordinately exert their functions? It is clear that both NrbI and Nrb II/spinophilin bind to PP1 and exhibit high sequence homology in their PDZ domain, which is responsible for protein-protein interactions [166]. In addition, Nrb I and Nrb II/spinophilin have been suggested to form a heterodimer through their coiled-coil domain [167]. If both of the proteins bind to the same molecules with the same interaction motif, do they act in a compensatory or antagonistic manner to regulate synaptic functions when both are present in spines? The answer is currently unknown, but would be interesting to investigate by determining whether Nrb I or Nrb II/spinophilin expression can rescue the knockout phenotype of the other protein.

α-N-catenin

α-N-catenin is a neuronal-specific member of the α-catenin family and has been proposed to bind to cadherins and to influence actin turnover by modulating Arp2/3 complex-mediated actin polymerization [168]. In neurons, synaptic targeting of α-N-catenin depends on neuronal activity, and expression of α-N-catenin affects the stabilization of spine motility and development [169]. Genetic disruption of α-N-catenin expression results in the formation of longer, immature spines that are highly motile and are unable to establish stable contacts with axonal terminals. In addition, overexpression of α-N-catenin reduces spine turnover and coincides with an increase in spine density [169]. Future studies are needed to examine the underlying mechanisms of how α-N-catenin stabilizes spine formation and motility in the context of actin turnover.

EPS8

Epidermal growth factor receptor pathway substrate 8 (EPS8) was first identified as a substrate for epidermal growth factor receptor (EGFR) and has been reported to transmit signals to remodel the actin cytoskeleton [170]. Two different mechanisms have been proposed for how EPS8 regulates actin reorganization. First, by capping the barbed ends of actin filaments, EPS8 can stabilize F-actin and prevent actin polymerization/depolymerization. Second, EPS8 activates and enhances the actin bundling activity of insulin receptor tyrosine kinase substrate p53 (IRSp53) [171]. In neurons, EPS8 is enriched at postsynaptic regions, and its activator Abelson interacting protein 1 (Abi 1) has been reported to regulate synaptic plasticity [172,173]. A study using cerebellum extracts has shown that EPS8 is isolated in a complex containing NMDAR (NR1, 2A, 2C) and regulates ethanol-induced synaptic transmission and NMDAR-mediated actin reorganization [174]. Even though the role of EPS8 in spine formation is currently unresolved, its regulatory function in synaptic plasticity is anticipated due to its interaction with NMDAR, and its connection to GTPases and their downstream ABPs.

Drebrin

Developmentally regulated brain protein (drebrin) has been shown to modulate actin bundling and prevent actin filaments from binding to ABPs, including α-actinin [175-179]. The expression of drebrin switches from an embryonic (E) to an adult (A) isoform by alternative splicing during postnatal development [180]. The importance of drebrin A is demonstrated by its close correlation with several neuronal diseases [176,181]. For example, drebrin immunoreactivity is markedly reduced in the brains of patients with Alzheimer's disease, particularly in the hippocampus, which is central to learning and memory [182]. Reduced levels of drebrin are also observed in patients with Down's syndrome [183]. The loss of drebrin in the hippocampus of patients with Alzheimer's disease is paralleled with a significant increase in the amount of cofilin [184]. Since cofilin competes with drebrin for binding to F-actin, the enhanced level of cofilin may impair the interaction of drebrin with actin, possibly leading to an increase in the degradation of drebrin and an alteration in actin reorganization, which may underlie the cognitive defects associated with Alzheimer's disease [181,184].

Several studies have shown that drebrin expression affects spine morphogenesis and maturation. In cultured cortex neurons, drebrin A localizes to dendritic spines through its actin-binding domain, and exogenous expression of this protein causes immature neurons to form longer and wider protrusions and mature neurons to form longer spines [185,186]. In addition, drebrin expression in cultured hippocampal neurons is important for the formation of PSD95 clusters and correlates with spine maturation [187]. When exogenous drebrin proteins were expressed in mature hippocampal neurons, they seemed to destabilize dendritic spines and lose their synaptic contacts [188]. This may have occurred through antagonistic competition with α-actinin, which when bound to actin filaments may stabilize spines through crosslinking of actin. In the same study, drebrin knockdown led to fewer protrusions and more mature spines, suggesting drebrin expression may impede spine development [188]. Growing evidence indicates that neuronal activity determines the localization of drebrin, which, in turn, regulates the localization of NMDAR and synaptic transmission. For instance, the glutamate-mediated activation of NMDAR induces drebrin translocation from spines to shafts, and blockade of

NMDAR activity with antagonists abolishes this translocation [189,190]. In addition, dentate gyrus LTP and spontaneous activation of GluR2-containing AMPARs induce the formation of drebrin clusters [34,191]. In turn, drebrin A-containing spines exhibit larger spine heads and possess more immunolabeled NMDAR compared with spines lacking drebrin A [192]. In support of this notion, drebrin A knockdown alters the synaptic targeting of NMDAR induced by an NMDAR antagonist [193]. These effects on NMDAR lead to alterations in the frequency and amplitude of synaptic transmission in glutamatergic synapses, indicating a functional role for drebrin in synaptic strength [194]. Given that drebrin expression is highly regulated during development and is correlated with neuronal disorders, future studies investigating the upstream regulators of drebrin expression and function should prove to be very fruitful.

CONCLUSIONS

Over the last decade, actin has been shown to be critical in regulating spine function. More recently, the underlying molecular mechanisms that modulate actin turnover and reorganization are beginning to be unravelled by studies focused on actin-binding proteins. Specifically, these studies show the role of various ABPs in regulating spine motility, morphogenesis, maturation, and synaptic transmission. However, many intriguing questions remain to be answered. Since neurons possess many ABPs, how do they work together to regulate actin dynamics and reorganization to control spine function? What are the spatiotemporal signals in spines that modulate the interplay of ABPs? Moreover, does the cytoskeleton facilitate communication between individual spines, and what role do ABPs play in this process? Since ABPs have been implicated in synaptic transmission, this raises the question of whether they regulate trafficking by remodeling the actin cytoskeleton or by affecting their associated signaling molecules. Evolving technologies will certainly prove to be beneficial in addressing these challenging questions. For example, newly developed photoactivatable fluorescence proteins can be used to track trafficking events with higher spatial and temporal resolution. In addition, visualization of ABP-promoted ultrastructural changes in the actin cytoskeleton may be obtained by using platinum replica electron microscopy. Indeed, the future looks exciting as emerging studies continue to unveil the role of ABPs in regulating the function of dendritic spines and thus, the complex neuronal circuitry of the CNS.

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REFERENCES

[1] Gray EG. Axo-somatic and axo-dendritic synapses of the cerebral cortex: an electron microscope study. J Anat 1959; 93: 420-33.

[2] Sorra KE, Harris KM. Overview on the structure, composition, function, development, and plasticity of hippocampal dendritic spines. Hippocampus 2000; 10: 501-11.

[3] Harris KM, Kater SB. Dendritic spines: cellular specializations imparting both stability and flexibility to synaptic function. Annu Rev Neurosci 1994; 17: 341-71.

[4] Peters A, Kaiserman-Abramof IR. The small pyramidal neuron of the rat cerebral cortex: the perikaryon, dendrites and spines. Am J Anat 1970; 127: 321-55.

[5] Chechlacz M, Gleeson JG. Is mental retardation a defect of synapse structure and function? Pediatr Neurol 2003; 29: 11-7.

[6] Grossman AW, Aldridge GM, Weiler IJ, Greenough WT. Local protein synthesis and spine morphogenesis: fragile X syndrome and beyond. J Neurosci 2006; 26: 7151-5.

[7] Swann JW, Al-Noori S, Jiang M, Lee CL. Spine loss and other dendritic abnormalities in epilepsy. Hippocampus 2000; 10: 617-25.

[8] Ferrer I, Gullotta F. Down's syndrome and Alzheimer's disease: dendritic spine counts in the hippocampus. Acta Neuropathol 1990; 79: 680-5.

[9] Suetsugu M, Mehraein P. Spine distribution along the apical dendrites of the pyramidal neurons in Down's syndrome: a quantitative Golgi study. Acta Neuropathol 1980; 50: 207-10.

[10] Ramakers GJ. Rho proteins, mental retardation and the cellular basis of cognition. Trends Neurosci 2002; 25: 191-9.

[11] van Galen EJ, Ramakers GJ. Rho proteins, mental retardation and the neurobiological basis of intelligence. Prog Brain Res 2005; 147: 295-317.

[12] Sheng M, Hoogenraad CC. The postsynaptic architecture of excitatory synapses: a more quantitative view. Annu Rev Biochem 2007; 76: 823-47.

[13] Collins MO, Grant SG. Supramolecular signalling complexes in the nervous system. Subcell Biochem 2007; 43: 185-207.

[14] Dillon C, Goda Y. The actin cytoskeleton: integrating form and function at the synapse. Annu Rev Neurosci 2005; 28: 25-55.

[15] Ethell IM, Pasquale EB. Molecular mechanisms of dendritic spine development and remodeling. Prog Neurobiol 2005; 75: 161-205.

[16] Carlier MF. Actin polymerization and ATP hydrolysis. Adv Biophys 1990; 26: 51-73.

[17] Oosawa F, Asakura S. Theory of polymerization equilibrium. In Thermodynamics of the polymerization of protein. New York: Academic Press 1975.

[18] Chesarone MA, Goode BL. Actin nucleation and elongation factors: mechanisms and interplay. Curr Opin Cell Biol 2009; 21: 28-37.

[19] Landis DM, Reese TS. Cytoplasmic organization in cerebellar dendritic spines. J Cell Biol 1983; 97: 1169-78.

[20] Fifkova E, Delay RJ. Cytoplasmic actin in neuronal processes as a possible mediator of synaptic plasticity. J Cell Biol 1982; 95: 345-50.

[21] Fischer M, Kaech S, Knutti D, Matus A. Rapid actin-based plasticity in dendritic spines. Neuron 1998; 20: 847-54.

[22] Star EN, Kwiatkowski DJ, Murthy VN. Rapid turnover of actin in dendritic spines and its regulation by activity. Nat Neurosci 2002; 5: 239-46.

[23] Honkura N, Matsuzaki M, Noguchi J, Ellis-Davies GC, Kasai H. The subspine organization of actin fibers regulates the structure and plasticity of dendritic spines. Neuron 2008; 57: 719-29.

[24] Allison DW, Gelfand VI, Spector I, Craig AM. Role of actin in anchoring postsynaptic receptors in cultured hippocampal neurons: differential attachment of NMDA versus AMPA receptors. J Neurosci 1998; 18: 2423-36.

[25] Allison DW, Chervin AS, Gelfand VI, Craig AM. Postsynaptic scaffolds of excitatory and inhibitory synapses in hippocampal neurons: maintenance of core components independent of actin filaments and microtubules. J Neurosci 2000; 20: 4545-54.

[26] Kuriu T, Inoue A, Bito H, Sobue K, Okabe S. Differential control of postsynaptic density scaffolds via actin-dependent and -independent mechanisms. J Neurosci 2006; 26: 7693-706.

[27] Zhang W, Benson DL. Stages of synapse development defined by dependence on F-actin. J Neurosci 2001; 21: 5169-81.

[28] Malinow R, Malenka RC. AMPA receptor trafficking and synaptic plasticity. Annu Rev Neurosci 2002; 25: 103-26.

[29] Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 1973; 232: 331-56.

[30] Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron 2004; 44: 5-21.

[31] Newpher TM, Ehlers MD. Glutamate receptor dynamics in dendritic microdomains. Neuron 2008; 58: 472-97.

[32] Sheng M, Kim MJ. Postsynaptic signaling and plasticity mechanisms. Science 2002; 298: 776-80.

[33] Shepherd JD, Huganir RL. The cell biology of synaptic plasticity: AMPA receptor trafficking. Annu Rev Cell Dev Biol 2007; 23: 613-43.

[34] Fukazawa Y, Saitoh Y, Ozawa F, *et al.* Hippocampal LTP is accompanied by enhanced F-actin content within the dendritic spine that is essential for late LTP maintenance *in vivo*. Neuron 2003; 38: 447-60.

[35] Lin B, Kramar EA, Bi X, *et al.* Theta stimulation polymerizes actin in dendritic spines of hippocampus. J Neurosci 2005; 25: 2062-9.

[36] Okamoto K, Nagai T, Miyawaki A, Hayashi Y. Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. Nat Neurosci 2004; 7: 1104-12.

[37] Kim CH, Lisman JE. A role of actin filament in synaptic transmission and long-term potentiation. J Neurosci 1999; 19: 4314-24.

[38] Krucker T, Siggins GR, Halpain S. Dynamic actin filaments are required for stable long-term potentiation (LTP) in area CA1 of the hippocampus. Proc Natl Acad Sci USA 2000; 97: 6856-61.

[39] Gerges NZ, Backos DS, Rupasinghe CN, Spaller MR, Esteban JA. Dual role of the exocyst in AMPA receptor targeting and insertion into the postsynaptic membrane. EMBO J 2006; 25: 1623-34.

[40] Park M, Salgado JM, Ostroff L, *et al.* Plasticity-induced growth of dendritic spines by exocytic trafficking from recycling endosomes. Neuron 2006; 52: 817-30.

[41] Yudowski GA, Puthenveedu MA, Leonoudakis D, *et al.* Real-time imaging of discrete exocytic events mediating surface delivery of AMPA receptors. J Neurosci 2007; 27: 11112-21.

[42] Park M, Penick EC, Edwards JG, Kauer JA, Ehlers MD. Recycling endosomes supply AMPA receptors for LTP. Science 2004; 305: 1972-5.

[43] Man HY, Lin JW, Ju WH, *et al.* Regulation of AMPA receptor-mediated synaptic transmission by clathrin-dependent receptor internalization. Neuron 2000; 25: 649-62.

[44] Correia SS, Bassani S, Brown TC, *et al.* Motor protein-dependent transport of AMPA receptors into spines during long-term potentiation. Nat Neurosci 2008; 11: 457-66.

[45] Lise MF, Wong TP, Trinh A, *et al.* Involvement of myosin Vb in glutamate receptor trafficking. J Biol Chem 2006; 281: 3669-78.

[46] Osterweil E, Wells DG, Mooseker MS. A role for myosin VI in postsynaptic structure and glutamate receptor endocytosis. J Cell Biol 2005; 168: 329-38.

[47] Ryu J, Liu L, Wong TP, *et al.* A critical role for myosin IIb in dendritic spine morphology and synaptic function. Neuron 2006; 49: 175-82.

[48] Wang Z, Edwards JG, Riley N, *et al.* Myosin Vb mobilizes recycling endosomes and AMPA receptors for postsynaptic plasticity. Cell 2008; 135: 535-48.

[49] Zhou Q, Xiao M, Nicoll RA. Contribution of cytoskeleton to the internalization of AMPA receptors. Proc Natl Acad Sci USA 2001; 98: 1261-6.

[50] Mullins RD, Heuser JA, Pollard TD. The interaction of Arp2/3 complex with actin: nucleation, high affinity pointed end capping, and formation of branching networks of filaments. Proc Natl Acad Sci USA 1998; 95: 6181-6.

[51] Pollard TD. Regulation of actin filament assembly by Arp2/3 complex and formins. Annu Rev Biophys Biomol Struct 2007; 36: 451-77.

[52] Bailly M, Macaluso F, Cammer M, *et al.* Relationship between Arp2/3 complex and the barbed ends of actin filaments at the leading edge of carcinoma cells after epidermal growth factor stimulation. J Cell Biol 1999; 145: 331-45.

[53] Li KW, Hornshaw MP, Van Der Schors RC, *et al.* Proteomics analysis of rat brain postsynaptic density. Implications of the diverse protein functional groups for the integration of synaptic physiology. J Biol Chem 2004; 279: 987-1002.

[54] Peng J, Kim MJ, Cheng D, *et al.* Semiquantitative proteomic analysis of rat forebrain postsynaptic density fractions by mass spectrometry. J Biol Chem 2004; 279: 21003-11.

[55] Racz B, Weinberg RJ. Organization of the Arp2/3 complex in hippocampal spines. J Neurosci 2008; 28: 5654-9.

[56] Wegner AM, Nebhan CA, Hu L, *et al.* N-wasp and the Arp2/3 complex are critical regulators of actin in the development of dendritic spines and synapses. J Biol Chem 2008; 283: 15912-20.

[57] Hotulainen P, Llano O, Smirnov S, *et al.* Defining mechanisms of actin polymerization and depolymerization during dendritic spine morphogenesis. J Cell Biol 2009; 185: 323-39.

[58] Rocca DL, Martin S, Jenkins EL, Hanley JG. Inhibition of Arp2/3-mediated actin polymerization by PICK1 regulates neuronal morphology and AMPA receptor endocytosis. Nat Cell Biol 2008; 10: 259-71.

[59] Weaver AM, Young ME, Lee WL, Cooper JA. Integration of signals to the Arp2/3 complex. Curr Opin Cell Biol 2003; 15: 23-30.

[60] Machesky LM, Mullins RD, Higgs HN, *et al.* Scar, a WASp-related protein, activates nucleation of actin filaments by the Arp2/3 complex. Proc Natl Acad Sci USA 1999; 96: 3739-44.

[61] Rohatgi R, Ma L, Miki H, *et al.* The interaction between N-WASP and the Arp2/3 complex links Cdc42-dependent signals to actin assembly. Cell 1999; 97: 221-31.

[62] Derry JM, Kerns JA, Weinberg KI, *et al.* WASP gene mutations in Wiskott-Aldrich syndrome and X-linked thrombocytopenia. Hum Mol Genet 1995; 4: 1127-35.

[63] Miki H, Miura K, Takenawa T. N-WASP, a novel actin-depolymerizing protein, regulates the cortical cytoskeletal rearrangement in a PIP2-dependent manner downstream of tyrosine kinases. EMBO J 1996; 15: 5326-35.

[64] Miki H, Suetsugu S, Takenawa T. WAVE, a novel WASP-family protein involved in actin reorganization induced by Rac. EMBO J 1998; 17: 6932-41.

[65] Suetsugu S, Miki H, Takenawa T. Identification of two human WAVE/SCAR homologues as general actin regulatory molecules which associate with the Arp2/3 complex. Biochem Biophys Res Commun 1999; 260: 296-302.

[66] Rohatgi R, Ho HY, Kirschner MW. Mechanism of N-WASP activation by CDC42 and phosphatidylinositol 4, 5-bisphosphate. J Cell Biol 2000; 150: 1299-310.

[67] Werbonat Y, Kleutges N, Jakobs KH, van Koppen CJ. Essential role of dynamin in internalization of M2 muscarinic acetylcholine and angiotensin AT1A receptors. J Biol Chem 2000; 275: 21969-74.

[68] Eden S, Rohatgi R, Podtelejnikov AV, Mann M, Kirschner MW. Mechanism of regulation of WAVE1-induced actin nucleation by Rac1 and Nck. Nature 2002; 418: 790-3.

[69] Kitamura T, Kitamura Y, Yonezawa K, *et al.* Molecular cloning of p125Nap1, a protein that associates with an SH3 domain of Nck. Biochem Biophys Res Commun 1996; 219: 509-14.

[70] Stradal TE, Rottner K, Disanza A, *et al.* Regulation of actin dynamics by WASP and WAVE family proteins. Trends Cell Biol 2004; 14: 303-11.

[71] Irie F, Yamaguchi Y. EphB receptors regulate dendritic spine development *via* intersectin, Cdc42 and N-WASP. Nat Neurosci 2002; 5: 1117-8.

[72] Kim Y, Sung JY, Ceglia I, *et al.* Phosphorylation of WAVE1 regulates actin polymerization and dendritic spine morphology. Nature 2006; 442: 814-7.

[73] Soderling SH, Langeberg LK, Soderling JA, *et al.* Loss of WAVE-1 causes sensorimotor retardation and reduced learning and memory in mice. Proc Natl Acad Sci USA 2003; 100: 1723-8.

[74] Soderling SH, Guire ES, Kaech S, *et al.* A WAVE-1 and WRP signaling complex regulates spine density, synaptic plasticity, and memory. J Neurosci 2007; 27: 355-65.

[75] Sung JY, Engmann O, Teylan MA, *et al.* WAVE1 controls neuronal activity-induced mitochondrial distribution in dendritic spines. Proc Natl Acad Sci USA 2008; 105: 3112-6.

[76] Weaver AM, Karginov AV, Kinley AW, *et al.* Cortactin promotes and stabilizes Arp2/3-induced actin filament network formation. Curr Biol 2001; 11: 370-4.

[77] Kinley AW, Weed SA, Weaver AM, *et al.* Cortactin interacts with WIP in regulating Arp2/3 activation and membrane protrusion. Curr Biol 2003; 13: 384-93.

[78] Hering H, Sheng M. Activity-dependent redistribution and essential role of cortactin in dendritic spine morphogenesis. J Neurosci 2003; 23: 11759-69.

[79] Racz B, Weinberg RJ. The subcellular organization of cortactin in hippocampus. J Neurosci 2004; 24: 10310-7.

[80] Iki J, Inoue A, Bito H, Okabe S. Bi-directional regulation of postsynaptic cortactin distribution by BDNF and NMDA receptor activity. Eur J Neurosci 2005; 22: 2985-94.

[81] Jaworski J, Kapitein LC, Gouveia SM, *et al.* Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. Neuron 2009; 61: 85-100.

[82] Pruyne D, Evangelista M, Yang C, *et al.* Role of formins in actin assembly: nucleation and barbed-end association. Science 2002; 297: 612-5.

[83] Sagot I, Rodal AA, Moseley J, Goode BL, Pellman D. An actin nucleation mechanism mediated by Bni1 and profilin. Nat Cell Biol 2002; 4: 626-31.

[84] Kovar DR, Kuhn JR, Tichy AL, Pollard TD. The fission yeast cytokinesis formin Cdc12p is a barbed end actin filament capping protein gated by profilin. J Cell Biol 2003; 161: 875-87.

[85] Li F, Higgs HN. The mouse Formin mDia1 is a potent actin nucleation factor regulated by autoinhibition. Curr Biol 2003; 13: 1335-40.

[86] Zigmond SH. Formin-induced nucleation of actin filaments. Curr Opin Cell Biol 2004; 16: 99-105.

[87] Frieden C, Patane K. Differences in G-actin containing bound ATP or ADP: the Mg^{2+}-induced conformational change requires ATP. Biochemistry 1985; 24: 4192-6.

[88] Tilney LG, Bonder EM, Coluccio LM, Mooseker MS. Actin from Thyone sperm assembles on only one end of an actin filament: a behavior regulated by profilin. J Cell Biol 1983; 97: 112-24.

[89] Pring M, Weber A, Bubb MR. Profilin-actin complexes directly elongate actin filaments at the barbed end. Biochemistry 1992; 31: 1827-36.

[90] Pollard TD, Cooper JA. Quantitative analysis of the effect of Acanthamoeba profilin on actin filament nucleation and elongation. Biochemistry 1984; 23: 6631-41.

[91] Witke W, Podtelejnikov AV, Di Nardo A*, et al.* In mouse brain profilin I and profilin II associate with regulators of the endocytic pathway and actin assembly. EMBO J 1998; 17: 967-76.

[92] Ackermann M, Matus A. Activity-induced targeting of profilin and stabilization of dendritic spine morphology. Nat Neurosci 2003; 6: 1194-200.

[93] Lamprecht R, Farb CR, Rodrigues SM, LeDoux JE. Fear conditioning drives profilin into amygdala dendritic spines. Nat Neurosci 2006; 9: 481-3.

[94] Pilo Boyl P, Di Nardo A, Mulle C*, et al.* Profilin2 contributes to synaptic vesicle exocytosis, neuronal excitability, and novelty-seeking behavior. EMBO J 2007; 26: 2991-3002.

[95] Neuhoff H, Sassoe-Pognetto M, Panzanelli P*, et al.* The actin-binding protein profilin I is localized at synaptic sites in an activity-regulated manner. Eur J Neurosci 2005; 21: 15-25.

[96] Yin HL, Stossel TP. Control of cytoplasmic actin gel-sol transformation by gelsolin, a calcium-dependent regulatory protein. Nature 1979; 281: 583-6.

[97] Yin HL. Gelsolin: calcium- and polyphosphoinositide-regulated actin-modulating protein. Bioessays 1987; 7: 176-9.

[98] Sun HQ, Yamamoto M, Mejillano M, Yin HL. Gelsolin, a multifunctional actin regulatory protein. J Biol Chem 1999; 274: 33179-82.

[99] Bamburg JR, Wiggan OP. ADF/cofilin and actin dynamics in disease. Trends Cell Biol 2002; 12: 598-605.

[100] Nishida E. Opposite effects of cofilin and profilin from porcine brain on rate of exchange of actin-bound adenosine 5'-triphosphate. Biochemistry 1985; 24: 1160-4.

[101] Carlier MF, Laurent V, Santolini J*, et al.* Actin depolymerizing factor (ADF/cofilin) enhances the rate of filament turnover: implication in actin-based motility. J Cell Biol 1997; 136: 1307-22.

[102] Andrianantoandro E, Pollard TD. Mechanism of actin filament turnover by severing and nucleation at different concentrations of ADF/cofilin. Mol Cell 2006; 24: 13-23.

[103] McGough A, Pope B, Chiu W, Weeds A. Cofilin changes the twist of F-actin: implications for actin filament dynamics and cellular function. J Cell Biol 1997; 138: 771-81.

[104] Arber S, Barbayannis FA, Hanser H*, et al.* Regulation of actin dynamics through phosphorylation of cofilin by LIM-kinase. Nature 1998; 393: 805-9.

[105] Yang N, Higuchi O, Ohashi K*, et al.* Cofilin phosphorylation by LIM-kinase 1 and its role in Rac-mediated actin reorganization. Nature 1998; 393: 809-12.

[106] Racz B, Weinberg RJ. Spatial organization of cofilin in dendritic spines. Neuroscience 2006; 138: 447-56.

[107] Shi Y, Pontrello CG, DeFea KA, Reichardt LF, Ethell IM. Focal adhesion kinase acts downstream of EphB receptors to maintain mature dendritic spines by regulating cofilin activity. J Neurosci 2009; 29: 8129-42.

[108] Zhou Q, Homma KJ, Poo MM. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron 2004; 44: 749-57.

[109] Zhou L, Martinez SJ, Haber M*, et al.* EphA4 signaling regulates phospholipase Cgamma1 activation, cofilin membrane association, and dendritic spine morphology. J Neurosci 2007; 27: 5127-38.

[110] Meng Y, Takahashi H, Meng J*, et al.* Regulation of ADF/cofilin phosphorylation and synaptic function by LIM-kinase. Neuropharmacology 2004; 47: 746-54.

[111] Lang C, Barco A, Zablow L*, et al.* Transient expansion of synaptically connected dendritic spines upon induction of hippocampal long-term potentiation. Proc Natl Acad Sci USA 2004; 101: 16665-70.

[112] Mori T, Okano I, Mizuno K, Tohyama M, Wanaka A. Comparison of tissue distribution of two novel serine/threonine kinase genes containing the LIM motif (LIMK-1 and LIMK-2) in the developing rat. Brain Res Mol Brain Res 1997; 45: 247-54.

[113] Meng Y, Zhang Y, Tregoubov V*, et al.* Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. Neuron 2002; 35: 121-33.

[114] Baron MD, Davison MD, Jones P, Critchley DR. The sequence of chick alpha-actinin reveals homologies to spectrin and calmodulin. J Biol Chem 1987; 262: 17623-9.

[115] Grazi E, Cuneo P, Magri E, Schwienbacher C. Preferential binding of alpha-actinin to actin bundles. FEBS Lett 1992; 314: 348-50.

[116] Wyszynski M, Kharazia V, Shanghvi R*, et al.* Differential regional expression and ultrastructural localization of alpha-actinin-2, a putative NMDA receptor-anchoring protein, in rat brain. J Neurosci 1998; 18: 1383-92.

[117] Nakagawa T, Engler JA, Sheng M. The dynamic turnover and functional roles of alpha-actinin in dendritic spines. Neuropharmacology 2004; 47: 734-45.

[118] Wyszynski M, Lin J, Rao A*, et al.* Competitive binding of alpha-actinin and calmodulin to the NMDA receptor. Nature 1997; 385: 439-42.

[119] Ehlers MD, Zhang S, Bernhadt JP, Huganir RL. Inactivation of NMDA receptors by direct interaction of calmodulin with the NR1 subunit. Cell 1996; 84: 745-55.

[120] Krupp JJ, Vissel B, Thomas CG, Heinemann SF, Westbrook GL. Interactions of calmodulin and alpha-actinin with the NR1 subunit modulate Ca^{2+}-dependent inactivation of NMDA receptors. J Neurosci 1999; 19: 1165-78.

[121] Robison AJ, Bartlett RK, Bass MA, Colbran RJ. Differential modulation of Ca^{2+}/calmodulin-dependent protein kinase II activity by regulated interactions with N-methyl-D-aspartate receptor NR2B subunits and alpha-actinin. J Biol Chem 2005; 280: 39316-23.

[122] Robison AJ, Bass MA, Jiao Y*, et al.* Multivalent interactions of calcium/calmodulin-dependent protein kinase II with the postsynaptic density proteins NR2B, densin-180, and alpha-actinin-2. J Biol Chem 2005; 280: 35329-36.

[123] Hoe HS, Lee JY, Pak DT. Combinatorial morphogenesis of dendritic spines and filopodia by SPAR and alpha-actinin2. Biochem Biophys Res Commun 2009; 384: 55-60.

[124] Asanuma K, Kim K, Oh J*, et al.* Synaptopodin regulates the actin-bundling activity of alpha-actinin in an isoform-specific manner. J Clin Invest 2005; 115: 1188-98.

[125] Kremerskothen J, Plaas C, Kindler S, Frotscher M, Barnekow A. Synaptopodin, a molecule involved in the formation of the dendritic spine apparatus, is a dual actin/alpha-actinin binding protein. J Neurochem 2005; 92: 597-606.

[126] Deller T, Merten T, Roth SU, Mundel P, Frotscher M. Actin-associated protein synaptopodin in the rat hippocampal formation: localization in the spine neck and close association with the spine apparatus of principal neurons. J Comp Neurol 2000; 418: 164-81.

[127] Kennedy MJ, Ehlers MD. Organelles and trafficking machinery for postsynaptic plasticity. Annu Rev Neurosci 2006; 29: 325-62.

[128] Spacek J, Harris KM. Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat. J Neurosci 1997; 17: 190-203.

[129] Deller T, Korte M, Chabanis S*, et al.* Synaptopodin-deficient mice lack a spine apparatus and show deficits in synaptic plasticity. Proc Natl Acad Sci USA 2003; 100: 10494-9.

[130] Cohen RS, Chung SK, Pfaff DW. Immunocytochemical localization of actin in dendritic spines of the cerebral cortex using colloidal gold as a probe. Cell Mol Neurobiol 1985; 5: 271-84.

[131] Deller T, Mundel P, Frotscher M. Potential role of synaptopodin in spine motility by coupling actin to the spine apparatus. Hippocampus 2000; 10: 569-81.

[132] Yamazaki M, Matsuo R, Fukazawa Y, Ozawa F, Inokuchi K. Regulated expression of an actin-associated protein, synaptopodin, during long-term potentiation. J Neurochem 2001; 79: 192-9.

[133] Vlachos A, Korkotian E, Schonfeld E*, et al.* Synaptopodin regulates plasticity of dendritic spines in hippocampal neurons. J Neurosci 2009; 29: 1017-33.

[134] Bardo S, Cavazzini MG, Emptage N. The role of the endoplasmic reticulum Ca^{2+} store in the plasticity of central neurons. Trends Pharmacol Sci 2006; 27: 78-84.

[135] Kennedy MB, Bennett MK, Erondu NE. Biochemical and immunochemical evidence that the "major postsynaptic density protein" is a subunit of a calmodulin-dependent protein kinase. Proc Natl Acad Sci USA 1983; 80: 7357-61.

[136] Kelly PT, McGuinness TL, Greengard P. Evidence that the major postsynaptic density protein is a component of a Ca^{2+}/calmodulin-dependent protein kinase. Proc Natl Acad Sci USA 1984; 81: 945-9.

[137] Malenka RC, Kauer JA, Perkel DJ*, et al.* An essential role for postsynaptic calmodulin and protein kinase activity in long-term potentiation. Nature 1989; 340: 554-7.

[138] McGlade-McCulloh E, Yamamoto H, Tan SE, Brickey DA, Soderling TR. Phosphorylation and regulation of glutamate receptors by calcium/calmodulin-dependent protein kinase II. Nature 1993; 362: 640-2.

[139] Barria A, Muller D, Derkach V, Griffith LC, Soderling TR. Regulatory phosphorylation of AMPA-type glutamate receptors by CaM-KII during long-term potentiation. Science 1997; 276: 2042-5.

[140] Mammen AL, Kameyama K, Roche KW, Huganir RL. Phosphorylation of the alpha-amino-3-hydroxy-5-methylisoxazole4-propionic acid receptor GluR1 subunit by calcium/calmodulin-dependent kinase II. J Biol Chem 1997; 272: 32528-33.

[141] Omkumar RV, Kiely MJ, Rosenstein AJ, Min KT, Kennedy MB. Identification of a phosphorylation site for calcium/calmodulindependent protein kinase II in the NR2B subunit of the N-methyl-D-aspartate receptor. J Biol Chem 1996; 271: 31670-8.

[142] Sessoms-Sikes S, Honse Y, Lovinger DM, Colbran RJ. CaMKIIalpha enhances the desensitization of NR2B-containing NMDA receptors by an autophosphorylation-dependent mechanism. Mol Cell Neurosci 2005; 29: 139-47.

[143] Stevens I, Rondelez E, Merlevede W, Goris J. Cloning and differential expression of new calcium, calmodulin-dependent protein kinase II isoforms in Xenopus laevis oocytes and several adult tissues. J Biochem 2001; 129: 551-60.

[144] Erondu NE, Kennedy MB. Regional distribution of type II Ca^{2+}/calmodulin-dependent protein kinase in rat brain. J Neurosci 1985; 5: 3270-7.

[145] Shen K, Teruel MN, Subramanian K, Meyer T. CaMKIIbeta functions as an F-actin targeting module that localizes CaMKIIalpha/beta heterooligomers to dendritic spines. Neuron 1998; 21: 593-606.

[146] Fink CC, Bayer KU, Myers JW*, et al.* Selective regulation of neurite extension and synapse formation by the beta but not the alpha isoform of CaMKII. Neuron 2003; 39: 283-97.

[147] Walikonis RS, Oguni A, Khorosheva EM*, et al.* Densin-180 forms a ternary complex with the (alpha)-subunit of Ca^{2+}/calmodulin-dependent protein kinase II and (alpha)-actinin. J Neurosci 2001; 21: 423-33.

[148] Lin YC, Redmond L. CaMKIIbeta binding to stable F-actin *in vivo* regulates F-actin filament stability. Proc Natl Acad Sci USA 2008; 105: 15791-6.

[149] Okamoto K, Narayanan R, Lee SH, Murata K, Hayashi Y. The role of CaMKII as an F-actin-bundling protein crucial for maintenance of dendritic spine structure. Proc Natl Acad Sci USA 2007; 104: 6418-23.

[150] Satoh A, Nakanishi H, Obaishi H*, et al.* Neurabin-II/spinophilin. An actin filament-binding protein with one pdz domain localized at cadherin-based cell-cell adhesion sites. J Biol Chem 1998; 273: 3470-5.

[151] Nakanishi H, Obaishi H, Satoh A*, et al.* Neurabin: a novel neural tissue-specific actin filament-binding protein involved in neurite formation. J Cell Biol 1997; 139: 951-61.

[152] Allen PB, Ouimet CC, Greengard P. Spinophilin, a novel protein phosphatase 1 binding protein localized to dendritic spines. Proc Natl Acad Sci USA 1997; 94: 9956-61.

[153] Hu XD, Huang Q, Roadcap DW, Shenolikar SS, Xia H. Actin-associated neurabin-protein phosphatase-1 complex regulates hippocampal plasticity. J Neurochem 2006; 98: 1841-51.

[154] Oliver CJ, Terry-Lorenzo RT, Elliott E*, et al.* Targeting protein phosphatase 1 (PP1) to the actin cytoskeleton: the neurabin I/PP1 complex regulates cell morphology. Mol Cell Biol 2002; 22: 4690-701.

[155] Allen PB, Zachariou V, Svenningsson P*, et al.* Distinct roles for spinophilin and neurabin in dopamine-mediated plasticity. Neuroscience 2006; 140: 897-911.

[156] Zito K, Knott G, Shepherd GM, Shenolikar S, Svoboda K. Induction of spine growth and synapse formation by regulation of the spine actin cytoskeleton. Neuron 2004; 44: 321-34.

[157] Terry-Lorenzo RT, Roadcap DW, Otsuka T*, et al.* Neurabin/protein phosphatase-1 complex regulates dendritic spine morphogenesis and maturation. Mol Biol Cell 2005; 16: 2349-62.

[158] Wu LJ, Ren M, Wang H*, et al.* Neurabin contributes to hippocampal long-term potentiation and contextual fear memory. PLoS ONE 2008; 3: e1407.

[159] Muly EC, Allen P, Mazloom M*, et al.* Subcellular distribution of neurabin immunolabeling in primate prefrontal cortex: comparison with spinophilin. Cereb Cortex 2004; 14: 1398-407.

[160] Ouimet CC, Katona I, Allen P, Freund TF, Greengard P. Cellular and subcellular distribution of spinophilin, a PP1 regulatory protein that bundles F-actin in dendritic spines. J Comp Neurol 2004; 479: 374-88.

[161] Futter M, Uematsu K, Bullock SA*, et al.* Phosphorylation of spinophilin by ERK and cyclin-dependent PK 5 (Cdk5). Proc Natl Acad Sci USA 2005; 102: 3489-94.

[162] Feng J, Yan Z, Ferreira A*, et al.* Spinophilin regulates the formation and function of dendritic spines. Proc Natl Acad Sci USA 2000; 97: 9287-92.

[163] Stafstrom-Davis CA, Ouimet CC, Feng J*, et al.* Impaired conditioned taste aversion learning in spinophilin knockout mice. Learn Mem 2001; 8: 272-8.

[164] Grossman SD, Futter M, Snyder GL*, et al.* Spinophilin is phosphorylated by Ca^{2+}/calmodulin-dependent protein kinase II resulting in regulation of its binding to F-actin. J Neurochem 2004; 90: 317-24.

[165] Hsieh-Wilson LC, Benfenati F, Snyder GL*, et al.* Phosphorylation of spinophilin modulates its interaction with actin filaments. J Biol Chem 2003; 278: 1186-94.

[166] Kelker MS, Dancheck B, Ju T*, et al.* Structural basis for spinophilin-neurabin receptor interaction. Biochemistry 2007; 46: 2333-44.

[167] MacMillan LB, Bass MA, Cheng N*, et al.* Brain actin-associated protein phosphatase 1 holoenzymes containing spinophilin, neurabin, and selected catalytic subunit isoforms. J Biol Chem 1999; 274: 35845-54.

[168] Drees F, Pokutta S, Yamada S, Nelson WJ, Weis WI. Alpha-catenin is a molecular switch that binds E-cadherin-beta-catenin and regulates actin-filament assembly. Cell 2005; 123: 903-15.

[169] Abe K, Chisaka O, Van Roy F, Takeichi M. Stability of dendritic spines and synaptic contacts is controlled by alpha N-catenin. Nat Neurosci 2004; 7: 357-63.

[170] Di Fiore PP, Scita G. Eps8 in the midst of GTPases. Int J Biochem Cell Biol 2002; 34: 1178-83.

[171] Disanza A, Mantoani S, Hertzog M*, et al.* Regulation of cell shape by Cdc42 is mediated by the synergic actin-bundling activity of the Eps8-IRSp53 complex. Nat Cell Biol 2006; 8: 1337-47.

[172] Proepper C, Johannsen S, Liebau S*, et al.* Abelson interacting protein 1 (Abi-1) is essential for dendrite morphogenesis and synapse formation. EMBO J 2007; 26: 1397-409.

[173] Disanza A, Carlier MF, Stradal TE*, et al.* Eps8 controls actin-based motility by capping the barbed ends of actin filaments. Nat Cell Biol 2004; 6: 1180-8.

[174] Offenhauser N, Castelletti D, Mapelli L*, et al.* Increased ethanol resistance and consumption in Eps8 knockout mice correlates with altered actin dynamics. Cell 2006; 127: 213-26.

[175] Shirao T, Obata K. Two acidic proteins associated with brain development in chick embryo. J Neurochem 1985; 44: 1210-6.

[176] Ishikawa R, Hayashi K, Shirao T*, et al.* Drebrin, a development-associated brain protein from rat embryo, causes the dissociation of tropomyosin from actin filaments. J Biol Chem 1994; 269: 29928-33.

[177] Shirao T, Hayashi K, Ishikawa R*, et al.* Formation of thick, curving bundles of actin by drebrin A expressed in fibroblasts. Exp Cell Res 1994; 215: 145-53.
[178] Sasaki Y, Hayashi K, Shirao T, Ishikawa R, Kohama K. Inhibition by drebrin of the actin-bundling activity of brain fascin, a protein localized in filopodia of growth cones. J Neurochem 1996; 66: 980-8.
[179] Majoul I, Shirao T, Sekino Y, Duden R. Many faces of drebrin: from building dendritic spines and stabilizing gap junctions to shaping neurite-like cell processes. Histochem Cell Biol 2007; 127: 355-61.
[180] Shirao T, Kojima N, Kato Y, Obata K. Molecular cloning of a cDNA for the developmentally regulated brain protein, drebrin. Brain Res 1988; 464: 71-4.
[181] Kojima N, Shirao T. Synaptic dysfunction and disruption of post-synaptic drebrin-actin complex: a study of neurological disorders accompanied by cognitive deficits. Neurosci Res 2007; 58: 1-5.
[182] Harigaya Y, Shoji M, Shirao T, Hirai S. Disappearance of actin-binding protein, drebrin, from hippocampal synapses in Alzheimer's disease. J Neurosci Res 1996; 43: 87-92.
[183] Shim KS, Lubec G. Drebrin, a dendritic spine protein, is manifold decreased in brains of patients with Alzheimer's disease and Down syndrome. Neurosci Lett 2002; 324: 209-12.
[184] Zhao L, Ma QL, Calon F*, et al.* Role of p21-activated kinase pathway defects in the cognitive deficits of Alzheimer disease. Nat Neurosci 2006; 9: 234-42.
[185] Mizui T, Takahashi H, Sekino Y, Shirao T. Overexpression of drebrin A in immature neurons induces the accumulation of F-actin and PSD-95 into dendritic filopodia, and the formation of large abnormal protrusions. Mol Cell Neurosci 2005; 30: 149-57.
[186] Hayashi K,Shirao T. Change in the shape of dendritic spines caused by overexpression of drebrin in cultured cortical neurons. J Neurosci 1999; 19: 3918-25.
[187] Takahashi H, Sekino Y, Tanaka S*, et al.* Drebrin-dependent actin clustering in dendritic filopodia governs synaptic targeting of post-synaptic density-95 and dendritic spine morphogenesis. J Neurosci 2003; 23: 6586-95.
[188] Biou V, Brinkhaus H, Malenka RC, Matus A. Interactions between drebrin and Ras regulate dendritic spine plasticity. Eur J Neurosci 2008; 27: 2847-59.
[189] Sekino Y, Tanaka S, Hanamura K*, et al.* Activation of N-methyl-D-aspartate receptor induces a shift of drebrin distribution: disappearance from dendritic spines and appearance in dendritic shafts. Mol Cell Neurosci 2006; 31: 493-504.
[190] Fujisawa S, Shirao T, Aoki C. *In vivo*, competitive blockade of N-methyl-D-aspartate receptors induces rapid changes in filamentous actin and drebrin A distributions within dendritic spines of adult rat cortex. Neuroscience 2006; 140: 1177-87.
[191] Takahashi H, Yamazaki H, Hanamura K, Sekino Y, Shirao T. Activity of the AMPA receptor regulates drebrin stabilization in dendritic spine morphogenesis. J Cell Sci 2009; 122: 1211-9.
[192] Kobayashi C, Aoki C, Kojima N, Yamazaki H, Shirao T. Drebrin a content correlates with spine head size in the adult mouse cerebral cortex. J Comp Neurol 2007; 503: 618-26.
[193] Takahashi H, Mizui T, Shirao T. Down-regulation of drebrin A expression suppresses synaptic targeting of NMDA receptors in developing hippocampal neurones. J Neurochem 2006; 97(Suppl 1): 110-5.
[194] Ivanov A, Esclapez M, Pellegrino C, Shirao T, Ferhat L. Drebrin A regulates dendritic spine plasticity and synaptic function in mature cultured hippocampal neurons. J Cell Sci 2009; 122: 524-34.

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