Accelerators, Brakes, and Gears of Actin Dynamics in Dendritic Spines

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Abstract: Dendritic spines are actin-rich structures that accommodate the postsynaptic sites of most excitatory synapses in the brain. Although dendritic spines form and mature as synaptic connections develop, they remain plastic even in the adult brain, where they can rapidly grow, change, or collapse in response to normal physiological changes in synaptic activity that underlie learning and memory. Pathological stimuli can adversely affect dendritic spine shape and number, and this is seen in neurodegenerative disorders and some forms of mental retardation and autism as well. Many of the molecular signals that control these changes in dendritic spines act through the regulation of filamentous actin (F-actin), some through direct interaction with actin, and others via downstream effectors. For example, cortactin, cofilin, and gelsolin are actin-binding proteins that directly regulate actin dynamics in dendritic spines. Activities of these proteins are precisely regulated by intracellular signaling events that control their phosphorylation state and localization. In this review, we discuss how actin-regulating proteins maintain the balance between F-actin assembly and disassembly that is needed to stabilize mature dendritic spines, and how changes in their activities may lead to rapid remodeling of dendritic spines.

1. INTRODUCTION

Excitatory postsynaptic sites in the brain are usually formed on dendritic spines, small protrusions on the surface of dendrites that are enriched in actin [1-5]. Dendritic spines form and mature as synaptic connections develop in the brain, and their morphogenesis directly correlates with synapse formation and maturation. The most widely-held view of dendritic spine formation suggests that dendritic spines originate from dendritic filopodia-like protrusions both *in vitro* and *in vivo* [6-15]. Although mature dendritic spines can also emerge from the dendritic shaft, it is widely accepted that long, thin filopodia-like morphologies are features of immature pre-cursors to spines, while mature spines are characterized by mushroom-like or stubby shapes [16-18]. Several studies have demonstrated a correlation between dendritic spine morphology and synaptic function [19-26]. While immature thin spines with smaller heads are flexible and can rapidly enlarge or shrink in response to changes in synaptic activity [19-22], mature mushroom-shaped spines with larger heads are less likely to change, but show higher sensitivity to glutamate than immature thin spines [23-26]. These differences in synaptic strength are suggested to relate to the number of neurotransmitter receptors. Mature spines have a large spine head area that is proportional to postsynaptic density (PSD) and synapse size, as well as receptor complement (Fig. **1**). Two-photon glutamate uncaging studies have shown that the mature mushroom-like spines have large PSDs with a high number of α-amino-3-hydroxy-5-methyl-4-isoxazolepro-pionic acid (AMPA) receptors [23]. Indeed, numbers of AMPA receptors and N-methyl-D-aspartate (NMDA) receptors directly correlate with PSD size [27, 28]. Spine head volume and PSD size are also proportional to the number of neurotransmitter-containing vesicles

at the presynaptic bouton [29] and the amount of neurotransmitter released at the synapse [30]. Mature dendritic spines also contain elements of endoplasmic reticulum, called the spine apparatus, and provide means for compartmentalization within the neuron, which results in localized control over factors such as intracellular Ca^{2+} concentration [31] and local protein synthesis [32].

Dendritic spines remain plastic in the adult brain and can rapidly grow, change, or collapse in response to normal physiological changes in synaptic activity that underlies learning and memory. Long-term potentiation (LTP) can result in spine head enlargement [19, 20], whereas long-term depression (LTD) has been reported to induce shrinkage of dendritic spine heads and spine elimination [33]. Synaptic activity was also shown to shape dendritic spines in area CA1 of the hippocampus [8], and long-lasting synaptic enhancement leads to new spine development [34]. Although changes in synaptic activity may not always lead to structural remodeling [35], experience-dependent motility of spines and change in their morphology has been reported using various learning paradigms in developing rat barrel cortex [36], motor cortex [37], and hippocampus [38, 39]. Pathological stimuli can also lead to changes in dendritic spine shape and number in the developing and adult brain. Immature dendritic spine profiles are found in subjects with Fragile X, Down and Rett syndromes, whose brains exhibit many long, thin spines and filopodia-like protrusions [40, 41]. Moreover, dendritic spine loss is a hallmark of several neurodegenerative diseases, and may also contribute to impaired brain function in these diseases [42]. The ability of spines to rapidly turnover can lead to recovery from damage [43] and stressors such as sleep deprivation [44].

2. ACTIN DYNAMICS IN DENDRITIC SPINES

Many molecular signals that control the changes in dendritic spine morphology act through the regulation of F-actin, some through direct interaction with actin, and others via downstream effectors [5]. Actin dynamics at the leading

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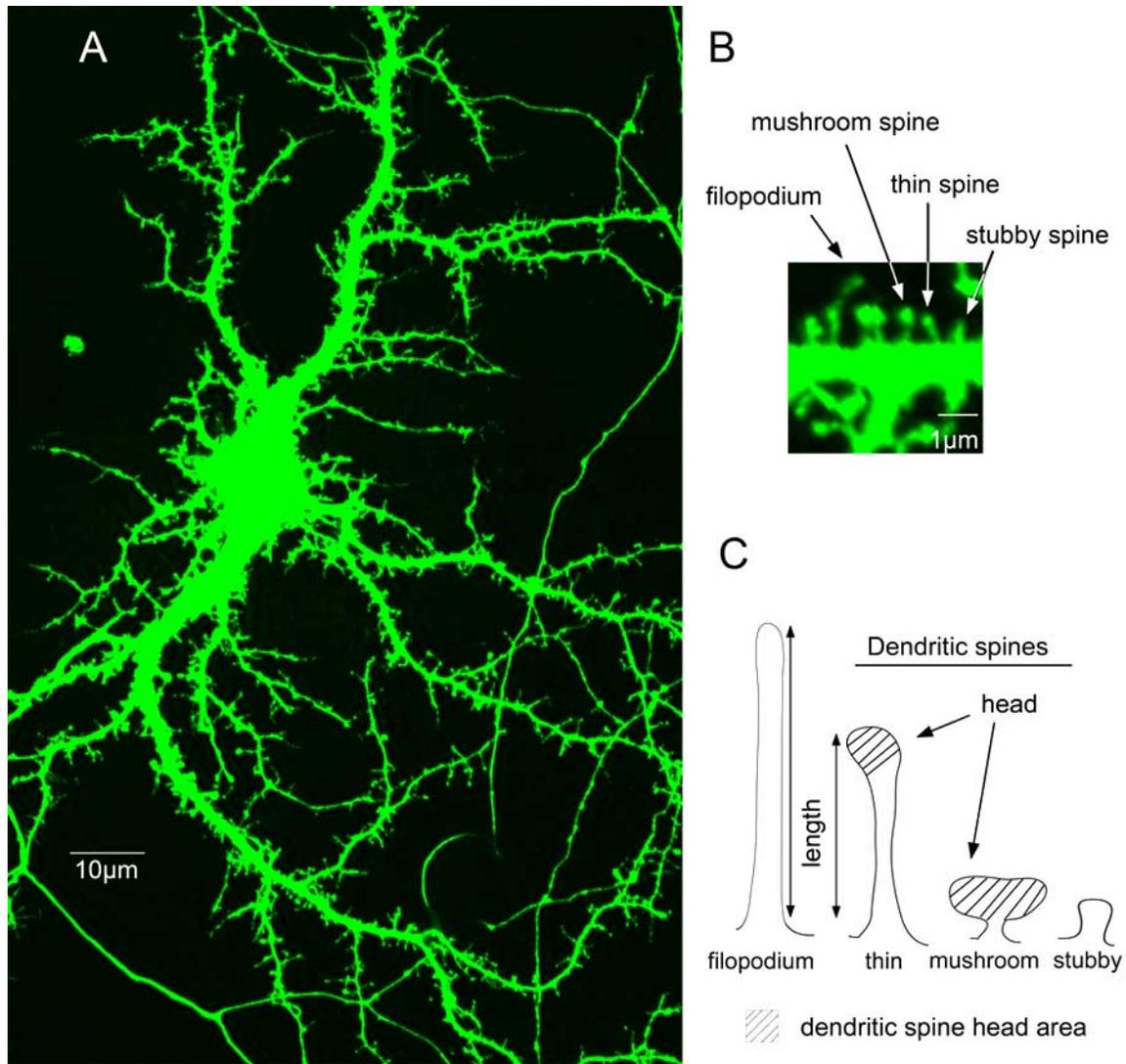
Fig. (1). (**A**) A GFP-expressing hippocampal neuron at day 14 in vitro displays dendritic filopodia-like protrusions and spines with different shapes and sizes (**B**, **C**) The high magnification image of the dendrite (**B**) and a drawing show examples of main categories of dendritic protrusions: filopodia-like protrusions, mushroom spine, thin spine, and stubby spine. (**C**) Filopodia-like protrusions are precursors of dendritic spines. Mature mushroom spines display the largest heads and thin necks.

edge in motile cells [45] and in growth cones [46] control cell locomotion and axon pathfinding, respectively. There is also a tight regulation of actin dynamics within dendritic spines and filopodia-like protrusions. While the stabilization of mature spines is required for synapse maintenance, F-actin remodeling underlies synaptic plasticity and may result in spine turnover, triggering both formation of new spines and filopodia, as well as pruning of existing spines [47, 48]. As globular actin (G-actin) monomers join together to form actin filaments (F-actin), there is a bidirectional polymerization that is biased toward what is known as the plus end or barbed end [49]. In this way, the F-actin barbed end is fast-growing, while the opposite pole of the filament, the minus end or pointed end, elongates more slowly. The constant turnover of the actin filaments in spines results from a steady-state of actin treadmilling, in which G-actin monomers are added quickly to the barbed end and are disassembled from the pointed end of F-actin filaments, while exchanging ATP for ADP [50-53]. However, this F-actin treadmilling may or may not lead to changes in dendritic spine shape and size.

3. PROTEINS REGULATING ACTIN DYNAMICS IN DENDRITIC SPINES

Actin assembly regulatory proteins are responsible for shifting the balance between spine assembly and disassembly that is required for normal synaptic function. Some regulate spine morphology through direct interaction with actin, while others control actin dynamics indirectly [54-56]. It is the interplay among many of these proteins that defines the rate of growth or disassembly of actin, and ultimately the morphology of dendritic spines and development of synapses. In this review, we discuss the role of actin-binding proteins that are found in dendritic spines and influence dendritic spine formation, maintenance or remodeling, including proteins that regulate elongation, branching, and bundling of actin filaments and those that trigger actin severing and depolymerization.
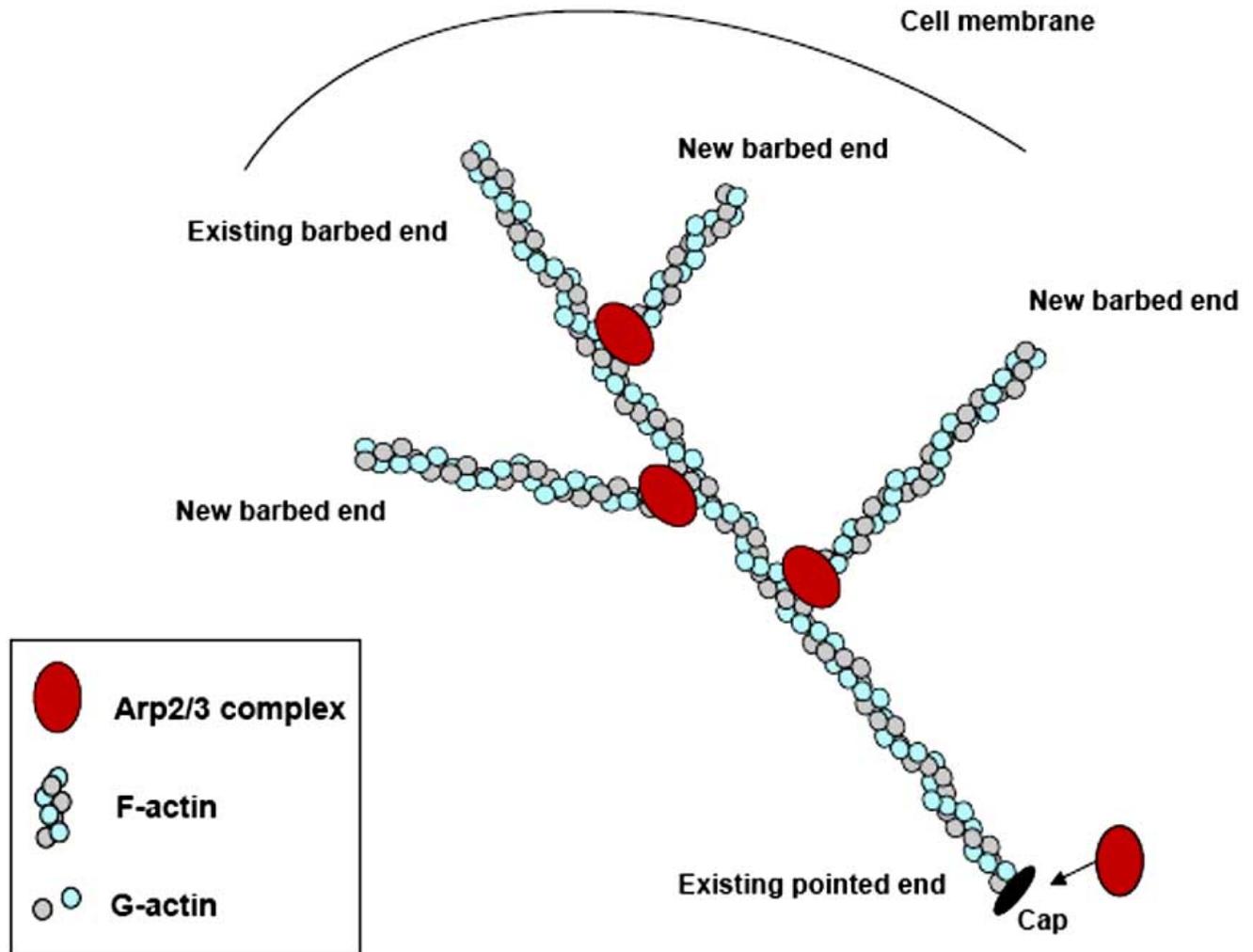
Fig. (2). Arp2/3 nucleates new branches from existing actin filaments, creating fast-growing barbed ends.

3.1. Actin Polymerization and Elongation

3.1.1. Arp2/3 Complex Promotes Nucleation and Branching of Actin Filaments

The Actin-Related Protein (Arp) 2/3 complex is comprised of seven proteins [57-59] and is responsible for nucleating branches from the sides of existing actin filaments and capping the pointed ends, thus creating additional fast-growing barbed ends for further actin polymerization and elongation (Fig. **2**) [60-62]. The Arp2/3 complex contributes to the cytoskeletal rearrangements necessary for a variety of cellular functions, including cell migration and outgrowth [63]. It can be found in protruding lamellipodia of fibroblasts [64] and at the leading edge of carcinoma cells, where its branching activity is needed for lamellipodia extension [65]. In dendritic spines, Arp2/3 is sparsely distributed in the PSD, and more concentrated in a specific domain that lies midway between the plasma membrane, the spine center, the PSD, and the spine neck [66]. This specificity of Arp2/3 localization suggests a restricted spine region dedicated to actin branching. In cooperation with members of the Ena/VASP family, Arp2/3 nucleates actin polymerization and branching for pathogenic bacteria motility [67] and growth cone protru-

sion [68]. Other cell functions that rely on F-actin assembly, including endocytosis [69], internal receptor trafficking [70], integrin-mediated cell adhesion [71], and phagocytosis [72] are also mediated by the Arp2/3 complex.

In maintaining the balance between assembly and disassembly of actin filaments, there are some proteins and factors that compete against the Arp2/3 complex, while others work in cooperation (Fig. **3**). Tropomyosin inhibits the branching activity of Arp2/3 [73], and ATP hydrolysis also acts to antagonize its activity by de-branching older actin filaments [74]. Conversely, the Arp2/3 complex acts in cooperation with gelsolin as it polymerizes actin in the presence of gelsolin-capped filaments [75]; and cortactin activates Arp2/3 and stabilizes new branch points on actin filaments [76]. The actin-severing protein ADF/cofilin dissociates Arp2/3 from actin filaments [77], but also uses its severing activity to increase the number of preferred ends for Arp2/3 nucleation [78]. Moreover, the Arp2/3 complex acts in opposition to ADF/cofilin in lamellipodia by cross-linking actin filaments and capping pointed ends, thus stabilizing actin filaments and preventing depolymerization [79].

Phosphorylation of the Arp2/3 complex is necessary for its nucleating activity and cellular localization [80]. Phos-
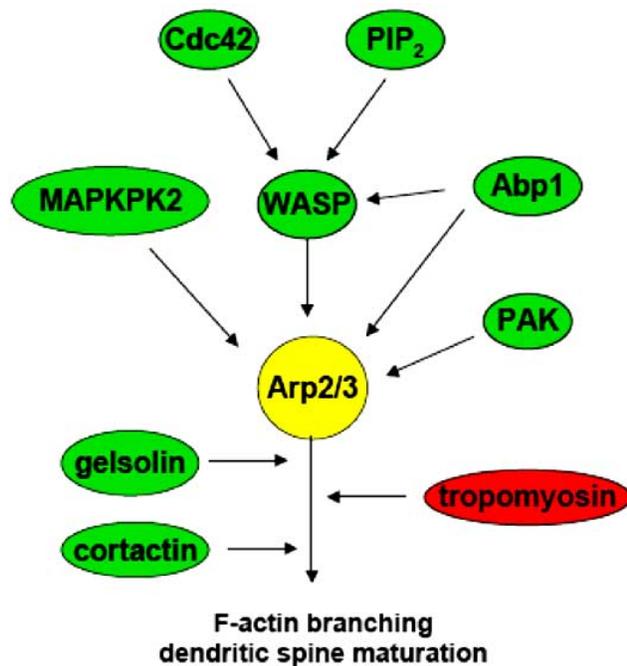
Fig. (3). Regulatory proteins affecting the activity of Arp2/3.

phorylation of Arp2/3 can be achieved by such proteins as MAPK-activated protein kinase 2 (MAPKPK2) [81] and the p21-activated kinase (PAK) [82]. Proteins of the Wiskott-Aldrich Syndrome protein (WASP) family, Neural-WASP (N-WASP), Scar, and the WASP-family verprolin-homologous protein (WAVE), are well-known to bind to and activate the Arp2/3 complex [83], each stimulating a different rate of actin nucleation [84]. Cdc42, a member of the Rho family of small GTPases, and Phosphatidylinositol 4,5 bisphosphate (PIP$_2$) stimulate Arp2/3 nucleation activity through WASP activation [85-88]. Moreover, the overexpression of actin-binding protein Abp1, which is similar to cortactin in structure [89] and can activate N-WASP [90] or phosphorylate Arp2/3 directly, increased the length and density of mature spines and synapses, whereas RNA interference (RNAi)-mediated knock-down of Abp1 reduced the number of mushroom-shaped spines and synapses in cultured hippocampal neurons [91]. In addition, EphB receptors were found to promote dendritic spine maturation through the Cdc42-N-WASP pathway, suggesting an involvement of the Arp2/3 complex in dendritic spine development [92].

The role of N-WASP in regulating spine morphogenesis was further supported by findings that show a decrease in the number of dendritic spines in hippocampal neurons with reduced N-WASP expression [93]. The changes in spine number and morphology following N-WASP knock-down were similar to those of the RNAi-mediated decrease of the Arp3 protein [93], suggesting that activation of the Arp2/3 complex is a mechanism by which N-WASP promotes the formation of mature spines and synapses. A decrease in number of mature dendritic spines was also seen with knock-down of WAVE1 by RNAi in primary hippocampal neurons, and in mouse striatal sections of WAVE1 knock-out mice [94]. Synaptic plasticity, as well as learning and memory, were also impaired in mice with a targeted WAVE1 muta-

tion and in WAVE1 knock-out mice [95, 96], suggesting a role of the WAVE1 pathway in regulating synaptic plasticity.

Knock-down of Arp2/3 through siRNA-targeting of the p34 subunit was recently shown to promote filopodia-like protrusions, while decreasing the number of mushroom, thin, and stubby spines and the overall protrusion density in hippocampal neurons [97]. This is similar to the effect seen when Arp2/3 localization was altered by expression of the Scar1-WA fragment, which further suggests an important role of the Arp2/3 complex in promotion of mature dendritic spine phenotype [97]. It will be interesting to determine whether the Arp2/3 complex and its regulatory proteins are also involved in the assembly of the postsynaptic scaffold and in glutamate receptor trafficking. Taken together, these results suggest that the Arp2/3 complex is tightly regulated in dendritic spines and contributes to spine morphogenesis, inducing formation of mature dendritic spines and synapses, as well as regulating synaptic plasticity.

3.1.2. Cortactin Promotes Branching and Stabilization of Actin Filaments

Another protein that can bind to and activate the Arp2/3 complex is cortactin [76, 98]. It was discovered as a cortical protein that binds to actin [99] and promotes branching and stabilization of actin filaments [100]. Cortactin is located at sites of actin assembly in lamellipodia [101], and is likely involved in endosomal movement in fibroblasts [102]. It is also implicated in controlling shape-changes of folliculostellate cells of the anterior pituitary [103], and in aberrant cell motility, such as cancer cell migration and invasion [104, 105].

In the brain, cortactin is enriched in dendritic spines, where it co-localizes with F-actin. There is a large cortactin pool in the actin core within the dendritic spine, which is implicated in regulating its shape, and a smaller pool near the PSD that may be involved in the regulation of synaptic function [106]. Cortactin has been implicated in spine morphogenesis in studies using gain- and loss-of-function approaches [107]. While overexpression of cortactin in hippocampal cultures led to spine elongation, knock-down of cortactin with small-interfering RNA (siRNA) resulted in loss of spines [107]. Cortactin interaction with the large GTPase dynamin-3 variant, Dyn3baa, also promoted filopodial extension in cultured rat hippocampal neurons [108]. The ability of cortactin to use its actin-branching and elongation activity for filopodia formation and outgrowth suggests its important role in spine morphogenesis.

In addition, cortactin regulates spine morphology by mediating the interaction between actin and microtubules. While stable microtubules that express microtubule-associated protein 2 (MAP2) are concentrated in dendritic shafts [109], dynamic microtubules can enter dendritic spines and affect actin dynamics [110]. Microtubule-associated protein EB3, which is located on the plus-end of dynamic microtubules, may act through a p140Cap-Src pathway to promote cortactin activity and mature dendritic spines. Knock-down of EB3 with shRNA induced a loss of F-actin in dendritic protrusions, as well as a reduction of mature mushroom spines and an increase in filopodia-like structures [110], which is similar to the result seen with

RNAi-mediated loss of p140Cap or cortactin [107]. These effects of EB3 knock-down were reversed by overexpression of p140Cap or cortactin. In this way, dynamic microtubules may contribute to the arrangement and activity of actin-regulating proteins such as cortactin, thus shaping dendritic spines.

Cortactin influences actin organization through interactions with several proteins that promote F-actin assembly, and these interactions are negatively regulated by cortactin phosphorylation [111, 112]. For example, cortactin's ability to activate WASP and induce actin branching through Arp2/3 is inhibited by its phosphorylation, which is mediated by Src non-receptor tyrosine kinase, and results in loss of cortactin from postsynaptic sites [113]. δ-Catenin can interact with cortactin, and this interaction was shown to promote F-actin elongation without branching, which was also inhibited by Src-mediated phosphorylation of cortactin [114]. Cortactin has the ability to link actin dynamics to the cell membrane through interaction with several PSD scaffolding proteins. In addition to Dyn3, cortactin interacts with the Shank family of proteins that are localized to the PSD of excitatory synapses [115]. Shank binds to Homer, which has been shown to anchor metabotropic glutamate receptors (mGluR) 1 and 5 [116]. It seems that cortactin's association with Shank and Homer could act to stabilize postsynaptic clusters of glutamate receptors during synaptogenesis.

Cortactin can be regulated by synaptic activity, as a decrease in overall cortactin level was observed in rat hippocampus 4 hours following Morris water maze learning [117]. This decrease in cortactin is dependent on NMDA receptor activity, and may mediate the actin reorganization that is necessary for learning-induced spine remodeling. In contrast, rats exposed to a novel environment exhibited an increase in cortactin levels in the hippocampus 12 hours later, but this upregulation of cortactin was abolished by 48 hours of Rapid Eye Movement Sleep (REMS) deprivation [118].

Cortactin localization within neurons is regulated by NMDA receptor activity and brain-derived neurotrophic factor (BDNF). NMDA receptor activation induces cortactin redistribution from dendritic spines to the shaft [107], which is mediated by Src non-receptor tyrosine kinases in hippocampal cultures [119]. Activation of Src kinases induces cortactin phosphorylation and cortactin depletion from the postsynaptic sites. Conversely, BDNF application stimulates a mitogen-activated protein (MAP) kinase-dependent redistribution of cortactin from the dendritic shaft to the spines [119, 120]. This shift in cortactin localization may play an important role in activity-dependent spine remodeling. A reduction in the level of cortactin in spines may allow for actin remodeling triggered by NMDA receptor activation, whereas BDNF-induced accumulation of cortactin in spines may increase actin stability necessary for the maintenance of mature spines and synapses. As BDNF itself is regulated by synaptic activity [121], it seems that these converse pathways indeed work together to regulate transient changes in dendritic spine morphology in response to changes in synaptic activity. The control exerted over cortactin activity by regulating its localization within neurons seems to have a critical role in spine development and synaptogenesis, as well as synaptic plasticity.

3.1.3. α-Actinin Promotes Bundling and Extension of Actin

α-Actinin induces bundling and cross-linking of actin networks in a concentration-dependent manner [122, 123] by forming anti-parallel homo-dimers that exhibit an actin-binding domain at each end [124-126]. This dimer formation may also target α-actinin to the cell membrane, as phospholipids and cytoplasmic regions of transmembrane receptors have an affinity for the exposed acidic surface of α-actinin rods [123, 127, 128]. α-Actinin can form short branched actin filaments or elongate existing ones, depending on certain conditions and factors, such as the α-actinin/actin ratio, Ca^{2+} concentration, and binding partners [129]. α-Actinin was first recognized as a protein that enhances the contraction of actomyosin fibers [130, 131], and several muscular pathologies have been linked to α-actinin [132, 133, 134]. It is implicated in maintaining cellular shape and adhesion in epithelial cells [135] and human neutrophils [136]. α-Actinin was also found in leading lamella of smooth muscle cells (A10) [137], in growth cones of PC12 cells [138] and in spinal cord neurons [139], and is suggested to play a role in cell and growth cone motility.

The muscle form of α-actinin is Ca^{2+}-insensitive, but the activity of the non-muscle form is controlled by Ca^{2+} concentration [140, 141]. At low Ca^{2+} levels, the actin-bundling activity of α-actinin is high, whereas an increase in Ca^{2+} levels inhibits the cross-linking activity by inducing a structural change in α-actinin [142]. In the brain, this has implications for the control of α-actinin by synaptic activity that regulates Ca^{2+} influx through NMDA receptors and voltage-gated Ca^{2+} channels. α-Actinin is also regulated by other actin-binding and signaling proteins. For example, tropomyosin and drebrin competitively inhibit α-actinin binding to actin [143], whereas focal adhesion kinase (FAK) reduces α-actinin affinity for actin by phosphorylation [144]. Conversely, PIP_2 binds to α-actinin and increases its gelation activity [145], and the protein actophorin promotes α-actinin bundling activity by severing and positioning actin filaments favorably for α-actinin interaction [146]. Moreover, α-actinin acts in cooperation with profilin, as it promotes the actin-polymerizing activity of the profilin-actin complex (profilactin; [147]).

The brain isoform of α-actinin [148] is enriched at the PSD of excitatory synapses and promotes the elongation of dendritic spines [149]. α-Actinin depends on F-actin for its spine localization, as actin depolymerization with latrunculin A disrupts its postsynaptic localization in cultured hippocampal neurons [150]. There is evidence that α-actinin may also be involved in the assembly of the spine apparatus via interaction with the postsynaptic protein synaptopodin [151]. Synaptopodin was shown to shift α-actinin activity from branching to elongation of existing actin filaments, and synaptopodin-deficient mice lack a spine apparatus and exhibit deficiencies in activity-dependent LTP [152].

In dendritic spines, α-actinin was shown to promote both actin filament elongation and branching depending on its interacting proteins. For example, α-actinin has been shown to interact with the Spine-Associated Rap GTPase-activating protein (SPAR), which promotes mature dendritic spines. α-Actinin2 appears to cooperate with SPAR in creating dendritic spines with large heads [153]. This study supports the

role for α-actinin in promoting actin branching in the heads of mature dendritic spines. α-Actinin could also indirectly contribute to actin-branching activity not only in spines, but in dendrites and axons as well, through its interaction with the guanine nucleotide exchange factor EFA6A [154]. EFA6A was shown to activate ADP ribosylation factor 6 (ARF6), which regulates axonal and dendritic branching in cultured rat hippocampal neurons [155]. Conversely, α-actinin can promote filopodia-like extensions through its actin-elongating activity, as overexpression of α-actinin2 increased the length and number of dendritic filopodia-like protrusions in cultured hippocampal neurons [156]. The ability of α-actinin to promote dendritic filopodia-like extensions may be accomplished through its co-localization and interaction with telencephalin (TLCN), a telencephalon-specific cell adhesion molecule, which is known to promote development of filopodia-like protrusions and to slow the maturation of dendritic spines [157,158].

α-Actinin was also shown to interact with the NMDA receptor in dendritic spines, promote its anchoring to the postsynaptic membrane [159], and regulate NMDA receptor activity [160, 161]. Both Ca^{2+}/calmodulin and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) compete with α-actinin for binding of the NR1 subunit of the NMDA receptor [162, 163]. While α-actinin binding to the NMDA receptor increases the receptor open probability, Ca^{2+}/calmo-dulin interaction with the NMDA receptor reduces it, resulting in NMDA receptor inactivation [164-167]. The role of α-actinin in enhancing NMDA receptor activity is consistent with its ability to induce dendritic filopodia-like protrusions, as NMDA receptor activation also leads to spine remodeling. It would be interesting to see if NMDA receptor anchoring is also affected by α-actinin binding to actin filaments or whether α-actinin can regulate NMDA receptor interactions with postsynaptic scaffolding proteins, such as PSD-95 [168]. Perhaps α-actinin can contribute to NMDA receptor anchoring by stabilizing the dendritic spines through its actin-branching and bundling activity.

There is evidence that may link α-actinin to several neural pathologies. For example, α-actinin2 levels were shown to be decreased in an Alzheimer's disease mouse model expressing mutant hAPP [169]. α-Actinin was accumulated in Hirano bodies, neuronal inclusions that increase with aging and are found in patients with Alzheimer's disease [170]. It is possible that the cross-linking activity of α-actinin contributes to the formation of these structures, which may deplete the postsynaptic pool of α-actinin. A decrease in postsynaptic α-actinin was also seen in the Huntington's disease mouse model R6/2 [171]. Through its actin branching and elongating activity, as well as its ability to regulate NMDA receptor activity, α-actinin is well positioned for modulating synaptic plasticity.

3.1.4. Drebrin Regulates Actin Assembly in Dendritic Spines

Drebrin is a developmentally regulated neuron-specific protein that competes with tropomyosin, fascin, α-actinin, gelsolin, cofilin, and myosin for actin-binding [172-175]. Drebrin was shown to bundle actin filaments into thick winding fibers in fibroblasts [176]. The embryonic drebrin isoform, drebrin E, exists in several cell types including neurons, while adult drebrin A is exclusively expressed in neu-

rons [177], and was found to be accumulated in the head area of mature mushroom-shaped dendritic spines with large PSDs and a high number of NMDA receptors in adult mouse cerebral cortex [178]. Interestingly, drebrin A is specifically localized at postsynaptic sites of excitatory synapses and barely detectable in presynaptic terminals, neuronal cell bodies, or axons [174, 179]. Deletion of the actin-binding domain of drebrin A [180] or depolymerization of F-actin with latrunculin A [150] leads to drebrin A re-distribution throughout various domains of dendrites, suggesting that it is dependent on F-actin for its postsynaptic localization.

Drebrin A has been implicated in the development of dendritic spines and synapses [179, 181, 182]. In support of this, it was found in submembranous zones of dendrites prior to the assembly of PSDs, formation of dendritic spine heads, and aggregation of presynaptic vesicles [179]. Furthermore, drebrin A overexpression in immature neurons induced accumulation of F-actin and PSD-95 at postsynaptic sites [181], whereas suppression of drebrin A expression decreased spine width and the density of spines and filopodia in developing hippocampal neurons in cultures [183]. Drebrin clustering was found to precede PSD-95 accumulation at postsynaptic sites and suppression of drebrin A expression disrupted PSD-95 postsynaptic localization [184]. Moreover, drebrin can also regulate NMDA receptor localization, as membrane targeting of NMDA receptors in cultured hippocampal neurons after AP5 treatment was abolished following reduction of drebrin A expression by antisense treatment [183].

Drebrin A postsynaptic localization is regulated by synaptic activity, and drebrin was shown to change its localization upon AMPA and NMDA receptor activation [182, 185]. While NMDA receptor activation induced a loss of drebrin from dendritic spines, an increase in drebrin A-immunoreactive spines was observed following NMDA receptor blockade *in vivo*, which occurred in the large mushroom-shaped spines [186]. On the other hand, drebrin clustering at postsynaptic sites was induced by AMPA receptor activation during spine morphogenesis and diminished with AMPA receptor blockade [182]. Together, these studies show that drebrin A induces postsynaptic differentiation, accumulates in mature dendritic spines, and stabilizes existing actin filaments. Therefore, the re-localization of drebrin seen upon NMDA receptor activation may be necessary to allow for spine remodeling.

Besides promoting dendritic spine formation and postsynaptic differentiation, drebrin was also implicated in learning and memory and the regulation of dendritic spine plasticity [180, 183]. For example, drebrin overexpression was shown to induce dendritic spine elongation in cultured cortical neurons [180]. Drebrin overexpression may promote spine elongation by inhibiting myosin association with actin filaments, thereby reducing actin contractility [174] or by competing with actin-stabilizing proteins for actin binding. Recent study has also suggested that drebrin-induced dendritic spine remodeling may involve activation of Ras family of small GTPases [187]. The significance of drebrin in normal synapse development and synaptic plasticity is further supported by observations that decreased levels of both drebrin isoforms were found in the hippocampi of Alzheimer's patients [188] and following cerebral ischemia [189], as well
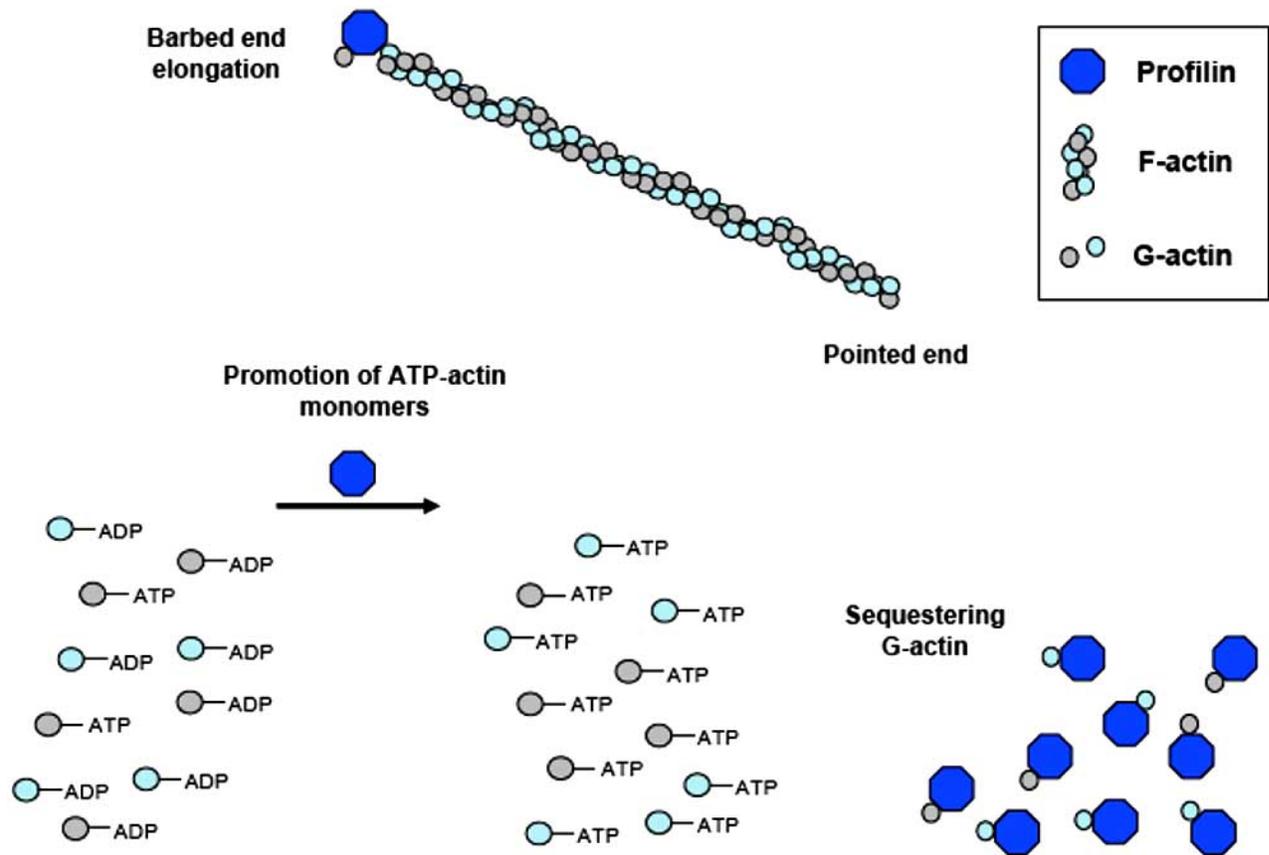
Fig. (4). Opposing actions of profilin on actin. G-actin-sequestering promotes F-actin depolymerization, while profilin-actin complex induces polymerization by binding to F-actin barbed ends and promoting formation of ATP-actin monomers.

as in the frontal and temporal cortex of patients with Down syndrome [190]. In the future, it would be interesting to determine the interplay between drebrin and other actin-binding proteins in promoting postsynaptic differentiation and spine maturation, or in regulating spine remodeling and synaptic plasticity.

3.1.5. Opposing Effects of Profilin on Actin Polymerization

Profilin was first identified as an actin monomer-sequestering protein that can inhibit actin polymerization and elongation [191-193] by forming a 1:1 complex with G-actin, thus decreasing its free concentration available to form F-actin polymers [194-197]. Conversely, profilin or the profilin-actin complex (profilactin) can promote actin polymerization by binding the barbed ends of actin filaments and directly elongating it (Fig. **4**) [198, 199]. A dose-dependent decrease in the amount of F-actin and lamellipodial size were seen upon microinjection of profilin into normal rat kidney (NRK) cells, whereas profilactin increased F-actin and lamellipodial ruffling [200]. Further, while profilin-bound actin monomers may be removed from the free actin pool and cannot nucleate new filaments, they can be added to F-actin barbed but not pointed ends, contributing to actin filament elongation [201]. While profilin can promote depolymerization by binding and sequestering actin monomers, it induces polymerization by lowering the critical concentration of ATP-actin and decreasing actin monomer affinity for its bound nucleotide, thereby favoring ATP-actin formation

[202]. Profilin can also promote the stability of actin filaments, as F-actin concentration was shown to increase with stable expression of profilin in Chinese hamster ovary (CHO) cells [203].

The ability of profilin to promote or inhibit actin polymerization under different circumstances can result in diverse cellular responses [204]. Profilin is implicated in cell motility, as it is localized with dynamic actin in fibroblast lamellipodia [205] and it was shown to regulate the movement of Listeria monocytogenes in infected host cells [206]. Profilin I mRNA was up-regulated in reactive hippocampal microglia following entorhinal deafferentation [207], which could also indicate a role for profilin in microglial migration following injury. Profilin regulates cell morphology, as it is involved in thrombin-induced platelet shape change [208] and endocytosis [209, 210]. Moreover, several abnormalities, including slow growth and loss of normal cell shape were seen with disruption or deletion of the profilin gene in yeast [211], whereas profilin gene deletion in Drosophila was lethal [212]. Profilin II was detected in neurons and its localization in dendritic spines was shown to be regulated by Ca^{2+} levels [213].

Profilin activity is also regulated by phosphorylation and its interaction with PIP_2. Profilin interaction with PIP_2 [214-216] inhibits PIP_2 hydrolysis by phospholipase C (PLC) [217], and dissociates the profilin-actin complex [218], which could lead to release of free G-actin monomers and

polymerization near the cell membrane. Conversely, PIP_2 binding to cofilin can stimulate profilin phosphorylation by protein kinase C (PKC) [219, 220]. Profilin phosphorylation, which can also be achieved by phosphatidylinositol 3-kinase (PI3-K), increases its affinity for G-actin and poly (L-proline) [221]. While PIP_2 binding can lead to increased actin polymerization, profilin phosphorylation would increase its association with G-actin and inhibit actin polymerization. Further, an increased affinity for poly (L-proline) may lead to enhanced profilin binding to membrane-associated proteins of the Mena/VASP family, resulting in F-actin elongation [213, 222]. It would be interesting to determine how profilin-PIP_2 binding and PKC phosphorylation of profilin regulate F-actin polymerization in dendritic spines.

Profilin expression is developmentally regulated in rat cerebellum [223] and is detected at synaptic sites in the adult cerebellar cortex [224], suggesting that it may play a role in synaptogenesis. Indeed, profilin associates with gephyrin and Mena to form a postsynaptic cortical scaffolding complex [225]. Upon NMDA receptor activation and Ca^{2+} influx, profilin is recruited to and stabilizes dendritic spines in a VASP-dependent manner [213, 226, 227]. Moreover, electrical stimulation that is known to produce LTP promoted similar recruitment of profilin to dendritic spines and spine stabilization [213], suggesting that profilin may be involved in regulation of dendritic spine and synapse dynamics underlying experience-dependent plasticity.

Besides the role of profilin II in normal dendritic spine development and plasticity, several studies have suggested that profilin II may mediate cytoskeletal changes in response to pathological conditions and disease processes. For example, profilin interacts with the Huntington Disease protein Huntingtin (Htt), and could be involved in causing the pathological aggregation of Htt. [228]. Inhibition of Rho-kinase (ROCK), which forms a complex with profilin II [229], reduces Htt aggregation [230]. On the other hand, profilin depletion can lead to neuronal deficits, as some patients with Miller-Dieker syndrome have been shown to exhibit partial profilin gene deletions [231]. The Fragile X mental retardation protein in Drosophila (dFMRP) was shown to regulate the neuronal cytoskeleton through profilin, as dFMRP binds mRNA of the profilin homolog and decreases its protein expression [232]. Profilin II knock-out mice demonstrated a lack of an actin polymerizing response to depolarization, which led to increased synaptic excitability due to increased vesicle exocytosis in glutamatergic neurons [233]. These studies correlate well, as some Fragile X phenotypes could also be explained by increased synaptic excitability, perhaps from decreased profilin levels. These studies show the remarkably diverse functions of profilin in controlling actin dynamics in dendritic spines. Depending on cellular signals and interacting proteins, profilin may promote actin polymerization or depolymerization, which could lead to formation, stabilization, or remodeling of dendritic spines.

3.1.6. Spinophilin (Neurabin II) and Neurabin I Promote cross-Linking of Actin

Spinophilin derives its name from its localization in the heads of dendritic spines [234], and neurabin I is a neural

tissue–specific actin–binding protein [235]. Both proteins are structurally related and display actin cross-linking and bundling activity. Spinophilin is expressed ubiquitously, but most abundantly in the brain, where it is localized in PSDs [236]. Neurabin I is accumulated in dendritic spines, as well as in growth cone lamellipodia of developing neurons.

A multitude of binding partners have been identified for spinophilin [237], including those with implications for synaptic function, such as protein phosphatase 1 (PP1). Spinophilin participates in targeting PP1 to the postsynaptic membrane (Fig. **5**) [234, 238], which allows PP1 to dephosphorylate its synaptic substrates. In this way, spinophilin can indirectly modify the activities of AMPA and NMDA receptors, two known substrates of PP1. *In vivo*, spinophilin takes part in the anchoring of AMPA receptors to the plasma membrane and promotes its dephosphorylation through PP1 [239]. Spinophilin knock-out mice exhibited an increased density of dendritic filopodia and immature spines, abnormal regulation of AMPA receptor activity by PP1, and impaired LTD, suggesting that spinophilin may regulate excitatory synaptic transmission and spine morphogenesis through PP1-mediated regulation of AMPA receptor activity [240]. Further, phosphorylation of spinophilin by protein kinase A (PKA) [241] or CaMKII [242] reduces the affinity of spinophilin for F-actin and causes a change in its cellular localization, which may also alter its binding with PP1 due to spatial segregation. Spinophilin phosphorylation by CaMKII is Ca^{2+}-dependent and may play a role in synaptic plasticity. In addition, a downregulation of the expression of spinophilin and GluR1 were observed during sleep following unilateral LTP induction in the prefrontal cortex of rats [243]. Taken together, these studies demonstrate that phosphorylation of spinophilin regulates its expression and specific localization within dendritic spines, where it is positioned to regulate synaptic activity and spine morphogenesis.

Although spinophilin and neurabin I are structurally similar, are localized in dendritic spines, and bind some of the same partners, they may have variable effects on dendritic spine morphology. While the actin-bundling activity of spinophilin seems to suppress outgrowth of immature dendritic filopodia-like protrusions [240], overexpression of neurabin I in immature neuronal cultures induced these protrusions [244]. Neurite formation was also reversibly abolished by neurabin I suppression following antisense oligonucleotide treatment of rat hippocampal neurons [236]. In contrast to the effects of spinophilin depletion, knock-out of neurabin I led to impaired LTP and enhanced AMPA receptor-mediated synaptic transmission; however, LTD was not altered [245]. Neurabin I may act as a competitive inhibitor of spinophilin, resulting in opposing effects on dendritic spines and synaptic activity, as they are structurally similar and share the same binding partners.

3.2. Actin Filaments Severing and De-Polymerization

3.2.1. Cofilin Regulates Actin Filament Treadmilling

Cofilin is a member of the ADF/cofilin family of actin-depolymerizing proteins that preferentially bind to ADP-actin subunits in a minor twisted conformation of F-actin and sever filaments (Fig. **6**). This increases the pool of G-actin monomers used by actin polymerizing factors and also creates free barbed ends that can nucleate filament growth [246-
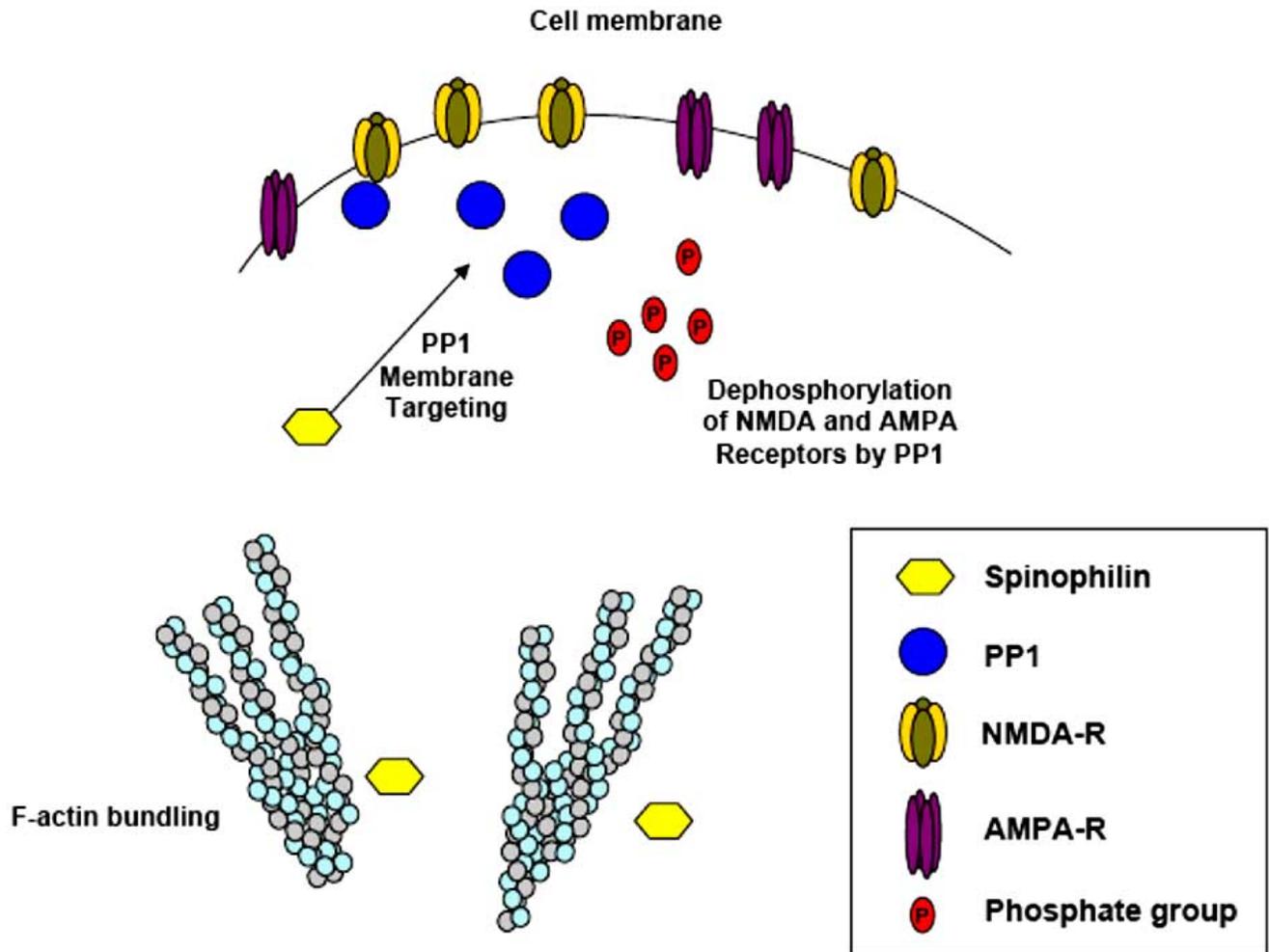
Fig. (5). Spinophilin participates in localization of PP1 to the cell membrane, where it dephosphorylates NMDA and AMPA receptors, down-regulating their activity. The actin-bundling activity of spinophilin prevents outgrowth of filopodia-like protrusions.

248]. Cofilin is expressed at high levels in the adult brain [249] and is more abundant in mammalian neurons than ADF [250]; therefore in this review, we will primarily discuss the role of cofilin in actin dynamics. Low levels of cofilin activity are detected in resting cells and contribute to F-actin depolymerization at the "pointed" ends and F-actin polymerization at the "barbed" ends, resulting in F-actin turnover at a slow rate [251]. On the other hand, enhanced cofilin activity is often detected in ruffling membranes at the leading edge of migrating cells and in neuronal growth cones, leading to fast F-actin dynamics [252-254]. The local concentration of cofilin in specific subcellular compartments determines the cofilin/actin ratio, thus influencing its effects on actin dynamics. While a low cofilin/actin ratio was shown to result in the highest severing of actin filaments, at high ratios cofilin can induce dissociation of the Arp2/3 complex and de-branching, resulting in formation of long, unbranched filaments [77, 255]. Therefore, the actions of cofilin in the cell largely depend on its localization and the level of activity [255].

Cofilin activity is regulated by phosphorylation. LIM kinase (LIMK) suppresses cofilin activity by phosphorylating cofilin at Serine 3, which inhibits its binding to F-actin

[256, 257]. The cofilin-specific phosphatases slingshot (SSH) and chronophin (CIN) dephosphorylate and activate cofilin [258-260]. The importance of cofilin phosphorylation in synaptic structural plasticity during LTP induction and protective effects of the inactive phospho-mimetic cofilin^{S3D} mutant against Aβ-mediated spine loss have been recently reported [261, 262]. Our studies have also shown that over-expression of inactive cofilin^{S3D} promoted stabilization of mature dendritic spines, whereas constitutively-active cofilin^{S3A} induced remodeling and elongation of actin-rich stable dendritic spines, and extension of new filopodia-like protrusions [263]. Moreover, depletion of cofilin-1 in cultured hippocampal neurons by overexpressing cofilin-1 siRNA was shown to decrease the number of mature dendritic spines and to induce the formation of abnormal filopodia-like branches [97]. Immunoelectron microscopy studies have found that cofilin accumulates near the PSD in the "shell" area of dendritic spines, a specific region containing a dynamic F-actin pool, while avoiding the spine "core" with a stable pool of F-actin [264]. The effect of actin-remodeling activity of cofilin on dendritic spine morphology and its localization within spines suggest that cofilin may play a role in dendritic spine plasticity.
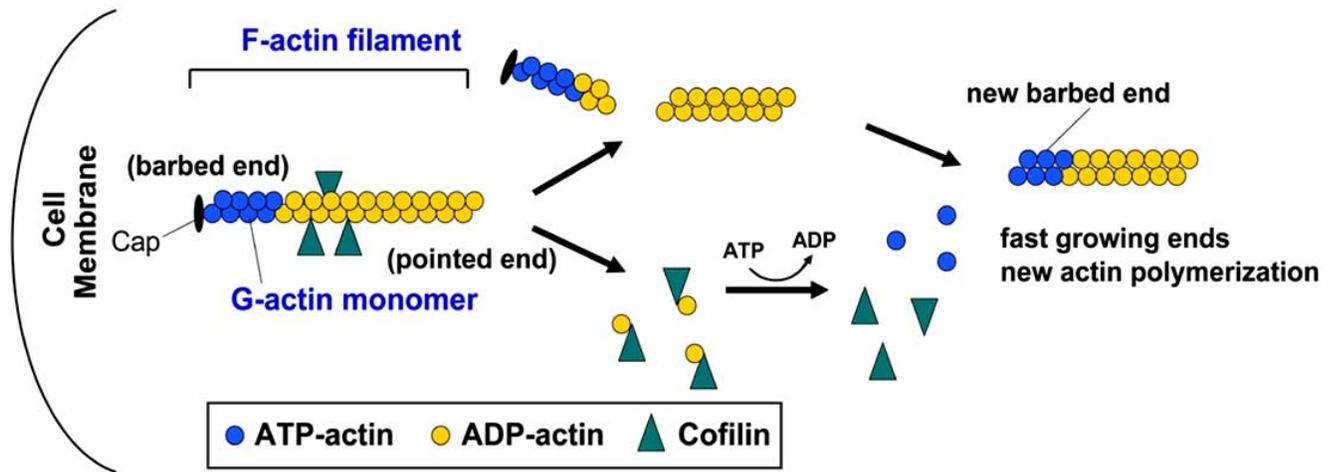
Fig. (6). Actin-severing activity of cofilin promotes F-actin and spine remodeling.

Several mechanisms that control cofilin activity in dendritic spines were recently proposed involving Rho GTPase-dependent regulation of LIMK activity (Fig. **7**) [263, 265]. Members of Rho family GTPases such as RhoA, Cdc42, and Rac can promote activation of LIMK through Pak and ROCK, respectively [257, 266, 267]. Pak1 and ROCK2 were demonstrated to regulate dendritic spine properties and synaptic density through LIMK-mediated regulation of cofilin activity [268, 269]. Moreover, the Rac-Pak-LIMK pathway was suggested to contribute to SynGAP-mediated regulation of steady-state cofilin phosphorylation in dendritic spines [265]. Our studies suggest that EphB2-mediated dendritic spine stabilization relies on the ability of EphB2 receptors to activate the RhoA-ROCK-LIMK-1 pathway that works to suppress cofilin activity by phosphorylation [263]. LIMK-1 is primarily expressed in neurons and was shown to be involved in dendritic spine development. Neurons from LIMK knock out mice formed morphologically immature dendritic spines with smaller heads and postsynaptic densities compared to wild-type neurons [270], and the inhibition of LIMK translation by microRNA-134 also resulted in smaller spine heads [271]. Cofilin phosphorylation can also be regulated independently of Rho GTPases. NMDA receptor activation in cultured hippocampal neurons was shown to trigger transient dephosphorylation and activation of cofilin [265]. Ca^{2+}-dependent changes in SSH activity were previously implicated in the regulation of cofilin activity [272]. Ca^{2+} influx through NMDA receptors can rapidly activate calcineurin [273], which in turn was shown to induce cofilin dephosphorylation through an upregulation of SSH activity [272]. In addition, the NMDA receptor-calcineurin pathway was shown to mediate reversible spine shrinkage in acute hippocampal slices following LTD by regulating cofilin activity [33]. While LTD induction depended on PP1, the change in spine morphology depended on cofilin, suggesting that these pathways may cooperate to regulate activity-dependent synapse pruning. In summary, the spine-remodeling activity of cofilin can be enhanced through a variety of signaling cascades that result in cofilin dephosphorylation through suppression of LIMK activity and/ or SSH activation.

Besides regulation of cofilin activity by phosphorylation, there are other mechanisms that influence the actin-severing ability of cofilin. Cofilin competes for actin binding with the actin-stabilizing protein drebrin [274]. Therefore, increased drebrin levels could lead to stabilization of actin filaments by preventing cofilin binding to actin filaments, whereas an increase in cofilin concentration could result in release of drebrin from actin filaments and enhance cofilin-mediated actin depolymerization. Cofilin-mediated actin depolymerization can also be inhibited by phosphoinositides, especially PIP_2, which interacts with the actin-binding domain of cofilin and triggers its association with the plasma membrane [275, 276]. On the other hand, the EphA4 receptor was shown to regulate cofilin activity in spines through activation of phospholipase Cγ, followed by hydrolysis of PIP_2 and release of active cofilin from the membrane [277]. PIP_2 was also shown to inhibit cofilin's ability to form cofilin-actin rods in myotubes [278]. In neurons, formation of cofilin-
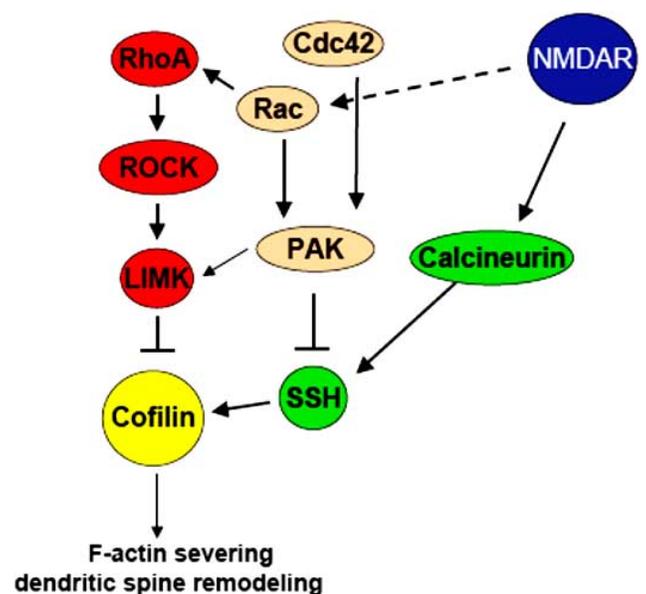

Fig. (7). Regulatory proteins that enhance or inhibit the activity of cofilin.

actin rods has been observed in response to neuronal stress [279, 280]. Treatment of hippocampal neurons with amyloid beta (Aβ)$_{1-42}$ peptide also led to the formation of cofilin-actin rods in dendrites and axons of neurons in both dissociated hippocampal cultures [281] and organotypic hippocampal slices [280]. Similar filamentous structures were detected in brains of subjects with Alzheimer's disease [282]. Therefore, it is possible that recruitment of a large number of cofilin molecules to actin rods would deplete the cofilin pool in dendritic spines, thus affecting dendritic spine maintenance and synaptic plasticity. Taken together, these studies indicate that cofilin is regulated by multiple mechanisms, which appear to be critical for dendritic spine maintenance and plasticity.

3.2.2. Gelsolin Severing Activity is Regulated by Ca^{2+}

Gelsolin derives its name from the process of "gel-sol" transformation of F-actin in the cortical cytoplasm of motile cells, which reversibly transitions from a highly cross-linked state ("gelation") to a disassembled state ("solation") in order to promote cell movement [283]. Gelsolin has a variety of functions, such as binding and severing F-actin and capping fast-growing barbed ends [284-287], as well as nucleating new filament polymerization [288]. Gelsolin binds selectively to ADP-actin [289, 290], introducing a conformational change, thus severing actin filaments [291, 292]. In combination with its capping activity, this leads to an increase in the number of pointed ends and ADP-actin dissociation. The structure of gelsolin has been delineated [293, 294], as well as its interaction with actin [295-300]. Structural provisions for gelsolin actin-severing [301-303] and polymerization activities [304] have also been well-studied in non-neuronal cells. Gelsolin is involved in the regulation of cell motility [305, 306] and phagocytosis [307], as well as inhibition of axonal transport of membranous organelles [308]. Mutated gelsolin was shown to inhibit fibroblast growth [309] and Rac-dependent motility was reduced in gelsolin-null fibroblasts [310].

Gelsolin activity can be regulated by different factors, including protein interactions and pH [311]. Tropomyosin competes with gelsolin for actin binding [312]. Moreover, phosphate analogs and activated GTP-Rac1 can reduce F-actin susceptibility to severing by promoting gelsolin dissociation from actin filaments [313, 314]. The actin severing and nucleating activities of gelsolin are inhibited by PIP$_2$ [315, 316]. Conversely, gelsolin can promote the phosphorylation of PIP$_2$ by activating PI3-K [317], and inhibit the hydrolysis of PIP$_2$ through competitive substrate binding [318, 319]. This has implications for linking the cell membrane with actin dynamics through gelsolin activity. Gelsolin-actin binding is also regulated by micromolar concentrations of Ca^{2+} [283, 320-323]. Ca^{2+} was shown to promote gelsolin severing activity [320, 324], and to increase the efficiency of its capping activity [325]. By occupying the Ca^{2+}-binding domain of gelsolin [326], Ca^{2+} ions induce structural changes in gelsolin [327-329].

Gelsolin is detected in the brain, spinal cord, and in cultured neurons [330], where it is implicated in plasticity. An upregulation in gelsolin mRNA [331] and gelsolin protein levels [332] was found in the rat hippocampus following entorhinal deafferentation, suggesting that gelsolin may play a role in brain remodeling following hippocampal injury.

Filopodia and lamellipodia are enriched with gelsolin [333, 334], and gelsolin knock-out mice exhibit slower filopodial retraction [335], further supporting the role of gelsolin in cell-protrusive activities. Gelsolin knock-out mice exhibit increased Ca^{2+} influx following glutamate exposure [336] and fail to display an NMDA receptor-dependent decrease in the actin turnover rate [337]. These studies implicate gelsolin's severing and capping activity in mediating NMDA receptor-induced spine stabilization.

Mutations in the gelsolin gene were found in subjects with familial amyloidosis [338-341]. This could partially explain the neuronal pathologies of the disease [342], including signs of de-myelination reported in these patients [343], as high levels of gelsolin are detected in myelin-forming cells and implicated in lamellipodial movement toward the axons during myelination [344-346]. Gelsolin mutations are also linked to Alzheimer's and Parkinson's diseases [347]. In addition, subjects with Down syndrome exhibited an increase in gelsolin levels in developing frontal cortex, and levels of gelsolin were shown to rise with aging in control subjects [348]. The ability of gelsolin to bind and sever F-actin and to cap fast-growing barbed ends, as well as to nucleate filament polymerization, supports its role in mediating actin remodeling in dendritic spines.

3.3. Myosins Influence Actin Dynamics at Synapses

Although F-actin assembly/disassembly determines actin dynamics, myosin motors posses ATPase activity and can also influence actin dynamics in dendritic spines. The myosin II, V, and VI isoforms were found in dendritic spines [349], and are suggested to regulate dendritic spine shape and synaptic plasticity, at least in part through interaction with actin and modulation of NMDA and AMPA receptor membrane insertion and function. Actin-myosin interaction is known to regulate dendritic spine shape and is inhibited by drebrin, which is enriched in mature dendritic spines [174, 178]. Although myosin IIB immunoreactivity was identified throughout neuronal cell bodies and various dendritic domains that lack drebrin immunoreactivity, a small pool of myosin IIB was also detected within the drebrin-positive fraction of F-actin in dendritic spines [350]. Drebrin overexpression, on the other hand, has been shown to elongate dendritic spines, so it may function here to inhibit actin-myosin contractility [174]. Myosin motors have been suggested to contribute to the formation of mature short mushroom-shaped and stubby spines. In support of this, myosin IIB depletion with RNAi causes a decrease in the number of short mushroom-shaped spines and an increase in long filopodia-like protrusions [351].

Myosins can also interact with NR1 and NR2 subunits of NMDA receptors through the myosin regulatory light chain [352] and control the trafficking of the GluR1 subunit of AMPA receptors from the dendritic shaft to dendritic spines in a Ca^{2+}-dependent manner [353]. Myosin Vb associates with recycling endosomes and mobilizes them for AMPA receptor insertion and spine growth upon LTP induction, whereas depletion of myosin Vb using RNAi prevents LTP-induced AMPA receptor insertion into the postsynaptic membrane and spine growth [354]. Further, the PSD-95 interacting protein guanylate kinase domain-associated protein (GKAP) interacts with the dynein light chain (DLC) of my-

osin V, which may implicate myosin V in NMDA receptor regulation [355].

Myosin VI is also enriched in the brain and localized to PSDs in synapses. Spine loss was seen upon myosin VI disruption through the expression of a dominant-negative mutant or in hippocampal cultures of myosin VI deficient mice [356]. In addition, increase in AMPA receptor internalization following AMPA or insulin stimulation was not observed in myosin VI deficient neurons [356]. Myosin VI promotes the formation of mature spines and synapses, but also allows for LTP termination by receptor internalization. Although myosin is perhaps best studied for its role in generation of contractile forces in non-neuronal cells, myosin II, V, and VI also exhibit important roles in promoting mature dendritic spine morphology and regulating synaptic plasticity through NMDA and AMPA receptor trafficking at synapses.

4. INTEGRATION OF ACTIN-BINDING PROTEINS IN THE REGULATION OF DENDRITIC SPINES AND SYNAPSES

There are many actin-binding proteins within the cell that directly regulate actin polymerization, branching, cross-linking and bundling, or severing and depolymerization. By affecting actin dynamics, actin-binding proteins have the ability to form, re-arrange, stabilize, or remodel dendritic spines. These proteins also aid in clustering postsynaptic proteins and in regulating neurotransmitter receptor activities to create functional synaptic connections. Some actin-regulatory proteins like profilin have multiple functions in dendritic spines and pose opposing effects on actin, depending on several factors and conditions, such as its subcellular localization, Ca^{2+} levels, interactions with other proteins, and phosphorylation state. Other proteins such as spinophilin and neurabin I are similar in structure and activity, but exhibit opposing effects on dendritic spines through yet unknown mechanisms. Arp2/3 and cortactin work together, each to promote the activity of the other, contributing to actin polymerization. While α-actinin elongates dendritic spines, myosins induce the formation of short mushroom-shaped spines by enhancing actomyosin contractility. Meanwhile, ADF/cofilin and gelsolin work by severing F-actin filaments, which can promote spine elongation and remodeling by increasing actin filament turnover, or lead to spine stabilization through gelsolin capping activity.

These actin-binding proteins are regulated by signaling cascades that are initiated at the cell surface through trans-synaptic interactions, neuron-glia communications, and contacts with the extracellular matrix [5]. Cell surface receptors, such as glutamate receptors, EphB receptors and ephrins, neuroligins and neurexins, integrins, cell adhesion molecules, growth factor receptors, and some proteoglycans, mediate these interactions linking extracellular events to the actin cytoskeleton in dendritic spines by initiating cytoplasmic signaling cascades. Cytoplasmic signaling proteins such as PIP_2 exhibit diverse control through a variety of mechanisms, from promoting α-actinin activity through direct binding, to activating Arp2/3 through WASP, to dissociating the profilactin complex from actin. The Rho family of small GTPases, such as Rac1, Cdc42, and RhoA, are also key regulators of actin-binding proteins in dendritic spines and play an important role in dendritic spine formation, mainte-

nance, and remodeling. In addition to the structural role of actin in dendritic spines, actin assembly was recently suggested to influence neuronal motility through a regulation of gene transcription [357]. This may have implications for a role of actin-binding proteins in regulating gene transcription and protein synthesis in spines.

Dendritic spine dynamics have been implicated in processes of learning and memory [358, 359], and abnormalities in the shape and number of spines are seen in neurodegenerative diseases, as well as some forms of mental retardation and autistic spectrum disorders [41, 42]. While the role of various actin-binding proteins in regulating spine dynamics has been studied, a challenge for future research is to understand the interplay between different actin-regulating factors under an array of physiological and pathological conditions.

ABBREVIATIONS

AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
ARF6	=	ADP ribosylation factor 6
Arp2/3	=	Actin-Related Protein
BDNF	=	brain-derived neurotrophic factor
CaMKII	=	Ca^{2+} calmodulin-dependent protein kinase II
CIN	=	chronophin
dFMRP	=	Drosophila Fragile X mental retardation protein
DLC	=	dynein light chain
F-actin	=	filamentous actin
FAK	=	focal adhesion kinase
G-actin	=	globular actin
GKAP	=	guanylate kinase domain-associated protein
Htt	=	Huntingtin
LIMK	=	LIM kinase
LTD	=	long-term depression
LTP	=	long-term potentiation
MAP	=	mitogen-activated protein
MAPKPK2	=	MAPK-activated protein kinase 2
mGluR	=	metabotropic glutamate receptors
NMDA	=	N-methyl-D-aspartate
N-WASP	=	Neural-WASP
PAK	=	p21-activated kinase
PI3-K	=	phosphatidylinositol 3-kinase

PIP$_2$	=	Phosphatidylinositol 4,5 bisphosphate
PKA	=	protein kinase A
PKC	=	protein kinase C
PLC	=	phospholipase C
PP1	=	protein phosphatase 1
PSD	=	postsynaptic density
REMS	=	Rapid Eye Movement Sleep
RNAi	=	RNA interference
ROCK	=	Rho-kinase
siRNA	=	small-interfering RNA
SPAR	=	Spine-Associated Rap GTPase-activating protein
SSH	=	slingshot
TLCN	=	telenceplalin
WASP	=	Wiskott-Aldrich Syndrome protein
WAVE	=	WASP-family verprolin-homologous protein

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