Hindawi Publishing Corporation
Neural Plasticity
Volume 2016, Article ID 2371970, 19 pages
http://dx.doi.org/10.1155/2016/2371970

Review Article

Regulation of the Postsynaptic Compartment of Excitatory Synapses by the Actin Cytoskeleton in Health and Its Disruption in Disease

Holly Stefen,[1,2] Chanchanok Chaichim,[1,2] John Power,[2] and Thomas Fath[1]

[1]*Neurodegeneration and Repair Unit, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia*
[2]*Translational Neuroscience Facility, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia*

Correspondence should be addressed to Thomas Fath; t.fath@unsw.edu.au

Received 9 December 2015; Accepted 9 March 2016

Academic Editor: Zygmunt Galdzicki

Disruption of synaptic function at excitatory synapses is one of the earliest pathological changes seen in wide range of neurological diseases. The proper control of the segregation of neurotransmitter receptors at these synapses is directly correlated with the intact regulation of the postsynaptic cytoskeleton. In this review, we are discussing key factors that regulate the structure and dynamics of the actin cytoskeleton, the major cytoskeletal building block that supports the postsynaptic compartment. Special attention is given to the complex interplay of actin-associated proteins that are found in the synaptic specialization. We then discuss our current understanding of how disruption of these cytoskeletal elements may contribute to the pathological events observed in the nervous system under disease conditions with a particular focus on Alzheimer's disease pathology.

1. Introduction

Memories are coded in the ensemble activity of small groups of neurons distributed throughout the brain. Glutamate is the primary excitatory neurotransmitter in the brain and the majority of synaptic connections between the glutamatergic neurons are made on dendritic spines. These specialized dendritic protrusions are supported by an actin-rich cytoskeletal protein matrix that not only provides structural support but also is essential for the delivery and anchoring of neurotransmitter receptors and other molecules involved in synaptic transmission. The synapse's capacity for change allows for memory formation and adaption to the environment. This synaptic remodelling is a dynamic process involving trafficking of neurotransmitter receptors into or out of the synaptic complex. These modifications require regulated disassembly and reassembly of the actin cytoskeleton. Orchestrating the controlled breakdown and reassembly of the actin cytoskeleton requires coordinated activity of an array of actin-associated proteins.

Alzheimer's disease (AD) is a neurodegenerative brain disorder that erodes memories and clouds thinking, gradually destroying one's sense of self. A loss of synaptic connectivity is thought to underlie the cognitive symptoms of AD. Synapse loss is observed in early stages of the pathology [1] and the correlation between synapse loss and severity of cognitive impairment is well established [2–4]. The early emergence of altered network connectivity has been confirmed by subsequent functional imaging studies [5, 6].

Cellular and murine models of AD have provided insight into the cellular mechanisms that underlie the loss of synaptic function in AD. It has become increasingly apparent that actin cytoskeletal function is disrupted in the pathology. Here we review the literature, describing the contribution of actin-associated proteins to synaptic function, and highlight recent findings implicating their involvement in AD pathology. Given the central role of the actin cytoskeleton in maintaining and modifying glutamatergic synaptic connections, proteins that modify or stabilize the cytoskeletal structures are potential therapeutic targets in the treatment of AD.

2. Structural and Functional Organization of the Postsynaptic Compartment of Excitatory Synapses

The majority of synaptic contacts between excitatory neurons are made on dendritic spines. These small structures house the postsynaptic molecules necessary for synaptic transmission. The prototypical spine contains a bulbous head (0.01–1 μm^3) and is connected to its parent dendrite via a thin (0.1 μm diameter) spine neck [7], which restricts diffusion between the two compartments, allowing concentration and segregation of signalling molecules [8, 9]. At the distal end of the spine head, directly across the synaptic cleft from the active zone of the presynaptic bouton, is an electron-dense postsynaptic density (the PSD), within which neurotransmitter receptors, cell adhesion molecules, cell signalling molecules, and a myriad of molecules involved in synapse stability are embedded [10, 11].

Spines are diverse in both shape and intracellular constituents. The neck length and width and head size vary along a continuum even within the same section of dendrite [12]. Despite this continuum they are usually classified based on the relative size of the spine head and neck [13, 14]. Mushroom spines have a large head and thin neck. Thin spines have a long neck and small head. Stubby spines are short with no obvious neck constriction. Synaptic function and structure are tightly intertwined and the different shapes are thought to reflect differences in synaptic strength and developmental stage [15–18]. Spine head volume has been found to be tightly correlated with PSD area [19] and the number of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) in the postsynaptic membrane [20]. Thus, spines with largest heads form the strongest synaptic connections. These mushroom spines are less motile and more persistent than thin spines [21–23]. Large spines are also more likely to contain organelles including endoplasmic reticulum and mitochondria [24], likely due to increased metabolic demands associated with maintaining the expanded synaptic machinery.

The morphology of dendritic spines is highly dynamic. Spines undergo functional and morphological changes during development and in response to neuronal activity. Nascent spines emerge as thin or filopodia-like protrusions [23, 25, 26]. Most of these newly formed spines will disappear, whereas others that find synaptic partners will undergo a morphological transition into the more stable "mushroom" spines [26]. Once established, spines continue to be sculpted by neuronal activity. As discussed above, spine morphology and function are linked with the spine head volume tightly correlated with the number of AMPARs in the postsynaptic membrane. Therefore, the trafficking of neurotransmitter receptors to the plasma membrane is essential for synapse maturation and activity-dependent changes in synapse strength thought to underlie memory formation. Note that memories and their synaptic substrates can persist for years, well beyond the lifetime of the proteins responsible for synaptic transmission. Thus, even synapse maintenance requires cycling of proteins in and out of the membrane for protein replenishment.

The synaptic cytoskeleton not only is necessary for the structural support of the synaptic connections but also is critical for the cycling of neurotransmitter receptor and other proteins between the plasma membrane and endoplasmic compartment. The primary cytoskeletal component found in dendritic spines is actin [27]. Actin is present in two forms: filamentous actin (F-actin), which is the insoluble, polymer form that makes up the cytoskeleton, and its soluble monomeric building block, globular actin (G-actin). F-actin in spines displays a compartment specific organization with more linear oriented actin filaments in the spine neck and a branched organization in the head compartment [28].

Time-lapse studies suggest that spines initially develop as filopodia, which grow the mushroom-shaped head, characteristic of mature spines through branching of actin filaments (comprehensively reviewed by Yoshihara et al. [26] and Hotulainen and Hoogenraad [29]). These studies also highlight the dynamic nature of the actin cytoskeleton. Spine shape changes follow changes in actin dynamics and have been observed occurring within seconds [30], responding to chemical or electrical stimulation [31]. Live-cell imaging of green fluorescent protein labelled actin (GFP-actin) has indicated that actin is organized into structurally and functionally distinct F-actin populations within the postsynaptic compartment [15, 30]. Dynamic and stable pools of F-actin were identified that consisted of differing rates of actin treadmilling [30]. The dynamic pool of F-actin was shown to have an actin turnover rate <1 min and is believed to be involved in generating force to expand the spine head and AMPAR insertion at the PSD. A stable pool of F-actin was localized to the base of the spine and had a slower turnover rate of approximately 17 min. The stable pool was suggested to provide resistance against the force generated by the active pool, maintaining the stability of the spine [15]. Honkura and colleagues also identified a third pool of F-actin, an enlargement pool, which was required for spine head enlargement during the induction of long-term potentiation (LTP).

A major challenge in the analysis of structural and functional changes at synapses is the extremely small size, with the spine heads being less than a micron in diameter. Advances in superresolution microscopy provide us with some fundamental understanding of actin dynamics in dendritic spines. Photoactivated localization microscopy (PALM) revealed a greater velocity of actin movement in the spine head and a net flow of G-actin from dendrite into the spine [32]. Stimulated emission depletion (STED) imaging shows not only size changes, but also small shape changes that are difficult to detect with other methods. Stimulation often causes spines to take on a cup-like shape [33].

In more recent years, superresolution imaging has been implemented in various studies to more accurately examine dendritic spine properties such as morphology and diffuse dynamics of proteins, calcium, and small molecules [34]. For instance, Lu and colleagues [35] were able to visualise single molecule dynamics of the actin cytoskeleton modulating kinase calcium/calmodulin dependent kinase II (CAMKII) [36] within dendritic spines by using PALM. By implementing this high resolution technique Lu and team were able to distinguish multiple subpopulations of CAMKII within the spine

head based on motility. Furthermore, STED imaging in combination with fluorescence recovery after photobleaching (FRAP) was able to show that, upon stimulation of spine-specific LTP, as spine heads become larger, spine necks become shorter and wider [37]. In addition to this finding, Tønnesen and colleagues showed that spines which appear stubby in two-photon imaging are mushroom headed with short necks when visualised with STED. These studies highlight the importance of using superresolution imaging techniques when investigating characteristics of spines.

3. Regulation of the Postsynaptic Actin Cytoskeleton

The actin cytoskeleton in eukaryotic cells is regulated by a host of actin-associated proteins. The complex actions of these proteins govern actin cytoskeleton dynamics, enabling functional and structural diversity of F-actin populations within dendritic spines. Actin regulators facilitate assembly, disassembly, branching, stabilization, and reorganization of the cytoskeleton, all critical requirements for synaptic plasticity.

Assembly of actin filaments and as such the actin cytoskeleton requires the formation of rod-like actin polymers known as actin filaments or filamentous actin (F-actin) from actin monomers (globular actin, G-actin). The process by which G-actin is accommodated into the fast growing (barbed) end of an actin filament and dispersed from the opposite pointed end is referred to as actin treadmilling. Various actin-associated proteins are involved in regulating the assembly of actin filaments. In the following section we will focus our attention on a select number of key regulators, including the actin sequestering protein profilin, the actin nucleators formin and actin-related proteins 2 and 3 complex (Arp2/3), the actin depolymerizing factor (ADF)/cofilin, the actin motor protein myosin, and the actin stabilizing protein tropomyosin.

3.1. Actin Sequestering and Nucleating Proteins. Actin filament nucleation can occur *de novo* or as filament branches that nucleate on preexisting filaments. Formins are a superfamily of proteins with at least 15 different proteins found in mammalian cells that promote the *de novo* nucleation of unbranched actin filaments (for reviews, see [38, 39]). Their activity is regulated by small GTPases thereby controlling the assembly of new actin filaments [40–42]. Formins play a critical role in supporting the early morphogenesis of filopodial spines [43], and it localizes to fine, filopodial structures that are found at the distal part of more mature spines [44].

Arp2/3 promotes nucleation of F-actin daughter branches of existing F-actin mother filaments [45]. Actin filaments within filopodia were found to originate from branch points in lamellipodia that were generated by Arp2/3 [46]. Arp2/3 complex is detected in the central region of the spine head approximately 200–400 nm from the PSD indicating a local segregation of morphologically distinct actin filament populations [47].

Depletion of Arp2/3 complex in both B35 neuroblastoma cells and primary hippocampal neurons was found to decrease growth cone F-actin and reduce lamellipodia protrusion and contraction [46]. In addition to this, cells with deficient levels of Arp2/3 had lamellipodia that were narrower and contained actin networks that were less complex and contained fewer branches [46]. Conversely, in a study by Yang and colleagues [48], inhibition of Arp2/3 using the reversible Arp2/3 inhibitor CK-666 unexpectedly resulted in an increase in actin retrograde flow, which was significantly reduced upon inhibition of myosin II, suggesting that Arp2/3 restricts myosin II mediated retrograde flow of actin [48].

Activation of Arp2/3 occurs via the activity of nucleation promoting factors (NPFs) such as neural Wiskott-Aldrich syndrome (N-WASP), WASP family verprolin-homologous protein (WAVE, also known as SCAR), and WASP and SCAR homolog (WASH) [49]. Arp2/3 and WASH have been implicated in early endosome morphology and function. Through immunocytochemical analysis of fibroblast-like cells, WASH was found to extensively associate with early endosome markers EEA1 and Rab5 and weakly associate with recycling endosome marker Rab11 [50]. siRNA-mediated knockdown of WASH resulted in larger and more elongated EEA1 positive structures compared to controls [50]. Knockdown of WASH reduced trafficking of epidermal growth factor (EGF) to late endosomes, an effect also observed in response to actin-polymerization disruption. However, knockdown of WASH was not found to affect reuptake or recycling of transferrin, implying specificity of WASH to the endocytic degradation pathway [50]. These results suggest that WASH activity affects endosomal trafficking of cargo, most likely via Arp2/3 mediated actin dynamics.

Profilin is thought to promote F-actin elongation at the barbed end by accelerating the nucleotide exchange of ADP for ATP on G-actin. Recent findings suggest that profilin has separable roles in G-actin regulation [51]. Suarez and colleagues found that profilin is required for actin contractile ring formation in fission yeast through interactions with formin as well as limiting Arp2/3-mediated actin branching by sequestering G-actin [51]. Profilin is thought to favour formin mediated F-actin elongation over Arp2/3 while reducing the ability of both formin and Arp2/3 to nucleate filaments [51].

3.2. Actin Filament Depolymerizing Proteins. Turnover and disassembly of F-actin occur through the actions of ADF/cofilin. With the continual addition of monomeric ATP-bound actin to the barbed end of the filament, previously incorporated actin monomers become progressively distal to the barbed end to form the body of the filament. As this occurs, the ATP is hydrolysed to ADP [52]. The resulting ADP-bound actin subunits are still able to maintain filament stability due to the presence of an inorganic phosphate ($P_{(i)}$). It is believed that once $P_{(i)}$ has been released cofilin is able to bind to the filament, inducing severing and depolymerization [53].

Severing of ADP-actin from the pointed end of filaments is facilitated by the actions of ADF/cofilin in its dephosphorylated active state [54]. ADF/cofilin interacts directly with actin filaments, and its activity is regulated by the actions of LIM-Kinase 1 (LIMK-1) and Slingshot (SSH) phosphatase.

Phosphorylation of cofilin at its serine 3 site by LIMK-1 inhibits ADF/cofilin severing of actin filaments and increases F-actin content in actin-rich regions of neurons [55, 56]. Conversely, dephosphorylation as well as activation of cofilin by SSH results in severing of actin filaments. Based on cryoelectron microscopy three-dimensional reconstructions of cofilin bound to actin filaments, Galkin and colleagues [57] postulate that filaments decorated with cofilin undergo a conformational change whereby the actin protomers bound to cofilin rotate in a manner that induces greater flexibility of the filament. Once rotated, the filament exposed regions that were then vulnerable to severing through further ADF/cofilin actions [57]. The ability of ADF/cofilin to disassemble F-actin networks has been suggested to be integral to the enlargement of dendritic spine heads, possibly by creating new barbed ends from severed filaments [58]. The activity of cofilin can be modified by upstream signalling proteins such as Cdc42, which has been shown to promote cofilin activation [59].

Gelsolin is an actin-associated protein predominantly activated by Ca^{2+} [60]. When activated by Ca^{2+}, gelsolin undergoes conformational changes that expose actin binding sites [60–62]. Active gelsolin severs and then caps F-actin at barbed ends, resulting in the disassembly of the F-actin network and prevention of further polymerization [63–65]. However, in the presence of phosphatidylinositol 4,5-bisphosphate (PIP_2), gelsolin activity is largely abolished [66]. Furthermore, a study by Hartwig and colleagues [67] found that inhibition of gelsolin by PIP_2 application increased the prevalence of barbed ends suggesting that PIP_2 facilitates the removal of gelsolin caps from F-actin barbed ends. With the inhibition of gelsolin, further polymerization of actin filaments is enabled [68]. Overexpression of gelsolin in a PC12 neuronal-like cell line differentiated with nerve growth factor led to an increase in neurite length and motility rate compared to controls possibly through increased F-actin turnover [69]. Importantly, gelsolin function is required for the morphological transition of filopodia to spines [70].

3.3. Actin Stabilizing Proteins and "Gatekeepers" of Actin Filament Dynamics and Stability. Drebrin A (DA) is the adult isoform of drebrin and is found in mature neurons at postsynaptic sites of dendritic spines [71]. Drebrin A binds to F-actin, inhibiting depolymerization of the filament predominantly at the barbed end [72, 73]. An atomic force spectroscopy study by Sharma and colleagues [74] found that drebrin binding resulted in a twisting of F-actin conformation that induced stiffening of the filament. The conformational twist induced by drebrin was found to occur in a manner that was opposite to cofilin induced twisting in F-actin structure, suggesting that drebrin and cofilin have antagonistic effects of F-actin structure [74].

Drebrin has been shown to compete with cofilin for F-actin binding sites [75]. Cosedimentation experiments showed that DA and cofilin are able to simultaneously bind to F-actin and inhibit the actions of each other [75]. Neurons transfected with DA-GFP were found to have dendritic spines that had significantly lengthened necks compared to controls [71]. Binding of drebrin to F-actin was also shown to inhibit myosin V binding. *In vitro* motility assays showed an impairment of F-actin binding to myosin V coated glass surfaces when in the presence of drebrin A [72]. However, F-actin that was able to bind to myosin V in the presence of drebrin did not show any impairment in F-actin-myosin sliding. This suggests that drebrin may also modulate myosin V activity.

Tropomyosins (Tpms) are a family of actin-associated proteins and key regulators of the actin cytoskeleton. In mammals, TPM1, TPM2, TPM3, and TPM4 genes have been shown to be responsible for the generation of more than 40 known tropomyosin isoforms [76] with gene products from TPM1, TPM3, and TPM4 found in neuronal cells. The primary structure of Tpm proteins consists of paired α-helices arranged in a coiled-coil manner [77, 78]. Although the primary structure of tropomyosin is highly conserved between the various isoforms, alternatively spliced exons allow functional diversity and differential localization within the cell [76, 79, 80].

Studies that have examined the interaction between Tpm and actin filaments have shown that Tpm isoforms have distinct F-actin regulatory effects as well as differential affinities to associate with F-actin [76, 78, 81] and facilitating functional diversity of cytoskeletal F-actin [82]. Tpm3.1, a tropomyosin isoform derived from the TPM3 gene, is involved in F-actin stabilization and reduced cell motility [76, 82] whereas Tpm1.12, derived from the TPM1 gene, promotes F-actin-ADF interactions resulting in F-actin severing [76].

Further studies exploring the effects of increased Tpm3.1 protein levels found an increase in the length and branching of dendrites and axons, along with increased growth cone size [83] and an increased pool of filamentous actin in growth cones [84]. A subsequent study showed altered growth cone dynamics in response to the knockdown of Tpm3.1 and Tpm3.2 [85]. These results suggest that this particular tropomyosin isoform may be involved in the stabilization of the actin cytoskeleton in neurons. Guven and colleagues [79] have detected Tpm3 gene products in the postsynaptic compartment of mature cultured neurons suggesting a potential role in the maintenance of synaptic connections.

Another mode of actin filament regulation and stabilization is through actin capping proteins, which bind to the barbed end of actin, preventing further elongation. This process limits the length of actin filaments. Actin capping protein (CP) has been found to be associated with the actin and Arp2/3 network in spine heads [28], and the level has been observed to be elevated during stages of synapse formation. Knockout of CP in rat hippocampal cultures has been shown to lead to altered spine morphology and a reduction in synapse density [86]. Another protein with actin capping function, Eps8, has been found to play a role in actin-based motility, such as filopodia growth and numbers [87]. Eps8 is also enriched in the PSD, and as in the case of CP knockdown, reduced expression levels alter spine morphology [88]. The actin severing protein gelsolin can also cap actin filaments, depending on calcium ion concentration [89]; however this has not been studied in detail in neurons.

3.4. Actin Motor Proteins. Myosins form a superfamily of actin motor proteins. The family contains motors with diverse

functions that range from building contractile elements (conventional family members) such as the sarcomere of muscle cells to driving intracellular transport of vesicles (unconventional family members). Characteristic to all myosins is the presence of catalytic head or motor domains that bind and hydrolyse ATP to produce motility. The tail of myosins can either align with other myosin molecules to form myosin filaments (e.g., the formation of the thick filaments in muscle, built by muscle isoforms of myosin II) or bind to different cargos allowing transport of these cargos along actin filaments. For a review on myosin function and diversity, see Hartman and Spudich [90]. The motor domains of the myosins bind to F-actin [91] and have been shown to travel along the filament in a hand-over-hand type movement using various imaging techniques [92–94]. The unconventional myosins V and VI have been implicated in vesicle trafficking within dendritic spines [95, 96].

Together these actin-associated proteins provide diverse regulation of the cytoskeleton within the postsynaptic compartment of dendritic spines.

4. Learning and Memory as Actin Cytoskeleton-Dependent Process

Long-term changes in connections between neurons are thought to be the basis of memory formation. At most synapses in the brain, activity-dependent synaptic plasticity is triggered by a rise in postsynaptic calcium, which triggers a series of downstream effectors that can initiate different forms of synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission [97]. Although the loci of expression can vary between pre- and postsynaptic structures depending on the synapse, developmental stage, and induction protocol, at forebrain glutamatergic synapses synaptic plasticity often manifests as a change in the number of AMPA receptors expressed at the synapse [98].

As discussed above, synaptic proteins are continuously shuttled in and out of the plasma membrane; thus the number of AMPARs at the synapse is governed by the relative rate of receptor exocytosis and endocytosis, resulting in concomitant spine head volume changes. Several studies have shown that LTP is accompanied by an increase in spine volume [22, 31, 99] whereas LTD is accompanied by a reduction in spine volume [31, 100].

Actin dynamics are integral to both structural and functional synaptic plasticity. The LTP-associated spine enlargement is associated with an increase in F-actin [101] that persisted for several weeks. Furthermore, blocking actin polymerization via application of latrunculin and cytochalasin toxins impairs LTP and spine enlargement [102–106]. Conversely, LTD is associated with a relative decrease in F-actin [31] and stabilization of the actin cytoskeleton impairs LTD and the associated reduction in spine volume [107]. Application of drugs impacting actin stability also disrupts a variety of associative learning tasks (see [108] for review).

Measurements of fluorescence recovery of photobleached green fluorescent protein-tagged actin (GFP-actin) in the spine head indicate that most of the actin in the spine head is found in filaments that rapidly turn over, with only a small fraction of actin being assembled in the form of stable filaments [30]. Actin dynamics are altered by neuronal activity. High frequency stimulation, which induces LTP and enlarges the spine head, is associated with an increase in proportion of actin present as F-actin in the spine head [31]. Conversely, LTD-inducing low-frequency stimulation was found to reduce the spine head volume and the F-actin : G-actin ratio [31].

Using photoactivatable GFP-actin, Honkura and colleagues [15] tracked the spatial temporal movement of actin. Their data provide evidence for three functional pools of F-actin: a dynamic pool at the tip of the spine head, a stable pool at the base of the spine, and an "enlargement pool" that emerges following repeated stimulation of the spine head with glutamate. The persistence of the enlargement pool in the spine head was associated with structural LTP.

In addition to actin, several actin-associated molecules show activity-dependent changes in phosphorylation state and distribution. LTP induces a transient increase in spines immunopositive for phosphorylated (deactivated) cofilin [109]. A recent study by Bosch et al. [110] describes the spatiotemporal dynamics of GFP tagged actin and several GFP tagged actin-associated proteins following the induction of LTP. They found that structural LTP was associated with the rapid translocation of actin and several actin-associated proteins into the spine head. Of particular note was cofilin, which became concentrated in the spine head.

Structural plasticity is not limited to the neurons. Actin-rich perisomatic astrocytic processes [111] at glutamatergic synapses show activity-dependent remodelling, expanding in concert with spine enlargement following the induction of LTP [112].

5. The Actin Cytoskeleton as Key Regulator in Glutamate Receptor Trafficking

Synaptic function directly correlates with the composition of neurotransmitter receptor integration at the postsynaptic membrane. The cellular and molecular mechanisms of ionotropic receptor trafficking have been extensively reviewed [113–115]; here we will focus on regulatory mechanisms by which the cytoskeleton controls the neurotransmitter receptor expression profile in excitatory synapses. See Figure 1 for a schematic summarising the mechanisms involved in glutamate receptor trafficking.

5.1. AMPA Receptor Trafficking. AMPARs are the primary ionotropic glutamate receptors responsible for fast excitatory synaptic transmission. At the postsynaptic membrane, regulation of AMPAR levels determines the strength of synaptic transmission. During LTP induction, AMPARs are inserted into the PSD and are removed during LTD. AMPARs comprise a combination of four subunits GluA1–4 (GluR1–4) [120] forming heterotetrameric channels [121]. However, the majority of synaptic AMPARs have GluA1/2 subunit composition [122].

AMPAR trafficking to and from the plasma membrane depends on actin dynamics. Prolonged treatment (24 h) of

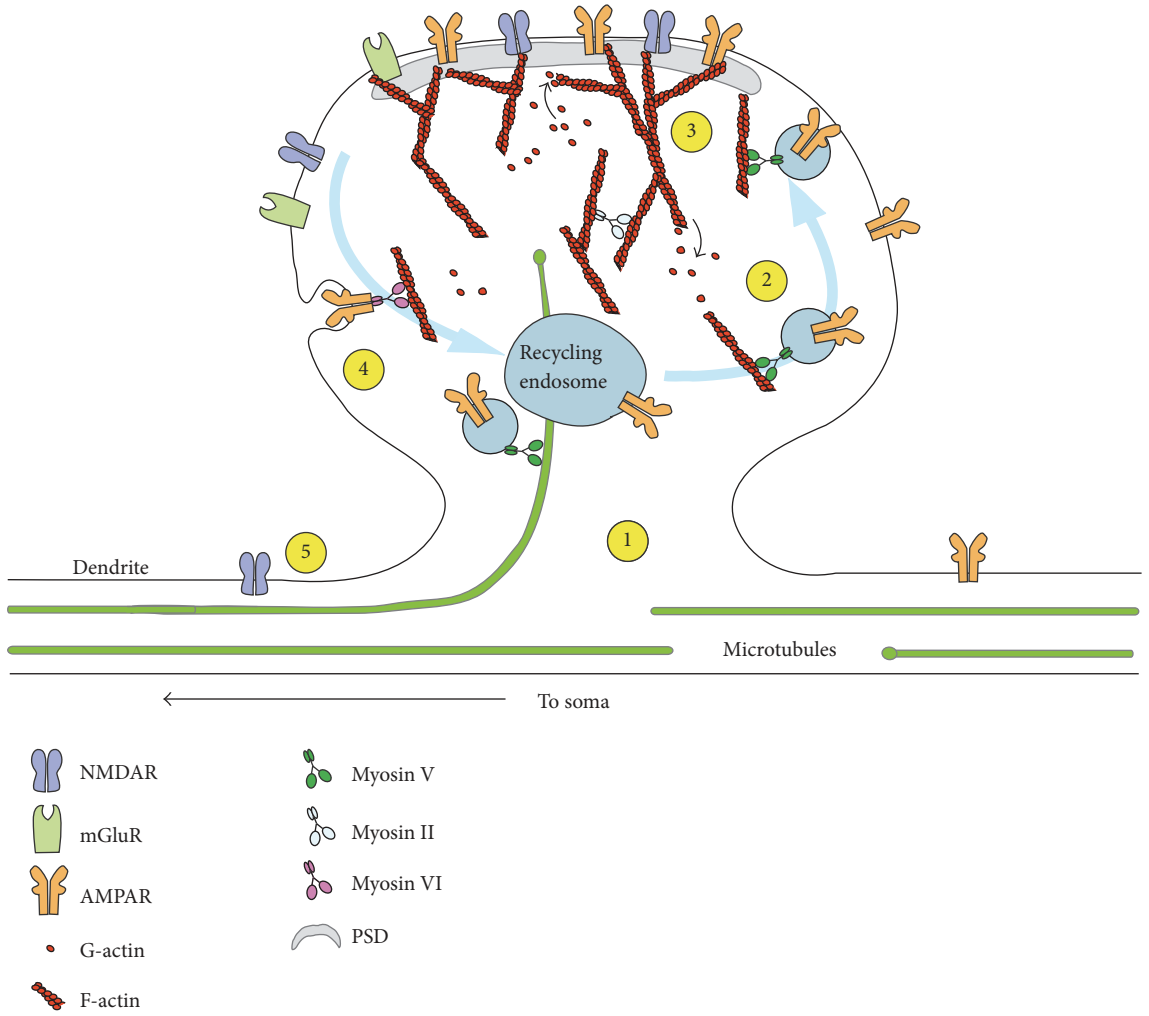

Figure 1: Schematic representation of the cytoskeleton-dependent trafficking of neurotransmitter receptors. Depicted are the key structures of the synapse and associated cytoskeletal molecules. Numbers indicate the following steps: (1) Myosin V traffics vesicles with receptors from the soma to the distal dendritic sites via microtubules (MT) [116]. MT plus ends are indicated by green circles. (2) Once within spines, myosin V transports receptors to plasma membrane via actin filaments [117]. (3) Anchoring of receptors in the PSD relies on myosin II contractile force on actin cytoskeleton in combination with constant actin treadmilling/turnover [48]. Lateral diffusion of receptors to and from the PSD to presynaptic regions can occur. (4) Receptor internalization involves myosin VI activity. Myosin VI transports internalized receptors to endosomal organelles, facilitating recycling of receptors back to the membrane or to degradation pathways [95]. (5) Receptors can also travel between the PSD and peripheral sites [118, 119].

cultured primary hippocampal neurons with latrunculin A, an inhibitor of F-actin nucleation, attenuates the expression of GluA1 AMPAR subunit in dendritic spines [123]. Hippocampal neurons, treated with latrunculin A prior to tetraethylammonium (TEA) LTP induction, prevented insertion of GluR1 during TEA LTP. Furthermore, treatment with 1 μM jasplakinolide prior to TEA also inhibited the insertion of GluR1 in response to TEA LTP induction [124]. Furthermore, treatment with jasplakinolide, an F-actin stabilizer, prevented AMPAR endocytosis during intense NMDAR activation [124]. These results suggest that expression of AMPARs at the postsynaptic membrane requires both polymerization and disassembly of the actin cytoskeleton, and F-actin stabilization is required to anchor AMPARs at the plasma membrane. Overall these studies show that AMPAR trafficking and anchoring require actin cytoskeletal dynamics and remodelling.

AMPAR trafficking processes are facilitated by actin cytoskeleton dynamics. GTPases such as Rho Ras and Rac activate downstream effectors that in turn stimulate or inhibit the activity of actin-associated proteins thereby regulating actin cytoskeletal dynamics [125]. Based on this, it is not surprising that actin-associated proteins and their upstream activators are able to affect trafficking of glutamate receptor subunits.

Vasodilator-Stimulated Phosphoprotein (VASP) regulates and modulates synaptic strength through actin polymerization. VASP has been shown to bind to both actin and profilin, promoting F-actin polymerization and preventing barbed end capping [126–128]. VASP has also been found

to be essential for synapse maintenance. Overexpression of VASP increased dendritic spine volume, F-actin content, and the expression GluR1 [129]. Conversely, knockdown of VASP reduced the density of dendritic spines and synapses and GluR1 subunits within the spine [129].

Arp2/3 gates the trafficking of endosomal vesicles and internalization of AMPARs. Arp2/3 is inhibited by protein interacting with C kinase 1 (PICK1) which is in turn inhibited by the activity of GTPase ADP-ribosylation factor 1 (Arf1). Inhibition of Arp2/3 by PICK1 overexpression facilitates endocytosis of AMPAR subunits during LTD [130]. Similarly, blocking Arf1 results in AMPAR endocytosis [131].

Further studies implied a role of PICK1 in LTD. Knockdown of PICK1 prevented NMDAR LTD induced removal of GluA1 subunits from the plasma membrane. More specifically, a time course analysis of AMPAR endocytosis in response to NMDAR-mediated LTD showed that PICK1 knockdown did not prevent the initial endocytosis of AMPARs but failed to retain the receptors intracellularly. Recycling of AMPARs back to the plasma membrane during knockdown of PICK1 inhibited NMDAR-induced LTD [132].

Myosin motor proteins are critical for AMPAR trafficking. Myosin motors Va and Vb are considered efficient organelle transporters, their long lever arms allowing them to travel along the top of actin filaments in a step-like fashion rather than spiralling around the filament [133]. Interference of myosin Va and Vb function has been shown to impact neuronal cell shape and function, including changes in the composition of the PSD and modulation of LTD and LTP induction [133]. Myosin Va binds directly with the C-terminal of GluA1 subunits [117] and is required for transportation of AMPARs from the dendritic shaft into spines. Furthermore, myosin Va is implicated in the induction of LTP. Imaging of GFP-GluR1 showed that depletion of myosin Va resulted in reduced expression of GluR1 to synapses in response to CAMKII mimicked LTP. Electrophysiological experiments using siRNA knockdown of myosin Va abolished LTP induction as indicated by AMPAR mediated responses [117]. In a separate study by Wagner and colleagues [134], myosin Va was found to be critically involved in the trafficking of smooth endoplasmic reticulum (ER) into the spines of Purkinje neurons. Attenuation of myosin Va motility along actin filaments inhibited the insertion of smooth ER tubules into the spines of Purkinje neurons [134]. Reduction of ER tubule insertion minimised transient Ca^{2+}-release upon mGluR activation, a process required for LTD within the cerebellum [134]. No changes were observed in fast AMPAR mediated Ca^{2+}-transients. These studies suggest that myosin Va is involved in various functional aspects of synaptic plasticity, including the trafficking of smooth ER into spines and the exocytosis of AMPARs.

Myosin Vb localizes to different regions of neurons in an age dependent manner. At 7–14 days *in vitro* (DIV) this particular motor protein was detected in the soma and dendrites while being absent at synapses [116]. At more mature ages, 21–28 DIV, myosin Vb was predominantly detected in the soma but was also observed in dendritic spines that were positive for synaptic markers synaptophysin and PSD95 [116]. Lisé and colleagues suggest that these results imply that myosin Vb is responsible for the initial transportation of cargo from the soma to distant dendritic sites early on in neuronal development and then remains locally at synaptic regions where it is involved in delivery and recycling of cargo to the synapse once the neuron has matured. A more recent study by Wang and colleagues [96] also detected myosin Vb enrichment in dendritic spines using immunocytochemical techniques. In addition to this, Wang et al. also determined that myosin Vb is involved in trafficking of recycling endosomes into spines. Recycling endosomes are a source of AMPARs and are responsible for directing these receptors back to the plasma membrane during LTP induction [135, 136].

The role of myosin Vb in the transportation of glutamate receptor subunits within the postsynaptic compartment was determined using transfection of functionally deficient or dominant negative versions of myosin Vb and the small GTPase Rab11 [116]. Expression of myosin Vb C-terminal tail constructs, fused to GFP, resulted in a reduction of GluR1 subunit clustering at sites, positive for synaptophysin. This suggests that full length myosin Vb is required for delivery of GluR1 subunits to the synapse [116]. Furthermore, Lisé and colleagues found that expression of this construct did not alter the localization of GluR2/3 subunits, implying that myosin Vb may specifically regulate pools of GluR1 homomeric AMPARs. Myosin Vb is thought to associate with GluR1 through RabII coupling [116]. RabII is a recycling endosome protein that binds to myosin Vb via C-terminal amino acids 1797–1846 [137]. Neurons transfected with myosin Vb mutants that lack the C-terminal domain required for RabII binding had reduced GluR1 clustering and surface expression, suggesting that myosin Vb trafficking of GluR1 is mediated by RabII binding [116]. Furthermore, binding of RabII requires a conformational change in the myosin Vb protein that occurs in response to Ca^{2+} [96].

Unlike myosin V, myosin VI has been reported to travel along F-actin towards the pointed/minus end of the filament [138, 139]. From coimmunoprecipitate assays myosin VI has been shown to associate with GluR1 and GluR2 subunits [95]. Furthermore, myosin VI has been shown to form a complex with GluR1 and the scaffolding protein SAP97, suggesting a functional link between the actin cytoskeleton AMPAR subunits and the postsynaptic scaffold [140]. Hippocampal neurons deficient in myosin VI had greatly reduced levels of internalized AMPARs after AMPA stimulation compared to controls suggesting that myosin VI is important for endocytosis of AMPARs. In addition to this Osterweil and colleagues [95] confirmed that myosin VI trafficking of AMPARs occurs via clathrin-mediated endocytosis.

Cofilin in AMPAR Trafficking. Using live imaging recordings, Gu et al. [141] found that inhibition of LIMK1 resulted in enhanced trafficking of GluR1 and inhibition of SSH resulted in diminished GluR1 trafficking to the spine surface during TEA-induced LTP. Due to the relationship between LIMK1 and SSH and cofilin, these results suggest that cofilin activation is required for expression of AMPARs during LTP. As there were no significant changes in spine head to neck ratios before and after 6 h treatment with LIMK1 and SSH inhibiting peptides, Gu and colleagues concluded that cofilin

mediates AMPAR trafficking independent of the actions of cofilin on cytoskeletal spine structure. Consistent with this finding, Yuen and colleagues [142] also found a reduction in AMPAR excitatory postsynaptic current (EPSC) amplitude and frequency in response to siRNA knockdown of SSH.

In an experiment investigating the role of cofilin in an aversive conditioning paradigm, it was observed that cofilin was temporally enhanced in the infralimbic cortex of rats after extinction of an aversive memory [143]. Furthermore, elevation of cofilin levels resulted in an increase in surface expression of GluA1 and GluA2 subunits and facilitated extinction learning. Conversely, inhibition of cofilin during extinction training prevented the insertion of these subunits at the plasma membrane and impaired extinction learning [143].

These studies imply that the F-actin severing properties of cofilin are required for AMPAR recruitment at the plasma membrane during LTP. This finding would fit well with the suggested cofilin mediated cytoskeletal reorganization during LTP posed by Chen and colleagues [58] whereby cofilin severing of F-actin allows for enlargement of dendritic spine volume during LTP. As AMPAR expression at the postsynaptic membrane and spine volume are tightly correlated it is plausible that cofilin activity mediates these processes.

Drebrin in AMPAR Trafficking. Electrophysiological recordings demonstrated that expression of DA-GFP in neurons enhances excitatory transmission compared to GFP controls. Inhibition of drebrin A by DA antisense oligonucleotides further supported a role of DA in synaptic transmission as inhibition of DA resulted in a decrease in excitatory transmission, indicated by decreases in miniature EPSC (mEPSC) amplitude and frequency, compared to controls [71]. Drebrin knockdown was found to impair AMPAR mediated mEPSC amplitude and frequency in hippocampal neurons. In addition, mEPSC amplitude and frequency in response to glutamate-induced LTP were reduced during drebrin knockdown. These results suggest that drebrin is involved in AMPAR trafficking and insertion at the plasma membrane [144].

4.1N in AMPAR Trafficking. Protein 4.1N is a homolog of 4.1R, a protein found to be an integral component of the cytoskeleton in erythrocytes. 4.1N has been found to localize in various regions of the brain including the CA1–CA3 areas of the hippocampus [145]. Furthermore, immunocytochemical analyses showed colocalization of 4.1N with PSD95, suggesting that 4.1N localizes to sites of synaptic connection [145]. Like its erythrocyte homolog, 4.1N is thought to associate with the actin cytoskeleton [145].

Using coimmunoprecipitation and deletion of various amino acids in GluR1 proteins, 4.1N was found to associate with GluR1 at the membrane proximal region of the C-terminal domain at amino acids 812–823 [146]. Truncations of GluR1 at this membrane proximal region resulted in GluR1 becoming incapable of associating with 4.1N and having decreased expression at the plasma membrane [146] suggesting that 4.1N activity is required for expression of GluR1 subunits in the plasma membrane.

5.2. NMDA Receptor Trafficking. N-Methyl-D-aspartate receptors (NMDARs) are glutamate receptors, present in smaller numbers than AMPARs, which serve to modulate excitatory transmission by affecting AMPAR expression [113]. Activation of AMPARs leads to removal of the Mg^{2+} block of NMDARs, allowing for calcium influx. This calcium influx affects a variety of pathways which regulate the expression of AMPARs.

NMDARs have a heterotetrameric structure, usually consisting of two GluN1 and two GluN2 subunits. The subunits are produced and assembled in the endoplasmic reticulum in the cell body and then moved to the spine by various kinesins, moving along microtubules [113]. While transport to the spine involves only microtubules and not actin, short distance transport in the spine head to the PSD seems to be dependent on actin and myosin motor proteins [147]. However, the exact proteins and mechanisms involved are still unclear. Myosin IIb has been shown to be involved in insertion of NMDARs at the membrane, but it is not believed that it is responsible for transporting it to the membrane [148]. At the surface of the synapse, NMDARs are associated with scaffolding proteins of the PSD [149].

Endocytosis of NMDA receptors can be triggered by low-frequency stimulation [150]. Receptor clusters can move laterally in and out of the synaptic site. When NMDARs were irreversibly blocked with a drug, recovery of NMDAR-mediated current was observed, suggesting receptors migrated to the synaptic site from the periphery [118]. Actin dynamics have also been shown to affect NMDAR placement at the synapse [123].

There is evidence that actin dynamics have a regulatory role in NMDAR function. Alpha-actinin-2, an actin binding protein present in the PSD, competes with calmodulin for binding to NMDARs [151]. Alpha-actinin is a protein that binds to both NMDARs [152] and components of the PSD [153] and has a role in spine morphology [154].

Severing of actin filaments or preventing polymerization of actin has been found to induce a rundown of NMDAR current. Inactivation of RhoA which promotes actin polymerization increases rundown of NMDAR current [155]. Similarly, administering cytochalasin, a drug blocking actin polymerization, also induces rundown [156]. Conversely, knockout of gelsolin enhances NDMAR current [157]. Modification of actin can also affect placement of receptors in the postsynapse. Latrunculin A, an inhibitor of actin polymerization, modifies localization of NMDA receptors [123].

Another way actin may be involved in NMDAR trafficking is through its function in microtubule extension. Drebrin, an actin stabilizing protein, interacts with both actin microfilaments and microtubules and promotes entry of microtubules into dendritic spines [158]. NMDARs also have a part in mediating spine morphology. Deletion of the NR1 subunit has been found to reduce spine density and increase head size [159]. The actin severing protein cofilin is required in spines for NMDAR-induced remodelling [160].

5.3. mGluR Receptor Trafficking. As well as the ionotropic glutamate receptors, there are also metabotropic receptors (mGluRs) present at the postsynaptic membrane. Unlike

NMDARs and AMPARs, metabotropic receptors are G-protein coupled receptors. They produce their effects through signalling pathways involving inositol phosphate (IP), diacylglycerol (DAG), activation of protein kinase C (PKC), and release of intracellular Ca^{2+} stores. There are three families of mGluRs: Groups I, II, and III. In neuronal tissue, Groups II and III are located on the presynaptic membrane, while Group I is located on the postsynaptic membrane. Group I includes mGluR1 and mGluR5. They are comprised of GluA1 and GluA5 receptor subunits. Little is known about synthesis and trafficking of mGluRs to the spine, but there is evidence that, like NMDARs, they are associated with the PSD [161].

mGluRs can move laterally on the postsynaptic membrane. It has been found that transport of mGluR5 on the membrane surface involves being bound to microtubules, and the movement of these microtubules was dependent on actin flow. Preventing actin polymerization through application of cytochalasin D disrupted the movement of mGluR5 on the membrane [119]. In cultured hippocampal neurons, mGluRs have been found to be located at perisynaptic regions of excitatory synapses [162]. mGluR function can be modified by signalling molecules. One example is Rab8, a small GTPase involved in vesicular trafficking. It binds to the C-terminal tail of mGluRs and inhibits the production of IP and the release of intracellular Ca^{2+} [163] Rab8 expression resulted in inhibition of mGluR1 endocytosis, maintaining cell surface expression of the receptors [163]. mGluRs are responsible for activity-dependent synaptic plasticity through their role in regulating trafficking of other glutamate receptors. It has been found that blocking both mGluR1 and mGluR5 prevented induction of LTD, suggesting that mGluRs have a role in mediating AMPAR endocytosis [164].

6. Disruption of the Actin Cytoskeleton and Neurotransmitter Receptor Trafficking in Disease

While current research on pathological mechanisms of AD encompasses the study of a diverse range of potential mechanisms, a central theme underlying AD pathology is the loss of synaptic connectivity. Neural connections within the brain underlie the most basic and fundamental requirements for successfully interacting with the world around us. The loss of these neural circuits can catastrophically impair one's ability to function independently, as observed in AD. Although various gene mutations have been implicated in familial forms of AD [165] the causes behind the onset of AD pathology are as yet unknown.

A considerable effort in Alzheimer's disease research has been to identify the brain regions most vulnerable to degeneration. Over the last two decades the literature has reported significant hippocampal deterioration in early AD pathology [1, 166–169]. Hippocampal volume is often used as a diagnostic tool for AD as the level of deterioration positively correlates with the severity of AD symptoms [170, 171]. Other features of the medial temporal lobe, wherein lies the hippocampus, such as cortical thickness, have also been described as reliable indicators of AD pathology [172–174]. These hippocampal measures have also been successful as an indicator of AD vulnerability in presymptomatic patients [175, 176].

The molecular mechanisms of AD pathogenesis are still not well understood. The two major pathological hallmarks of AD are the extracellular accumulation of proteolytic derivations of amyloid precursor protein (APP) called amyloid-β (Aβ) peptides and intracellular aggregation of tau protein fibrils. Accumulation of these abnormal proteins is thought to be responsible for the breakdown of synapses, decreases in spine density, and impairment of synaptic plasticity [177–179]. Although studies have highlighted interplay between these two pathological markers [180–182], evidence suggests that the accumulation of Aβ oligomers accelerates tau aggregation and synaptic loss [183, 184]. The biosynthesis of Aβ arises as a residual product from α-secretase failing to cleave APP [185]. In the absence of α-secretase activity, β- and γ-secretases cleave APP, generating Aβ peptides. Large oligomeric peptides have been shown to be neurotoxic in comparison to small Aβ oligomers and soluble monomers, which have been implicated in neuroprotective processes [186, 187].

6.1. Pathological Role of Soluble and Aggregated Forms of Amyloid β Peptide. Amyloid fibrils are aggregations of long, insoluble fibres of Aβ peptide. Protofibrils (shorter, soluble aggregations that are precursors to fibrils) and fibrils have been observed to have an overexcitatory effect on neurons and interactions with NMDA receptors [188]. Amyloid plaques, large extracellular deposits of Aβ fibrils, are the most obvious form of pathophysiology, associated with Alzheimer's disease. Behavioural deficits of dementia have previously been found to be correlated with the size of the cortical area affected by plaques [189]. In the study by Cummings and Cotman, deposition of Aβ was found to strongly correlate with scores on the Mini-Mental State Exam (MMSE), the Blessed Information Memory Concentration (IMC) test, and Clinical Dementia Rating (CDR) with higher deposition resulting in poorer scores. In brain slice cultures, plaque-covered areas contained only few dendritic spines and spine volume was reduced in the areas around the plaque [190]. However, synaptic deficits can occur in the absence of plaques [191] and the extent of plaque formation does not always correlate with the degree of neurodegeneration or clinical status of AD [192, 193]. More recent studies are still debating as to whether or not plaque formation is responsible for behavioural deficits in AD. In some of these studies, behavioural deficits could be rescued in response to a reduction in amyloid plaques [194, 195]. However, these studies also observed reductions in soluble Aβ, which is believed to be highly toxic when in oligomeric form [187]. Cramer and colleagues [196] used a mouse model of AD to show that increasing levels of apolipoprotein E (apoE) can lead to a reduction of soluble and insoluble Aβ. ApoE is involved in the proteolytic degradation of soluble forms of Aβ. Acute increases in apoE resulted in significant reductions in both soluble Aβ and plaque quantity. AD-associated learning deficits were also reduced in both the Morris water maze and contextual fear conditioning paradigms upon treatment with apoE [196]. However, these behavioural measurements were found to only correlate with reduced levels of soluble

Aβ and not with plaque removal. Plaque formation can be present without cognitive decline [197]. This shifted the focus to an increased interest in understanding the pathological role of soluble forms of Aβ. Soluble Aβ forms include monomers, dimers, and larger oligomers of Aβ protein. Soluble Aβ is localized to the postsynaptic compartment in both animal models of Alzheimer's disease [198] and human patients [199]. Aβ oligomers cause alterations to pre- and postsynaptic morphology, including spine shrinkage and collapse [200]. LTP has been found to be inhibited in brain slices after application of oligomers sourced from cell cultures [201], dimers extracted from human AD brains [178], and synthetic Aβ oligomers [202]. Aβ can also facilitate LTD. Application of oligomers from different sources allowed LTD to be induced in conditions that are normally insufficient to do so [203].

6.2. The Effects of Amyloid β on the Regulation of the Actin Cytoskeleton. There are many conflicting pathways in which Aβ is proposed to alter actin cytoskeletal dynamics. The predominant theories involve modulation of cofilin activity. Conflicting evidence is found throughout the literature that suggests that cofilin is either activated or inhibited in response to Aβ toxicity (see Figure 2). Petratos and colleagues [204] reported an increase in active RhoA in SH-SY5Y cells treated with Aβ. RhoA activates Rho kinase II (ROCKII), which leads to the deactivation of myosin light chain kinase, dephosphorylating and thereby inhibiting the actions of LIMK [205]. Another pathway in which Aβ is proposed to increase cofilin activation is through inhibition of Rac1. RhoA activation requires deactivation of Rac1 [206]. Therefore it is suggested that Aβ induced increases of RhoA antagonistically decrease levels of Rac1. Rac1 inhibition reduces PAK1 signalling, which reduces the phosphorylation and activation of LIMK [207, 208]. This pathway is supported by findings of decreased PAK1 in the brains of AD patients [209]. Inactivation of LIMK in both pathways would result in reduced phosphorylation and as such the activation of cofilin [56]. Increased activation of cofilin may then disrupt receptor trafficking through disassembly of the actin cytoskeleton [208] and/or formation of cofilin rods [210]. Conversely, various studies suggest that Aβ ultimately inhibits cofilin activation through alternate signalling pathways. Mendoza-Naranjo and colleagues [211] found an increase in levels of GTPase Cdc42 in hippocampal neurons treated with fibrillar Aβ. Cdc42-PAK1-LIMK signalling cascades result in decreased cofilin activation [56, 212] which would have implications for actin cytoskeleton dynamics.

The formation of cofilin rods, abnormal aggregates of bound actin and cofilin, has been shown to disrupt vesicle transport and cause accumulation of Aβ and APP [210, 213, 214]. Blocking intracellular trafficking by cofilin aggregation induces synaptic loss in hippocampal neurons [215]. Hippocampal neurons transfected with wild-type GFP-cofilin resulted in the formation of cofilin-actin rods. Transfections using cofilin mutants, phosphomimetic GFP-cofilin and constitutively active GFP-cofilin, resulted in no or reduced cofilin rod formation, respectively. This suggests that both active and inactive cofilin are required for the formation of cofilin rods, a requirement potentially fulfilled by the contradicting pathways mentioned above. As these mutations involved the phosphorylation Ser3 site on cofilin it is believed that the formation of cofilin rods is critically dependent on this site [215]. Immunostaining detected rod localization in distal dendrites and occasionally in axons. An additional observation was made in that decreased MAP2 fluorescence was apparent in regions containing rod formation compared to neighbouring regions absent of rods. The authors suggest that this could imply impairment of microtubule integrity [215]. Formation of cofilin rods from endogenous levels of cofilin was observed in response to glutamate treatment or neurotoxic ATP depletion [215].

Immunostaining of RFP-cofilin and GFP-Rab5, a small GTPase that localizes to early endosomes [216], showed that, in areas where cofilin rods appeared, early endosomes positive for Rab5 were either largely absent or positioned at the distal or proximal ends of rods suggesting that they were immobilised at these regions. This finding was similar for imaging of GFP-mitochondria, where localization was found to be either largely absent in regions containing rods or trapped between rods. These results imply that rod formation disrupts intracellular organelle distribution [215]. This was further confirmed using live imaging techniques. Prior to rod formation, mitochondria appeared to be able to freely move within the cell; however, after rod formation mitochondria trajectory was significantly restricted and slower than that before rod formation [215].

Rod formation was also found to affect synaptic transmission and induce synaptic loss. Markers of pre- and postsynaptic regions were significantly reduced in areas containing rods. In addition to this, dendritic spine density was also decreased in rod rich areas. The cofilin rod reduction in spine density was in part supported by electrophysiological recordings of hippocampal neurons expressing varying quantities of cofilin rods. A significant reduction in mEPSC frequency but not amplitude was observed in neurons with exceptionally high levels of rods [215]. Neurons with mild levels of rods had mEPSC frequencies and amplitudes that were comparable to controls. These results suggest that aggregation of cofilin rod formation induces synaptic loss, which eventually leads to the loss of neuronal function [215].

Decreased levels of gelsolin were found in AD patients' plasma. The level of decrease was correlated to progression of disease, as measured with a Mini-Mental Status Examination [219]. Gelsolin has also been found to be involved with removal of Aβ. Gelsolin forms a complex with Aβ, making it less neurotoxic [220].

6.3. The Effects of Amyloid β on the Trafficking of Neurotransmitter Receptors. It is plausible then that neurotoxic stimulation via soluble Aβ activity drives the formation of cofilin rod formation in AD pathology and through this pathway disrupts synaptic properties such as AMPAR trafficking via early endosomes. AMPARs can be internalized to early endosomal organelles where they are then transferred to recycling endosomes for reinsertion at the plasma membrane, or to late endosomes for degradation depending on the type of synaptic stimulation [221]. AMPAR stimulation induces endocytosis

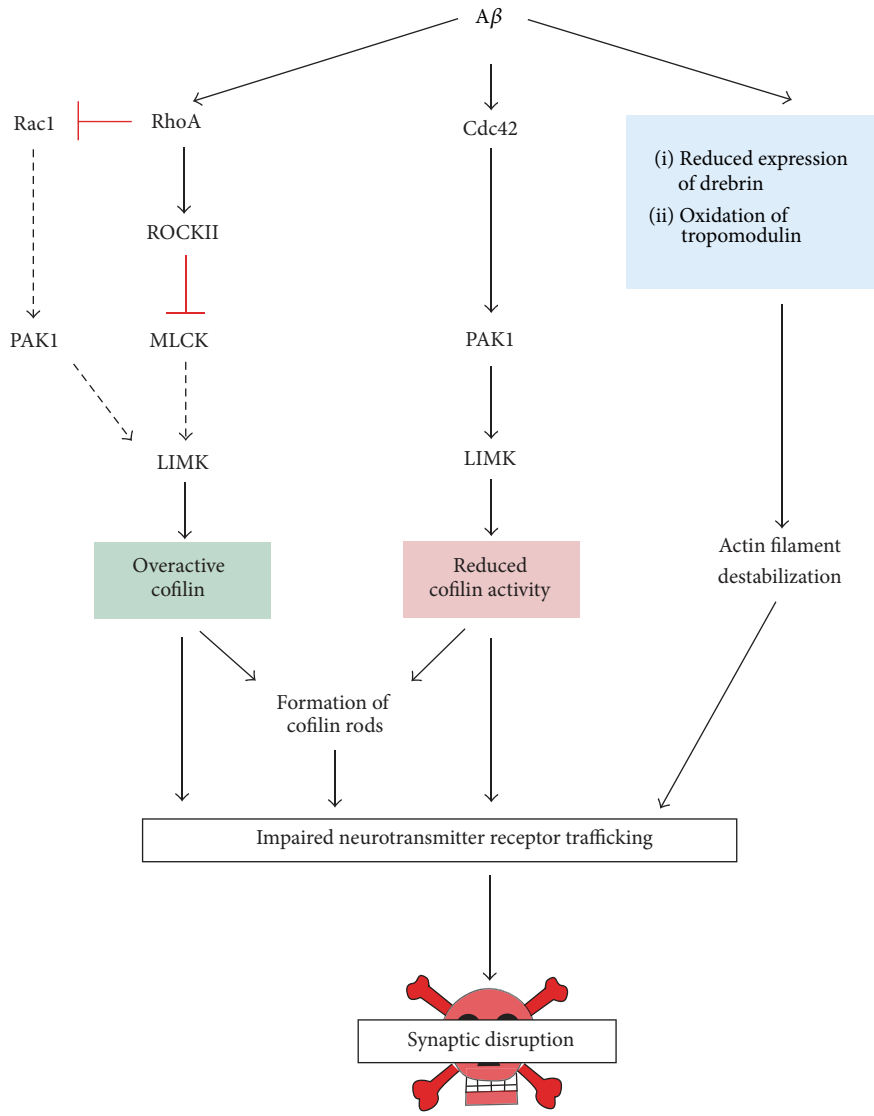

FIGURE 2: Amyloid-β disrupts the actin cytoskeleton and receptor trafficking through multiple pathways. There are many conflicting pathways through which Aβ is proposed to alter the actin cytoskeleton. These may involve both up- and downregulation of cofilin activity. Activation of RhoA by Aβ [204] antagonistically inhibits Rac1 [206], both leading to increased cofilin activity. In contrast, Aβ can cause decrease in cofilin activity via activation of Cdc42 [211]. Both active and inactive cofilin are thought to be required for the formation of cofilin rods, which lead to impairment of intracellular transport [215]. Alternatively or in addition to this, altered expression and/or processing of actin filament stabilizing proteins [217, 218] may impact the trafficking of neurotransmitter receptors.

of AMPARs to early endosomes followed by transferral to late endosomal organelles and subsequent degradation [135, 221]. NMDAR excitation on the other hand results in AMPAR internalization to early endosomes and then to recycling endosomes ultimately leading to the reinsertion at the plasma membrane [135, 221]. As Aβ is thought to weakly activate NMDARs [222], it is postulated that AMPARs are endocytosed to early endosomes but are possibly unable to be transferred to recycling endosomes due to cofilin-actin rod obstructions. This would result in weakening and eventual loss of synapses as is observed in both neurons with extensive cofilin-actin rod formation and also neurons afflicted by Aβ. Recent research confirms the importance of recycling endosome location on synaptic potential. Positioning of endosomes has been found to be important for AMPAR trafficking and synapse architecture, with the removal of recycling endosomes from the spine resulting in decreased surface AMPAR levels [223].

A potential way by which synapses are destabilized is the loss or functional disruption of actin stabilizing proteins at the synapses. Drebrin has been found to be reduced in the brains of AD and Down syndrome patients [217]. Drebrin reduction is also associated with impaired synaptic plasticity [224] and altered movement of NMDAR clusters to synapses [225]. In brains from AD cases, Tpms were found in neurofibrillary tangles (NFT), intracellular protein aggregates of abnormally phosphorylated tau protein [226, 227]. However, studies are limited, because antibodies used were not specific

for Tm isoforms: identities of specific isoforms in NFTs are unknown. Interestingly, Tpm3.1 is a major target of oxidative damage in AD, suggesting that disruption of Tpm3.1 may contribute to pathological changes in the disease [218]. Pathways by which Aβ affects the nucleation of actin filaments may be closely connected to those disrupting microtubule dynamics. Knockdown of the formin mDia1 in NIH3T3 cells reduces Aβ induced pathological stabilization of MTs [228].

7. Conclusions

In this paper we discussed the current understanding of the role that the actin cytoskeleton plays in the regulation of the postsynaptic compartment, how it drives structural changes, how it supports neurotransmitter receptor trafficking and synaptic function, and how these processes are disrupted in neurodegenerative diseases. Currently, there are no efficient treatments for stopping or even reversing the pathological mechanisms in neurodegenerative diseases such as AD. A more detailed understanding of the regulatory mechanisms of the postsynaptic cytoskeleton may allow us to develop new strategies for protecting synaptic connections and to increase their resistance to pathological effects in the disease. In particular, it remains to be fully understood how the trafficking of glutamate receptors is disrupted by the presence of Aβ. As many actin-associated proteins exist in the cell in antagonistic relationships with other actin-associated proteins, it would be interesting to know the extent to which alteration of one regulatory protein affects others. Furthermore, studies involving *in vivo* techniques would provide a more accurate picture of how actin cytoskeleton dynamics influence the trafficking of AMPARs and ultimately synaptic plasticity. In addition to these studies, new advances in superresolution imaging could be implemented to examine not only the mobility of AMPARs in response to alterations in various actin-associated proteins but also changes in the distribution and localization of these proteins. Eventually, this leads us to the question of whether we can develop strategies that target specifically the synaptic actin cytoskeleton *in vivo*. Most actin cytoskeleton targeting drugs are rather unspecific for the actin filament populations that are manipulated. More recent approaches have shown that specific subpopulations of actin filaments can now be directly manipulated [229]. To exploit the use of these drugs for the potential therapeutic use in treating neurological disease, a detailed understanding of how different actin filament populations at synapses are formed, maintained, and turned over will be essential considerations for future studies.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Holly Stefen and Chanchanok Chaichim contributed equally to this work.

References

[1] S. W. Scheff, D. A. Price, F. A. Schmitt, and E. J. Mufson, "Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment," *Neurobiology of Aging*, vol. 27, no. 10, pp. 1372–1384, 2006.

[2] S. T. DeKosky and S. W. Scheff, "Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity," *Annals of Neurology*, vol. 27, no. 5, pp. 457–464, 1990.

[3] R. D. Terry, E. Masliah, D. P. Salmon et al., "Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment," *Annals of Neurology*, vol. 30, no. 4, pp. 572–580, 1991.

[4] T. Arendt, "Synaptic degeneration in Alzheimer's disease," *Acta Neuropathologica*, vol. 118, no. 1, pp. 167–179, 2009.

[5] B. C. Dickerson and R. A. Sperling, "Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging," *Behavioural Neurology*, vol. 21, no. 1-2, pp. 63–75, 2009.

[6] K. Herholz, S. Westwood, C. Haense, and G. Dunn, "Evaluation of a calibrated 18F-FDG PET score as a biomarker for progression in alzheimer disease and mild cognitive impairment," *Journal of Nuclear Medicine*, vol. 52, no. 8, pp. 1218–1226, 2011.

[7] K. M. Harris and S. B. Kater, "Dendritic spines: cellular specializations imparting both stability and flexibility to synaptic function," *Annual Review of Neuroscience*, vol. 17, pp. 341–371, 1994.

[8] J. Noguchi, M. Matsuzaki, G. C. R. Ellis-Davies, and H. Kasai, "Spine-neck geometry determines NMDA receptor-dependent Ca^{2+} signaling in dendrites," *Neuron*, vol. 46, no. 4, pp. 609–622, 2005.

[9] J. M. Power and P. Sah, "Dendritic spine heterogeneity and calcium dynamics in basolateral amygdala principal neurons," *Journal of Neurophysiology*, vol. 112, no. 7, pp. 1616–1627, 2014.

[10] M. Sheng and E. Kim, "The postsynaptic organization of synapses," *Cold Spring Harbor Perspectives in Biology*, vol. 3, no. 12, 2011.

[11] S. Okabe, "Molecular dynamics of the excitatory synapse," *Advances in Experimental Medicine and Biology*, vol. 970, pp. 131–152, 2012.

[12] K. E. Sorra and K. M. Harris, "Overview on the structure, composition, function, development, and plasticity of hippocampal dendritic spines," *Hippocampus*, vol. 10, no. 5, pp. 501–511, 2000.

[13] A. Peters and I. R. Kaiserman-Abramof, "The small pyramidal neuron of the rat cerebral cortex. The perikaryon, dendrites and spines," *American Journal of Anatomy*, vol. 127, no. 4, pp. 321–355, 1970.

[14] E. A. Nimchinsky, B. L. Sabatini, and K. Svoboda, "Structure and function of dendritic spines," *Annual Review of Physiology*, vol. 64, pp. 313–353, 2002.

[15] N. Honkura, M. Matsuzaki, J. Noguchi, G. C. R. Ellis-Davies, and H. Kasai, "The subspine organization of actin fibers regulates the structure and plasticity of dendritic spines," *Neuron*, vol. 57, no. 5, pp. 719–729, 2008.

[16] J. Noguchi, A. Nagaoka, S. Watanabe et al., "In vivo two-photon uncaging of glutamate revealing the structure-function relationships of dendritic spines in the neocortex of adult mice," *The Journal of Physiology*, vol. 589, no. 10, pp. 2447–2457, 2011.

[17] M. Bosch and Y. Hayashi, "Structural plasticity of dendritic spines," *Current Opinion in Neurobiology*, vol. 22, no. 3, pp. 383–388, 2012.

[18] D. Meyer, T. Bonhoeffer, and V. Scheuss, "Balance and stability of synaptic structures during synaptic plasticity," *Neuron*, vol. 82, no. 2, pp. 430–443, 2014.

[19] K. M. Harris and J. K. Stevens, "Dendritic spines of CA 1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics," *The Journal of Neuroscience*, vol. 9, no. 8, pp. 2982–2997, 1989.

[20] M. Matsuzaki, G. C. R. Ellis-Davies, T. Nemoto, Y. Miyashita, M. Iino, and H. Kasai, "Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons," *Nature Neuroscience*, vol. 4, no. 11, pp. 1086–1092, 2001.

[21] J. T. Trachtenberg, B. E. Chen, G. W. Knott et al., "Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex," *Nature*, vol. 420, no. 6917, pp. 788–794, 2002.

[22] M. Matsuzaki, N. Honkura, G. C. R. Ellis-Davies, and H. Kasai, "Structural basis of long-term potentiation in single dendritic spines," *Nature*, vol. 429, no. 6993, pp. 761–766, 2004.

[23] A. Holtmaat, L. Wilbrecht, G. W. Knott, E. Welker, and K. Svoboda, "Experience-dependent and cell-type-specific spine growth in the neocortex," *Nature*, vol. 441, no. 7096, pp. 979–983, 2006.

[24] J. Spacek and K. M. Harris, "Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat," *Journal of Neuroscience*, vol. 17, no. 1, pp. 190–203, 1997.

[25] A. J. G. D. Holtmaat, J. T. Trachtenberg, L. Wilbrecht et al., "Transient and persistent dendritic spines in the neocortex in vivo," *Neuron*, vol. 45, no. 2, pp. 279–291, 2005.

[26] Y. Yoshihara, M. De Roo, and D. Muller, "Dendritic spine formation and stabilization," *Current Opinion in Neurobiology*, vol. 19, no. 2, pp. 146–153, 2009.

[27] E. Fifková and R. I. Delay, "Cytoplasmic actin in neuronal processes as a possible mediator of synaptic plasticity," *The Journal of Cell Biology*, vol. 95, no. 1, pp. 345–350, 1982.

[28] F. Korobova and T. M. Svitkina, "Molecular architecture of synaptic actin cytoskeleton in hippocampal neurons reveals a mechanism of dendritic spine morphogenesis," *Molecular Biology of the Cell*, vol. 21, no. 1, pp. 165–176, 2010.

[29] P. Hotulainen and C. C. Hoogenraad, "Actin in dendritic spines: connecting dynamics to function," *Journal of Cell Biology*, vol. 189, no. 4, pp. 619–629, 2010.

[30] E. N. Star, D. J. Kwiatkowski, and V. N. Murthy, "Rapid turnover of actin in dendritic spines and its regulation by activity," *Nature Neuroscience*, vol. 5, no. 3, pp. 239–246, 2002.

[31] K.-I. Okamoto, T. Nagai, A. Miyawaki, and Y. Hayashi, "Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity," *Nature Neuroscience*, vol. 7, no. 10, pp. 1104–1112, 2004.

[32] N. A. Frost, H. Shroff, H. Kong, E. Betzig, and T. A. Blanpied, "Single-molecule discrimination of discrete perisynaptic and distributed sites of actin filament assembly within dendritic spines," *Neuron*, vol. 67, no. 1, pp. 86–99, 2010.

[33] U. V. Nägerl, K. I. Willig, B. Hein, S. W. Hell, and T. Bonhoeffer, "Live-cell imaging of dendritic spines by STED microscopy," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 48, pp. 18982–18987, 2008.

[34] H. D. MacGillavry and C. C. Hoogenraad, "The internal architecture of dendritic spines revealed by super-resolution imaging: what did we learn so far?" *Experimental Cell Research*, vol. 335, no. 2, pp. 180–186, 2015.

[35] H. E. Lu, H. D. MacGillavry, N. A. Frost, and T. A. Blanpied, "Multiple spatial and kinetic subpopulations of CaMKII in spines and dendrites as resolved by single-molecule tracking PALM," *Journal of Neuroscience*, vol. 34, no. 22, pp. 7600–7610, 2014.

[36] K. Okamoto, M. Bosch, and Y. Hayashi, "The roles of CaMKII and F-actin in the structural plasticity of dendritic spines: a potential molecular identity of a synaptic tag?" *Physiology*, vol. 24, no. 6, pp. 357–366, 2009.

[37] J. Tønnesen, G. Katona, B. Rózsa, and U. V. Nägerl, "Spine neck plasticity regulates compartmentalization of synapses," *Nature Neuroscience*, vol. 17, no. 5, pp. 678–685, 2014.

[38] E. S. Harris and H. N. Higgs, "Actin cytoskeleton: formins lead the way," *Current Biology*, vol. 14, no. 13, pp. R520–R522, 2004.

[39] B. L. Goode and M. J. Eck, "Mechanism and function of formins in the control of actin assembly," *Annual Review of Biochemistry*, vol. 76, pp. 593–627, 2007.

[40] N. Watanabe, T. Kato, A. Fujita, T. Ishizaki, and S. Narumiya, "Cooperation between mDia1 and ROCK in Rho-induced actin reorganization," *Nature Cell Biology*, vol. 1, no. 3, pp. 136–143, 1999.

[41] P. Aspenström, N. Richnau, and A.-S. Johansson, "The diaphanous-related formin DAAM1 collaborates with the Rho GTPases RhoA and Cdc42, CIP4 and Src in regulating cell morphogenesis and actin dynamics," *Experimental Cell Research*, vol. 312, no. 12, pp. 2180–2194, 2006.

[42] T. Matusek, R. Gombos, A. Szécsényi et al., "Formin proteins of the DAAM subfamily play a role during axon growth," *The Journal of Neuroscience*, vol. 28, no. 49, pp. 13310–13319, 2008.

[43] P. Hotulainen, O. Llano, S. Smirnov et al., "Defning mechanisms of actin polymerization and depolymerization during Dendritic spine morphogenesis," *Journal of Cell Biology*, vol. 185, no. 2, pp. 323–339, 2009.

[44] A. Chazeau, A. Mehidi, D. Nair et al., "Nanoscale segregation of actin nucleation and elongation factors determines dendritic spine protrusion," *EMBO Journal*, vol. 33, no. 23, pp. 2745–2764, 2014.

[45] I. Rouiller, X.-P. Xu, K. J. Amann et al., "The structural basis of actin filament branching by the Arp2/3 complex," *The Journal of Cell Biology*, vol. 180, no. 5, pp. 887–895, 2008.

[46] F. Korobova and T. Svitkina, "Arp2/3 complex is important for filopodia formation, growth cone motility, and neuritogenesis in neuronal cells," *Molecular Biology of the Cell*, vol. 19, no. 4, pp. 1561–1574, 2008.

[47] B. Rácz and R. J. Weinberg, "Organization of the Arp2/3 complex in hippocampal spines," *Journal of Neuroscience*, vol. 28, no. 22, pp. 5654–5659, 2008.

[48] Q. Yang, X.-F. Zhang, T. D. Pollard, and P. Forscher, "Arp2/3 complex-dependent actin networks constrain myosin II function in driving retrograde actin flow," *Journal of Cell Biology*, vol. 197, no. 7, pp. 939–956, 2012.

[49] J. D. Rotty, C. Wu, and J. E. Bear, "New insights into the regulation and cellular functions of the ARP2/3 complex," *Nature Reviews Molecular Cell Biology*, vol. 14, no. 1, pp. 7–12, 2013.

[50] S. N. Duleh and M. D. Welch, "WASH and the Arp2/3 complex regulate endosome shape and trafficking," *Cytoskeleton*, vol. 67, no. 3, pp. 193–206, 2010.

[51] C. Suarez, R. T. Carroll, T. A. Burke et al., "Profilin regulates F-Actin network homeostasis by favoring formin over Arp2/3 complex," *Developmental Cell*, vol. 32, no. 1, pp. 43–53, 2015.

[52] E. D. Korn, M.-F. Carlier, and D. Pantaloni, "Actin polymerization and ATP hydrolysis," *Science*, vol. 238, no. 4827, pp. 638–644, 1987.

[53] A. Muhlrad, D. Pavlov, Y. M. Peyser, and E. Reisler, "Inorganic phosphate regulates the binding of cofilin to actin filaments," *FEBS Journal*, vol. 273, no. 7, pp. 1488–1496, 2006.

[54] B. W. Bernstein and J. R. Bamburg, "ADF/Cofilin: a functional node in cell biology," *Trends in Cell Biology*, vol. 20, no. 4, pp. 187–195, 2010.

[55] S. Arber, F. A. Barbayannis, H. Hanser et al., "Regulation of actin dynamics through phosphorylation of cofilin by LIM- kinase," *Nature*, vol. 393, no. 6687, pp. 805–809, 1998.

[56] N. Yang, O. Higuchi, K. Ohashi et al., "Cofflin phosphorylation by LIM-kinase 1 and its role in Rac-mediated actin reorganization," *Nature*, vol. 393, no. 6687, pp. 809–812, 1998.

[57] V. E. Galkin, A. Orlova, D. S. Kudryashov et al., "Remodeling of actin filaments by ADF/cofilin proteins," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 51, pp. 20568–20572, 2011.

[58] J.-H. Chen, Y. Kellner, M. Zagrebelsky, M. Grunwald, M. Korte, and P. J. Walla, "Two-photon correlation spectroscopy in single dendritic spines reveals fast actin filament reorganization during activity-dependent growth," *PLoS ONE*, vol. 10, no. 5, Article ID e0128241, 2015.

[59] B. K. Garvalov, K. C. Flynn, D. Neukirchen et al., "Cdc42 regulates cofilin during the establishment of neuronal polarity," *Journal of Neuroscience*, vol. 27, no. 48, pp. 13117–13129, 2007.

[60] Ashish, M. S. Paine, P. B. Perryman, L. Yang, H. L. Yin, and J. K. Krueger, "Global structure changes associated with Ca^{2+} activation of full-length human plasma gelsolin," *Journal of Biological Chemistry*, vol. 282, no. 35, pp. 25884–25892, 2007.

[61] H. Choe, L. D. Burtnick, M. Mejillano, H. L. Yin, R. C. Robinson, and S. Choe, "The calcium activation of gelsolin: insights from the 3Å structure of the G4-G6/actin complex," *Journal of Molecular Biology*, vol. 324, no. 4, pp. 691–702, 2002.

[62] L. D. Burtnick, D. Urosev, E. Irobi, K. Narayan, and R. C. Robinson, "Structure of the N–terminal half of gelsolin bound to actin: roles in severing, apoptosis and FAF," *The EMBO Journal*, vol. 23, no. 14, pp. 2713–2722, 2004.

[63] P. A. Janmey, C. Chaponnier, S. E. Lind, K. S. Zaner, T. P. Stossel, and H. L. Yin, "Interactions of gelsolin and gelsolin-actin complexes with actin. Effects of calcium on actin nucleation, filament severing, and end blocking," *Biochemistry*, vol. 24, no. 14, pp. 3714–3723, 1985.

[64] H. J. Kinosian, J. Newman, B. Lincoln, L. A. Selden, L. C. Gershman, and J. E. Estes, "Ca^{2+} regulation of gelsolin activity: binding and severing of F-actin," *Biophysical Journal*, vol. 75, no. 6, pp. 3101–3109, 1998.

[65] P. Silacci, L. Mazzolai, C. Gauci, N. Stergiopulos, H. L. Yin, and D. Hayoz, "Gelsolin superfamily proteins: key regulators of cellular functions," *Cellular and Molecular Life Sciences*, vol. 61, no. 19-20, pp. 2614–2623, 2004.

[66] P. A. Janmey and T. P. Stossel, "Modulation of gelsolin function by phosphatidylinositol 4,5-bisphosphate," *Nature*, vol. 325, no. 6102, pp. 362–364, 1987.

[67] J. H. Hartwig, G. M. Bokoch, C. L. Carpenter et al., "Thrombin receptor ligation and activated rac uncap actin filament barbed ends through phosphoinositide synthesis in permeabilized human platelets," *Cell*, vol. 82, no. 4, pp. 643–653, 1995.

[68] S. Nag, M. Larsson, R. C. Robinson, and L. D. Burtnick, "Gelsolin: the tail of a molecular gymnast," *Cytoskeleton*, vol. 70, no. 7, pp. 360–384, 2013.

[69] E. J. Furnish, W. Zhou, C. C. Cunningham, J. A. Kas, and C. E. Schmidt, "Gelsolin overexpression enhances neurite outgrowth in PC12 cells," *FEBS Letters*, vol. 508, no. 2, pp. 282–286, 2001.

[70] H.-T. Hu and Y.-P. Hsueh, "Calcium influx and postsynaptic proteins coordinate the dendritic filopodium-spine transition," *Developmental Neurobiology*, vol. 74, no. 10, pp. 1011–1029, 2014.

[71] A. Ivanov, M. Esclapez, C. Pellegrino, T. Shirao, and L. Ferhat, "Drebrin A regulates dendritic spine plasticity and synaptic function in mature cultured hippocampal neurons," *Journal of Cell Science*, vol. 122, no. 4, pp. 524–534, 2009.

[72] R. Ishikawa, K. Katoh, A. Takahashi et al., "Drebrin attenuates the interaction between actin and myosin-V," *Biochemical and Biophysical Research Communications*, vol. 359, no. 2, pp. 398–401, 2007.

[73] M. A. Mikati, E. E. Grintsevich, and E. Reisler, "Drebrin-induced stabilization of actin filaments," *Journal of Biological Chemistry*, vol. 288, no. 27, pp. 19926–19938, 2013.

[74] S. Sharma, E. E. Grintsevich, M. L. Phillips, E. Reisler, and J. K. Gimzewski, "Atomic force microscopy reveals drebrin induced remodeling of F-actin with subnanometer resolution," *Nano Letters*, vol. 11, no. 2, pp. 825–827, 2011.

[75] E. E. Grintsevich and E. Reisler, "Drebrin inhibits cofilin-induced severing of F-actin," *Cytoskeleton*, vol. 71, no. 8, pp. 472–483, 2014.

[76] P. W. Gunning, G. Schevzov, A. J. Kee, and E. C. Hardeman, "Tropomyosin isoforms: divining rods for actin cytoskeleton function," *Trends in Cell Biology*, vol. 15, no. 6, pp. 333–341, 2005.

[77] X. Li, K. C. Holmes, W. Lehman, H. Jung, and S. Fischer, "The shape and flexibility of tropomyosin coiled coils: implications for actin filament assembly and regulation," *Journal of Molecular Biology*, vol. 395, no. 2, pp. 327–339, 2010.

[78] X. Li, L. S. Tobacman, J. Y. Mun, R. Craig, S. Fischer, and W. Lehman, "Tropomyosin position on F-actin revealed by EM reconstruction and computational chemistry," *Biophysical Journal*, vol. 100, no. 4, pp. 1005–1013, 2011.

[79] K. Guven, P. Gunning, and T. Fath, "TPM3 and TPM4 gene products segregate to the postsynaptic region of central nervous system synapses," *Bioarchitecture*, vol. 1, no. 6, pp. 284–289, 2011.

[80] G. Schevzov, S. P. Whittaker, T. Fath, J. J. Lin, and P. W. Gunning, "Tropomyosin isoforms and reagents," *Bioarchitecture*, vol. 1, pp. 135–164, 2011.

[81] W. Lehman, V. Hatch, V. Korman et al., "Tropomyosin and actin isoforms modulate the localization of tropomyosin strands on actin filaments," *Journal of Molecular Biology*, vol. 302, no. 3, pp. 593–606, 2000.

[82] N. S. Bryce, G. Schevzov, V. Ferguson et al., "Specification of actin filament function and molecular composition by tropomyosin isoforms," *Molecular Biology of the Cell*, vol. 14, no. 3, pp. 1002–1016, 2003.

[83] G. Schevzov, N. S. Bryce, R. Almonte-Baldonado et al., "Specific features of neuronal size and shape are regulated by tropomyosin isoforms," *Molecular Biology of the Cell*, vol. 16, no. 7, pp. 3425–3437, 2005.

[84] G. Schevzov, T. Fath, B. Vrhovski et al., "Divergent regulation of the sarcomere and the cytoskeleton," *The Journal of Biological Chemistry*, vol. 283, no. 1, pp. 275–283, 2008.

[85] T. Fath, Y.-K. Agnes Chan, B. Vrhovski et al., "New aspects of tropomyosin-regulated neuritogenesis revealed by the deletion of Tm5NM1 and 2," *European Journal of Cell Biology*, vol. 89, no. 7, pp. 489–498, 2010.

[86] Y. Fan, X. Tang, E. Vitriol, G. Chen, and J. Q. Zheng, "Actin capping protein is required for dendritic spine development and synapse formation," *Journal of Neuroscience*, vol. 31, no. 28, pp. 10228–10233, 2011.

[87] M. Hertzog, F. Milanesi, L. Hazelwood et al., "Molecular basis for the dual function of Eps8 on actin dynamics: bundling and capping," *PLoS Biology*, vol. 8, no. 6, Article ID e1000387, 2010.

[88] E. Stamatakou, A. Marzo, A. Gibb, and P. C. Salinas, "Activity-dependent spine morphogenesis: a role for the actin-capping protein Eps8," *The Journal of Neuroscience*, vol. 33, no. 6, pp. 2661–2670, 2013.

[89] D. Gremm and A. Wegner, "Gelsolin as a calcium-regulated actin filament-capping protein," *European Journal of Biochemistry*, vol. 267, no. 14, pp. 4339–4345, 2000.

[90] M. A. Hartman and J. A. Spudich, "The myosin superfamily at a glance," *Journal of Cell Science*, vol. 125, no. 7, pp. 1627–1632, 2012.

[91] M. L. Walker, S. A. Burgess, J. R. Sellers et al., "Two-headed binding of a processive myosin to F-actin," *Nature*, vol. 405, no. 6788, pp. 804–807, 2000.

[92] J. N. Forkey, M. E. Quinlan, M. A. Shaw, J. E. T. Corrie, and Y. E. Goldman, "Three-dimensional structural dynamics of myosin V by single-molecule fluorescence polarization," *Nature*, vol. 422, no. 6930, pp. 399–404, 2003.

[93] G. E. Snyder, T. Sakamoto, J. A. Hammer III, J. R. Sellers, and P. R. Selvin, "Nanometer localization of single fluorescent proteins: evidence that myosin V walks hand-over-hand via telemark configuration," *Biophysical Journal*, vol. 87, no. 3, pp. 1776–1783, 2004.

[94] D. M. Warshaw, G. G. Kennedy, S. S. Work, E. B. Krementsova, S. Beck, and K. M. Trybus, "Differential labeling of myosin V heads with quantum dots allows direct visualization of hand-over-hand processivity," *Biophysical Journal*, vol. 88, no. 5, pp. L30–L32, 2005.

[95] E. Osterweil, D. G. Wells, and M. S. Mooseker, "A role for myosin VI in postsynaptic structure and glutamate receptor endocytosis," *Journal of Cell Biology*, vol. 168, no. 2, pp. 329–338, 2005.

[96] Z. Wang, J. G. Edwards, N. Riley et al., "Myosin Vb mobilizes recycling endosomes and AMPA receptors for postsynaptic plasticity," *Cell*, vol. 135, no. 3, pp. 535–548, 2008.

[97] N. L. Rochefort and A. Konnerth, "Dendritic spines: from structure to in vivo function," *EMBO Reports*, vol. 13, no. 8, pp. 699–708, 2012.

[98] R. C. Malenka and M. F. Bear, "LTP and LTD: an embarrassment of riches," *Neuron*, vol. 44, no. 1, pp. 5–21, 2004.

[99] Y. Yang, X.-B. Wang, M. Frerking, and Q. Zhou, "Delivery of AMPA receptors to perisynaptic sites precedes the full expression of long-term potentiation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 32, pp. 11388–11393, 2008.

[100] Q. Zhou, K. J. Homma, and M.-M. Poo, "Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses," *Neuron*, vol. 44, no. 5, pp. 749–757, 2004.

[101] Y. Fukazawa, Y. Saitoh, F. Ozawa, Y. Ohta, K. Mizuno, and K. Inokuchi, "Hippocampal LTP is accompanied by enhanced F-actin content within the dendritic spine that is essential for late LTP maintenance in vivo," *Neuron*, vol. 38, no. 3, pp. 447–460, 2003.

[102] T. Krucker, G. R. Siggins, and S. Halpain, "Dynamic actin filaments are required for stable long-term potentiation (LTP) in area CA1 of the hippocampus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 12, pp. 6856–6861, 2000.

[103] H. Udo, I. Jin, J.-H. Kim et al., "Serotonin-induced regulation of the actin network for learning-related synaptic growth requires Cdc42, N-WASP, and PAK in Aplysia sensory neurons," *Neuron*, vol. 45, no. 6, pp. 887–901, 2005.

[104] F. Huang, J. K. Chotiner, and O. Steward, "Actin polymerization and ERK phosphorylation are required for Arc/Arg3.1 mRNA targeting to activated synaptic sites on dendrites," *Journal of Neuroscience*, vol. 27, no. 34, pp. 9054–9067, 2007.

[105] B. Ramachandran and J. U. Frey, "Interfering with the actin network and its effect on long-term potentiation and synaptic tagging in hippocampal CA1 neurons in slices in vitro," *The Journal of Neuroscience*, vol. 29, no. 39, pp. 12167–12173, 2009.

[106] R. Fonseca, "Activity-dependent actin dynamics are required for the maintenance of long-term plasticity and for synaptic capture," *The European Journal of Neuroscience*, vol. 35, no. 2, pp. 195–206, 2012.

[107] W. Morishita, H. Marie, and R. C. Malenka, "Distinct triggering and expression mechanisms underlie LTD of AMPA and NMDA synaptic responses," *Nature Neuroscience*, vol. 8, no. 8, pp. 1043–1050, 2005.

[108] R. Lamprecht, "The actin cytoskeleton in memory formation," *Progress in Neurobiology*, vol. 117, pp. 1–19, 2014.

[109] L. Y. Chen, C. S. Rex, M. S. Casale, C. M. Gall, and G. Lynch, "Changes in synaptic morphology accompany actin signaling during LTP," *Journal of Neuroscience*, vol. 27, no. 20, pp. 5363–5372, 2007.

[110] M. Bosch, J. Castro, T. Saneyoshi, H. Matsuno, M. Sur, and Y. Hayashi, "Structural and molecular remodeling of dendritic spine substructures during long-term potentiation," *Neuron*, vol. 82, no. 2, pp. 444–459, 2014.

[111] A. Reichenbach, A. Derouiche, and F. Kirchhoff, "Morphology and dynamics of perisynaptic glia," *Brain Research Reviews*, vol. 63, no. 1-2, pp. 11–25, 2010.

[112] Y. Bernardinelli, J. Randall, E. Janett et al., "Activity-dependent structural plasticity of perisynaptic astrocytic domains promotes excitatory synapse stability," *Current Biology*, vol. 24, no. 15, pp. 1679–1688, 2014.

[113] M. Horak, R. S. Petralia, M. Kaniakova, and N. Sans, "ER to synapse trafficking of NMDA receptors," *Frontiers in Cellular Neuroscience*, vol. 8, article 394, 2014.

[114] R. L. Huganir and R. A. Nicoll, "AMPARs and synaptic plasticity: the last 25 years," *Neuron*, vol. 80, no. 3, pp. 704–717, 2013.

[115] L. Ladépêche, J. P. Dupuis, and L. Groc, "Surface trafficking of NMDA receptors: gathering from a partner to another," *Seminars in Cell and Developmental Biology*, vol. 27, pp. 3–13, 2014.

[116] M.-F. Lisé, T. P. Wong, A. Trinh et al., "Involvement of myosin Vb in glutamate receptor trafficking," *The Journal of Biological Chemistry*, vol. 281, no. 6, pp. 3669–3678, 2006.

[117] S. S. Correia, S. Bassani, T. C. Brown et al., "Motor protein-dependent transport of AMPA receptors into spines during long-term potentiation," *Nature Neuroscience*, vol. 11, no. 4, pp. 457–466, 2008.

[118] K. R. Tovar and G. L. Westbrook, "Mobile NMDA receptors at hippocampal synapses," *Neuron*, vol. 34, no. 2, pp. 255–264, 2002.

[119] A. Sergé, L. Fourgeaud, A. Hémar, and D. Choquet, "Active surface transport of metabotropic glutamate receptors through

binding to microtubules and actin flow," *Journal of Cell Science*, vol. 116, no. 24, pp. 5015–5022, 2003.

[120] G. L. Collingridge, R. W. Olsen, J. Peters, and M. Spedding, "A nomenclature for ligand-gated ion channels," *Neuropharmacology*, vol. 56, no. 1, pp. 2–5, 2009.

[121] M. L. Mayer and N. Armstrong, "Structure and function of glutamate receptor ion channels," *Annual Review of Physiology*, vol. 66, pp. 161–181, 2004.

[122] W. Lu, Y. Shi, A. C. Jackson et al., "Subunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach," *Neuron*, vol. 62, no. 2, pp. 254–268, 2009.

[123] D. W. Allison, V. I. Gelfand, I. Spector, and A. M. Craig, "Role of actin in anchoring postsynaptic receptors in cultured hippocampal neurons: differential attachment of NMDA versus AMPA receptors," *The Journal of Neuroscience*, vol. 18, no. 7, pp. 2423–2436, 1998.

[124] Q. Zhou, M.-Y. Xiao, and R. A. Nicoll, "Contribution of cytoskeleton to the internalization of AMPA receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 3, pp. 1261–1266, 2001.

[125] P. Penzes and M. E. Cahill, "Deconstructing signal transduction pathways that regulate the actin cytoskeleton in dendritic spines," *Cytoskeleton*, vol. 69, no. 7, pp. 426–441, 2012.

[126] D. A. Applewhite, M. Barzik, S.-I. Kojima, T. M. Svitkina, F. B. Gertler, and G. G. Borisy, "Ena/VASP proteins have an anti-capping independent function in filopodia formation," *Molecular Biology of the Cell*, vol. 18, no. 7, pp. 2579–2591, 2007.

[127] L. Pasic, T. Kotova, and D. A. Schafer, "Ena/VASP proteins capture actin filament barbed ends," *Journal of Biological Chemistry*, vol. 283, no. 15, pp. 9814–9819, 2008.

[128] S. D. Hansen and R. D. Mullins, "VASP is a processive actin polymerase that requires monomeric actin for barbed end association," *Journal of Cell Biology*, vol. 191, no. 3, pp. 571–584, 2010.

[129] W.-H. Lin, C. A. Nebhan, B. R. Anderson, and D. J. Webb, "Vasodilator-stimulated phosphoprotein (VASP) induces actin assembly in dendritic spines to promote their development and potentiate synaptic strength," *The Journal of Biological Chemistry*, vol. 285, no. 46, pp. 36010–36020, 2010.

[130] D. L. Rocca, S. Martin, E. L. Jenkins, and J. G. Hanley, "Inhibition of Arp2/3-mediated actin polymerization by PICK1 regulates neuronal morphology and AMPA receptor endocytosis," *Nature Cell Biology*, vol. 10, no. 3, pp. 259–271, 2008.

[131] D. L. Rocca, M. Amici, A. Antoniou et al., "The small GTPase Arf1 modulates Arp2/3-mediated actin polymerization via PICK1 to regulate synaptic plasticity," *Neuron*, vol. 79, no. 2, pp. 293–307, 2013.

[132] A. Citri, S. Bhattacharyya, C. Ma et al., "Calcium binding to PICK1 is essential for the intracellular retention of AMPA receptors underlying long-term depression," *The Journal of Neuroscience*, vol. 30, no. 49, pp. 16437–16452, 2010.

[133] J. A. Hammer III and W. Wagner, "Functions of class V myosins in neurons," *The Journal of Biological Chemistry*, vol. 288, no. 40, pp. 28428–28434, 2013.

[134] W. Wagner, S. D. Brenowitz, and J. A. Hammer III, "Myosin-Va transports the endoplasmic reticulum into the dendritic spines of Purkinje neurons," *Nature Cell Biology*, vol. 13, no. 1, pp. 40–47, 2011.

[135] S. H. Lee, A. Simonetta, and M. Sheng, "Subunit rules governing the sorting of internalized AMPA receptors in hippocampal neurons," *Neuron*, vol. 43, no. 2, pp. 221–236, 2004.

[136] M. Park, E. C. Penick, J. G. Edwards, J. A. Kauer, and M. D. Ehlers, "Recycling endosomes supply AMPA receptors for LTP," *Science*, vol. 305, no. 5692, pp. 1972–1975, 2004.

[137] L. A. Lapierre, R. Kumar, C. M. Hales et al., "Myosin Vb is associated with plasma membrane recycling systems," *Molecular Biology of the Cell*, vol. 12, no. 6, pp. 1843–1857, 2001.

[138] A. L. Wells, A. W. Lin, L.-Q. Chen et al., "Myosin VI is an actin-based motor that moves backwards," *Nature*, vol. 401, no. 6752, pp. 505–508, 1999.

[139] J. Ménétrey, A. Bahloul, A. L. Wells et al., "The structure of the myosin VI motor reveals the mechanism of directionality reversal," *Nature*, vol. 435, no. 7043, pp. 779–785, 2005.

[140] H. Wu, J. E. Nash, P. Zamorano, and C. C. Garner, "Interaction of SAP97 with minus-end-directed actin motor myosin VI. Implications for AMPA receptor trafficking," *The Journal of Biological Chemistry*, vol. 277, no. 34, pp. 30928–30934, 2002.

[141] J. Gu, C. W. Lee, Y. Fan et al., "ADF/cofilin-mediated actin dynamics regulate AMPA receptor trafficking during synaptic plasticity," *Nature Neuroscience*, vol. 13, no. 10, pp. 1208–1215, 2010.

[142] E. Y. Yuen, W. Liu, T. Kafri, H. van Praag, and Z. Yan, "Regulation of AMPA receptor channels and synaptic plasticity by cofilin phosphatase Slingshot in cortical neurons," *Journal of Physiology*, vol. 588, no. 13, pp. 2361–2371, 2010.

[143] Y. Wang, Q. Dong, X.-F. Xu et al., "Phosphorylation of cofilin regulates extinction of conditioned aversive memory via AMPAR trafficking," *The Journal of Neuroscience*, vol. 33, no. 15, pp. 6423–6433, 2013.

[144] K. Kato, T. Shirao, H. Yamazaki, K. Imamura, and Y. Sekino, "Regulation of AMPA receptor recruitment by the actin binding protein drebrin in cultured hippocampal neurons," *Journal of Neuroscience and Neuroengineering*, vol. 1, no. 2, pp. 153–160, 2012.

[145] L. D. Walensky, S. Blackshaw, D. Liao et al., "A novel neuron-enriched homolog of the erythrocyte membrane cytoskeletal protein 4.1," *The Journal of Neuroscience*, vol. 19, no. 15, pp. 6457–6467, 1999.

[146] L. Shen, F. Liang, L. D. Walensky, and R. L. Huganir, "Regulation of AMPA receptor GluR1 subunit surface expression by a 4.1 N-linked actin cytoskeletal association," *The Journal of Neuroscience*, vol. 20, no. 21, pp. 7932–7940, 2000.

[147] L. C. Kapitein and C. C. Hoogenraad, "Which way to go? Cytoskeletal organization and polarized transport in neurons," *Molecular and Cellular Neuroscience*, vol. 46, no. 1, pp. 9–20, 2011.

[148] Y. Bu, N. Wang, S. Wang et al., "Myosin IIb-dependent regulation of actin dynamics is required for N-Methyl-D-aspartate receptor trafficking during synaptic plasticity," *Journal of Biological Chemistry*, vol. 290, no. 42, pp. 25395–25410, 2015.

[149] M. Sheng, "Molecular organization of the postsynaptic specialization," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 13, pp. 7058–7061, 2001.

[150] J. M. Montgomery, J. C. Selcher, J. E. Hanson, and D. V. Madison, "Dynamin-dependent NMDAR endocytosis during LTD and its dependence on synaptic state," *BMC Neuroscience*, vol. 6, article 48, 2005.

[151] M. Wyszynski, J. Lin, A. Rao et al., "Competitive binding of α-actinin and calmodulin to the NMDA receptor," *Nature*, vol. 385, no. 6615, pp. 439–442, 1997.

[152] A. W. Dunah, M. Wyszynski, D. M. Martin, M. Sheng, and D. G. Standaert, "α-Actinin-2 in rat striatum: localization

and interaction with NMDA glutamate receptor subunits," *Molecular Brain Research*, vol. 79, no. 1-2, pp. 77–87, 2000.

[153] J. Peng, M. J. Kim, D. Cheng, D. M. Duong, S. P. Gygi, and M. Sheng, "Semiquantitative proteomic analysis of rat forebrain postsynaptic density fractions by mass spectrometry," *The Journal of Biological Chemistry*, vol. 279, no. 20, pp. 21003–21011, 2004.

[154] T. Nakagawa, J. A. Engler, and M. Sheng, "The dynamic turnover and functional roles of α-actinin in dendritic spines," *Neuropharmacology*, vol. 47, no. 5, pp. 734–745, 2004.

[155] W. Nörenberg, F. Hofmann, P. Illes, K. Aktories, and D. K. Meyer, "Rundown of somatodendritic N-methyl-D-aspartate (NMDA) receptor channels in rat hippocampal neurones: evidence for a role of the small GTPase RhoA," *British Journal of Pharmacology*, vol. 127, no. 5, pp. 1060–1063, 1999.

[156] C. Rosenmund and G. L. Westbrook, "Calcium-induced actin depolymerization reduces NMDA channel activity," *Neuron*, vol. 10, no. 5, pp. 805–814, 1993.

[157] K. Furukawa, W. Fu, Y. Li, W. Witke, D. J. Kwiatkowski, and M. P. Mattson, "The actin-severing protein gelsolin modulates calcium channel and NMDA receptor activities and vulnerability to excitotoxicity in hippocampal neurons," *Journal of Neuroscience*, vol. 17, no. 21, pp. 8178–8186, 1997.

[158] E. B. Merriam, M. Millette, D. C. Lumbard et al., "Synaptic regulation of microtubule dynamics in dendritic spines by calcium, F-actin, and drebrin," *The Journal of Neuroscience*, vol. 33, no. 42, pp. 16471–16482, 2013.

[159] S. K. Ultanir, J.-E. Kim, B. J. Hall, T. Deerinck, M. Ellisman, and A. Ghosh, "Regulation of spine morphology and spine density by NMDA receptor signaling in vivo," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 49, pp. 19553–19558, 2007.

[160] C. G. Pontrello, M.-Y. Sun, A. Lin, T. A. Fiacco, K. A. DeFea, and I. M. Ethell, "Cofilin under control of β-arrestin-2 in NMDA-dependent dendritic spine plasticity, long-term depression (LTD), and learning," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 7, pp. E442–E451, 2012.

[161] M.-Y. Xiao, B. Gustafsson, and Y.-P. Niu, "Metabotropic glutamate receptors in the trafficking of ionotropic glutamate and GABAA receptors at central synapses," *Current Neuropharmacology*, vol. 4, no. 1, pp. 77–86, 2006.

[162] R. Luján, Z. Nusser, J. D. B. Roberts, R. Shigemoto, and P. Somogyi, "Perisynaptic location of metabotropic glutamate receptors mGluR1 and mGluR5 on dendrites and dendritic spines in the rat hippocampus," *European Journal of Neuroscience*, vol. 8, no. 7, pp. 1488–1500, 1996.

[163] J. L. Esseltine, F. M. Ribeiro, and S. S. G. Ferguson, "Rab8 modulates metabotropic glutamate receptor subtype 1 intracellular trafficking and signaling in a protein kinase C-dependent manner," *The Journal of Neuroscience*, vol. 32, no. 47, pp. 16933–16942, 2012.

[164] L. J. Volk, C. A. Daly, and K. M. Huber, "Differential roles for group 1 mGluR subtypes in induction and expression of chemically induced hippocampal long-term depression," *Journal of Neurophysiology*, vol. 95, no. 4, pp. 2427–2438, 2006.

[165] U. Finckh, C. Kuschel, M. Anagnostouli et al., "Novel mutations and repeated findings of mutations in familial Alzheimer disease," *Neurogenetics*, vol. 6, no. 2, pp. 85–89, 2005.

[166] M. J. Ball, V. Hachinski, A. Fox et al., "A new definition of Alzheimer's disease: a hippocampal dementia," *The Lancet*, vol. 325, no. 8419, pp. 14–16, 1985.

[167] W. G. Honer, D. W. Dickson, J. Gleeson, and P. Davies, "Regional synaptic pathology in Alzheimer's disease," *Neurobiology of Aging*, vol. 13, no. 3, pp. 375–382, 1992.

[168] H. B. M. Uylings and J. M. De Brabander, "Neuronal changes in normal human aging and Alzheimer's disease," *Brain and Cognition*, vol. 49, no. 3, pp. 268–276, 2002.

[169] K. K. Leung, J. W. Bartlett, J. Barnes, E. N. Manning, S. Ourselin, and N. C. Fox, "Cerebral atrophy in mild cognitive impairment and Alzheimer disease: rates and acceleration," *Neurology*, vol. 80, no. 7, pp. 648–654, 2013.

[170] M. Grundman, D. Sencakova, C. R. Jack Jr. et al., "Brain MRI hippocampal volume and prediction of clinical status in a mild cognitive impairment trial," *Journal of Molecular Neuroscience*, vol. 19, no. 1-2, pp. 23–27, 2002.

[171] E. Frankó and O. Joly, "Evaluating Alzheimer's disease progression using rate of regional hippocampal atrophy," *PLoS ONE*, vol. 8, no. 8, Article ID e71354, 2013.

[172] J. P. Lerch, J. C. Pruessner, A. Zijdenbos, H. Hampel, S. J. Teipel, and A. C. Evans, "Focal decline of cortical thickness in Alzheimer's disease identified by computational neuroanatomy," *Cerebral Cortex*, vol. 15, no. 7, pp. 995–1001, 2005.

[173] V. Singh, H. Chertkow, J. P. Lerch, A. C. Evans, A. E. Dorr, and N. J. Kabani, "Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease," *Brain*, vol. 129, no. 11, pp. 2885–2893, 2006.

[174] P. J. Hsu, H. Shou, T. Benzinger et al., "Amyloid burden in cognitively normal elderly is associated with preferential hippocampal subfield volume loss," *Journal of Alzheimer's Disease*, vol. 45, no. 1, pp. 27–33, 2015.

[175] J. M. Schott, N. C. Fox, C. Frost et al., "Assessing the onset of structural change in familial Alzheimer's disease," *Annals of Neurology*, vol. 53, no. 2, pp. 181–188, 2003.

[176] J. H. Morra, Z. Tu, L. G. Apostolova et al., "Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls," *Human Brain Mapping*, vol. 30, no. 9, pp. 2766–2788, 2009.

[177] F. Kamenetz, T. Tomita, H. Hsieh et al., "APP processing and synaptic function," *Neuron*, vol. 37, no. 6, pp. 925–937, 2003.

[178] G. M. Shankar, S. Li, T. H. Mehta et al., "Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory," *Nature Medicine*, vol. 14, no. 8, pp. 837–842, 2008.

[179] H. W. Querfurth and F. M. LaFerla, "Alzheimer's disease," *The New England Journal of Medicine*, vol. 362, no. 4, pp. 329–344, 2010.

[180] L. M. Ittner, Y. D. Ke, F. Delerue et al., "Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models," *Cell*, vol. 142, no. 3, pp. 387–397, 2010.

[181] O. A. Shipton, J. R. Leitz, J. Dworzak et al., "Tau protein is required for amyloid β-induced impairment of hippocampal long-term potentiation," *Journal of Neuroscience*, vol. 31, no. 5, pp. 1688–1692, 2011.

[182] M. E. Seward, E. Swanson, A. Norambuena et al., "Amyloid-β signals through tau to drive ectopic neuronal cell cycle re-entry in alzheimer's disease," *Journal of Cell Science*, vol. 126, no. 5, pp. 1278–1286, 2013.

[183] D. E. Hurtado, L. Molina-Porcel, M. Iba et al., "Aβ accelerates the spatiotemporal progression of tau pathology and augments tau amyloidosis in an Alzheimer mouse model," *American Journal of Pathology*, vol. 177, no. 4, pp. 1977–1988, 2010.

[184] M. A. Chabrier, D. Cheng, N. A. Castello, K. N. Green, and F. M. LaFerla, "Synergistic effects of amyloid-beta and wild-type human tau on dendritic spine loss in a floxed double transgenic model of Alzheimer's disease," *Neurobiology of Disease*, vol. 64, pp. 107–117, 2014.

[185] K. T. Dineley, A. A. Pandya, and J. L. Yakel, "Nicotinic ACh receptors as therapeutic targets in CNS disorders," *Trends in Pharmacological Sciences*, vol. 36, no. 2, pp. 96–108, 2015.

[186] M. L. Giuffrida, F. Caraci, B. Pignataro et al., "β-Amyloid monomers are neuroprotective," *The Journal of Neuroscience*, vol. 29, no. 34, pp. 10582–10587, 2009.

[187] M. Guglielmotto, D. Monteleone, A. Piras et al., "Aβ1-42 monomers or oligomers have different effects on autophagy and apoptosis," *Autophagy*, vol. 10, no. 10, pp. 1827–1843, 2014.

[188] C. Ye, D. M. Walsh, D. J. Selkoe, and D. M. Hartley, "Amyloid β-protein induced electrophysiological changes are dependent on aggregation state: N-methyl-D-aspartate (NMDA) versus non-NMDA receptor/channel activation," *Neuroscience Letters*, vol. 366, no. 3, pp. 320–325, 2004.

[189] B. J. Cummings and C. W. Cotman, "Image analysis of β-amyloid load in Alzheimer's disease and relation to dementia severity," *The Lancet*, vol. 346, no. 8989, pp. 1524–1528, 1995.

[190] C. M. Kirkwood, J. Ciuchta, M. D. Ikonomovic et al., "Dendritic spine density, morphology, and fibrillar actin content surrounding amyloid-β plaques in a mouse model of amyloid-β deposition," *Journal of Neuropathology and Experimental Neurology*, vol. 72, no. 8, pp. 791–800, 2013.

[191] L. Mucke, E. Masliah, G.-Q. Yu et al., "High-level neuronal expression of Aβ(1–42) in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation," *The Journal of Neuroscience*, vol. 20, no. 11, pp. 4050–4058, 2000.

[192] C. A. McLean, R. A. Cherny, F. W. Fraser et al., "Soluble pool of Aβ amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease," *Annals of Neurology*, vol. 46, no. 6, pp. 860–866, 1999.

[193] A. J. Furst, G. D. Rabinovici, A. H. Rostomian et al., "Cognition, glucose metabolism and amyloid burden in Alzheimer's disease," *Neurobiology of Aging*, vol. 33, no. 2, pp. 215–225, 2012.

[194] S. Zhu, J. He, R. Zhang et al., "Therapeutic effects of quetiapine on memory deficit and brain β-amyloid plaque pathology in a transgenic mouse model of Alzheimer's disease," *Current Alzheimer Research*, vol. 10, no. 3, pp. 270–278, 2013.

[195] A.-G. Xuan, X.-B. Pan, P. Wei et al., "Valproic acid alleviates memory deficits and attenuates amyloid-β deposition in transgenic mouse model of Alzheimer's disease," *Molecular Neurobiology*, vol. 51, no. 1, pp. 300–312, 2014.

[196] P. E. Cramer, J. R. Cirrito, D. W. Wesson et al., "ApoE-directed therapeutics rapidly clear β-amyloid and reverse deficits in AD mouse models," *Science*, vol. 335, no. 6075, pp. 1503–1506, 2012.

[197] E. J. Mufson, E.-Y. Chen, E. J. Cochran, L. A. Beckett, D. A. Bennett, and J. H. Kordower, "Entorhinal cortex β-amyloid load in individuals with mild cognitive impairment," *Experimental Neurology*, vol. 158, no. 2, pp. 469–490, 1999.

[198] P. N. Lacor, M. C. Buniel, P. W. Furlow et al., "Aβ oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease," *The Journal of Neuroscience*, vol. 27, no. 4, pp. 796–807, 2007.

[199] K. H. Gylys, J. A. Fein, F. Yang, D. Wiley, C. A. Miller, and G. M. Cole, "Synaptic changes in Alzheimer's disease accompanied by decreased PSD-95 fluorescence," *American Journal of Pathology*, vol. 165, no. 5, pp. 1809–1817, 2004.

[200] B. Calabrese, G. M. Shaked, I. V. Tabarean, J. Braga, E. H. Koo, and S. Halpain, "Rapid, concurrent alterations in pre- and postsynaptic structure induced by naturally-secreted amyloid-β protein," *Molecular and Cellular Neuroscience*, vol. 35, no. 2, pp. 183–193, 2007.

[201] D. M. Walsh, I. Klyubin, J. V. Fadeeva et al., "Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo," *Nature*, vol. 416, no. 6880, pp. 535–539, 2002.

[202] H.-W. Wang, J. F. Pasternak, H. Kuo et al., "Soluble oligomers of β amyloid (1–42) inhibit long-term potentiation but not long-term depression in rat dentate gyrus," *Brain Research*, vol. 924, no. 2, pp. 133–140, 2002.

[203] S. Li, S. Hong, N. E. Shepardson, D. M. Walsh, G. M. Shankar, and D. Selkoe, "Soluble oligomers of amyloid β protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake," *Neuron*, vol. 62, no. 6, pp. 788–801, 2009.

[204] S. Petratos, Q.-X. Li, A. J. George et al., "The β-amyloid protein of Alzheimer's disease increases neuronal CRMP-2 phosphorylation by a Rho-GTP mechanism," *Brain*, vol. 131, no. 1, pp. 90–108, 2008.

[205] A. Schmandke, A. Schmandke, and S. Strittmatter, "ROCK and Rho: biochemistry and neuronal functions of Rho-associated protein kinases," *Neurology*, vol. 13, no. 5, pp. 454–469, 2010.

[206] B. Niederöst, T. Oertle, J. Fritsche, R. A. McKinney, and C. E. Bandtlow, "Nogo-A and myelin-associated glycoprotein mediate neurite growth inhibition by antagonistic regulation of RhoA and Rac1," *The Journal of Neuroscience*, vol. 22, no. 23, pp. 10368–10376, 2002.

[207] C. Hofmann, M. Shepelev, and J. Chernoff, "The genetics of Pak," *Journal of Cell Science*, vol. 117, no. 19, pp. 4343–4354, 2004.

[208] J. Pozueta, R. Lefort, and M. L. Shelanski, "Synaptic changes in Alzheimer's disease and its models," *Neuroscience*, vol. 251, pp. 51–65, 2013.

[209] L. Zhao, Q.-L. Ma, F. Calon et al., "Role of p21-activated kinase pathway defects in the cognitive deficits of Alzheimer disease," *Nature Neuroscience*, vol. 9, no. 2, pp. 234–242, 2006.

[210] M. T. Maloney, L. S. Minamide, A. W. Kinley, J. A. Boyle, and J. R. Bamburg, "β-secretase-cleaved amyloid precursor protein accumulates at actin inclusions induced in neurons by stress or amyloid β: a feedforward mechanism for alzheimer's disease," *Journal of Neuroscience*, vol. 25, no. 49, pp. 11313–11321, 2005.

[211] A. Mendoza-Naranjo, E. Contreras-Vallejos, D. R. Henriquez et al., "Fibrillar amyloid-β1-42 modifies actin organization affecting the cofilin phosphorylation state: a role for Rac1/cdc42 effector proteins and the slingshot phosphatase," *Journal of Alzheimer's Disease*, vol. 29, no. 1, pp. 63–77, 2012.

[212] S. Simó and J. A. Cooper, "Regulation of dendritic branching by Cdc42 GAPs," *Genes and Development*, vol. 26, no. 15, pp. 1653–1658, 2012.

[213] L. S. Minamide, A. M. Striegl, J. A. Boyle, P. J. Meberg, and J. R. Bamburg, "Neurodegenerative stimuli induce persistent ADF/cofilin-actin rods that disrupt distal neurite function," *Nature Cell Biology*, vol. 2, no. 9, pp. 628–636, 2000.

[214] J. R. Bamburg, B. W. Bernstein, R. C. Davis et al., "ADF/Cofilin-actin rods in neurodegenerative diseases," *Current Alzheimer Research*, vol. 7, no. 3, pp. 241–250, 2010.

[215] J. Cichon, C. Sun, B. Chen et al., "Cofilin aggregation blocks intracellular trafficking and induces synaptic loss in hippocampal neurons," *Journal of Biological Chemistry*, vol. 287, no. 6, pp. 3919–3929, 2012.

[216] E. Nielsen, F. Severin, J. M. Backer, A. A. Hyman, and M. Zerial, "Rab5 regulates motility of early endosomes on microtubules," *Nature Cell Biology*, vol. 1, no. 6, pp. 376–382, 1999.

[217] K. S. Shim and G. Lubec, "Drebrin, a dendritic spine protein, is manifold decreased in brains of patients with Alzheimer's disease and Down syndrome," *Neuroscience Letters*, vol. 324, no. 3, pp. 209–212, 2002.

[218] E. Perez-Gracia, R. Blanco, M. Carmona, E. Carro, and I. Ferrer, "Oxidative stress damage and oxidative stress responses in the choroid plexus in Alzheimer's disease," *Acta Neuropathologica*, vol. 118, no. 4, pp. 497–504, 2009.

[219] A. Güntert, J. Campbell, M. Saleem et al., "Plasma gelsolin is decreased and correlates with rate of decline in Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 21, no. 2, pp. 585–596, 2010.

[220] Y. Matsuoka, M. Saito, J. LaFrancois et al., "Novel therapeutic approach for the treatment of Alzheimer's disease by peripheral administration of agents with an affinity to beta-amyloid," *The Journal of Neuroscience*, vol. 23, no. 1, pp. 29–33, 2003.

[221] M. D. Ehlers, "Reinsertion or degradation of AMPA receptors determined by activity-dependent endocytic sorting," *Neuron*, vol. 28, no. 2, pp. 511–525, 2000.

[222] G. M. Shankar, B. L. Bloodgood, M. Townsend, D. M. Walsh, D. J. Selkoe, and B. L. Sabatini, "Natural oligomers of the Alzheimer amyloid-β protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway," *The Journal of Neuroscience*, vol. 27, no. 11, pp. 2866–2875, 2007.

[223] M. Esteves da Silva, M. Adrian, P. Schätzle et al., "Positioning of AMPA receptor-containing endosomes regulates synapse architecture," *Cell Reports*, vol. 13, no. 5, pp. 933–943, 2015.

[224] G. Jung, E.-J. Kim, A. Cicvaric et al., "Drebrin depletion alters neurotransmitter receptor levels in protein complexes, dendritic spine morphogenesis and memory-related synaptic plasticity in the mouse hippocampus," *Journal of Neurochemistry*, vol. 134, no. 2, pp. 327–339, 2015.

[225] H. Takahashi, T. Mizui, and T. Shirao, "Down-regulation of drebrin A expression suppresses synaptic targeting of NMDA receptors in developing hippocampal neurones," *Journal of neurochemistry*, vol. 97, no. 1, pp. 110–115, 2006.

[226] P. G. Galloway, G. Perry, and P. Gambetti, "Hirano body filaments contain actin and actin-associated proteins," *Journal of Neuropathology and Experimental Neurology*, vol. 46, no. 2, pp. 185–199, 1987.

[227] P. G. Galloway, P. Mulvihill, S. Siedlak et al., "Immunochemical demonstration of tropomyosin in the neurofibrillary pathology of Alzheimer's disease," *American Journal of Pathology*, vol. 137, no. 2, pp. 291–300, 1990.

[228] B. Pianu, R. Lefort, L. Thuiliere, E. Tabourier, and F. Bartolini, "The Aβ1-42 peptide regulates microtubule stability independently of tau," *Journal of Cell Science*, vol. 127, no. 5, pp. 1117–1127, 2014.

[229] J. R. Stehn, N. K. Haass, T. Bonello et al., "A novel class of anticancer compounds targets the actin cytoskeleton in tumor cells," *Cancer Research*, vol. 73, no. 16, pp. 5169–5182, 2013.