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REVIEW

Dendritic spine morphology and dynamics in health and disease

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Abstract: Dendritic spines are actin-rich structures that form the postsynaptic terminals of excitatory synapses in the brain. The development and plasticity of spines are essential for cognitive processes, such as learning and memory, and defects in their density, morphology, and size underlie a number of neurological disorders. In this review, we discuss the contribution and regulation of the actin cytoskeleton in spine formation and plasticity as well as learning and memory. We also highlight the role of key receptors and intracellular signaling pathways in modulating the development and morphology of spines and cognitive function. Moreover, we provide insight into spine/synapse defects associated with several neurological disorders and the molecular mechanisms that underlie these spine defects.

Keywords: dendritic spines, synapses, synaptic plasticity, actin cytoskeleton, glutamate receptors, neurological disorders

Structure and function of dendritic spines

Santiago Ramón y Cajal first described dendritic spines, using Golgi staining, near the end of the 19th century and proposed that these spines were sites of axonal and dendritic contact.[1,2] Decades later, with the advent of electron microscopy, these spines were indeed shown to be sites of excitatory synaptic contact between neurons, proving that Cajal's hypothesis was correct.[3,4] These and subsequent studies highlight the importance of dendritic spines and pose interesting questions as to the specific functions of these structures.[5,6] Dendritic spines most likely have functions other than to simply connect axons and dendrites. This is supported by the observation that many inhibitory synaptic inputs occur on dendritic shafts in the absence of spines; however, it should be noted that recent data indicate that some inhibitory neurons have functional spines, and inhibitory synaptic inputs can occur on spines of cortical pyramidal neurons.[7–10] A widely held theory is that spines serve as biochemical compartments in the cell.[5,11] The unique morphology of spines, which consists of an enlarged head and a thin neck, makes them ideal structures to function as postsynaptic biochemical compartments that separate synaptic terminals from dendritic shafts.[11,12] In addition, spines could serve as electrical compartments, which can maintain membrane potentials that are distinct from those of the parent dendrites.[13–15] The electrical isolation of individual spines might provide a mechanism to allow neurons to integrate and independently regulate the strength of a large number of synaptic inputs.[14] Moreover, the compartmentalization of spines most likely contributes significantly to the efficiency of synaptic transmission and plasticity.[15–17] Intriguingly, the spine neck width is reported to be an important factor in regulating compartmentalization.[16] Other roles

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for dendritic spines have been proposed,[6,17,18] and the specific functions of spines are an active area of interest and debate that warrants continued research.

The functions of dendritic spines are governed, at least in part, by their morphology. They range in morphology from filopodia-like protrusions, which are thought to be spine precursors, to more mature stubby, thin, or mushroom-shaped structures.[19] Stubby spines do not have a neck whereas thin and mushroom-shaped spines consist of long necks that are connected to small and large bulbous heads, respectively; filopodia-like protrusions are extensions from the dendrite that lack a bulbous head. Spine morphology is malleable, and their shape can change over time, even on a time scale of minutes or less[20–22] (Figure 1). In the case of dendritic filopodia, the dynamic, exploratory nature of these structures could be beneficial in forming connections with axons.[23] After an initial interaction between dendritic filopodia and axons, synapses can assemble on a relatively rapid time scale (hours).[24,25] For most mammals, spine and synapse formation is widespread during early postnatal development and is followed by a pruning phase during adolescence that eliminates unnecessary or improper synaptic connections.[26,27] In adults, dendritic spine formation and elimination are at an equilibrium with a fraction of spines being consistently added or removed.[26] Morphological changes, which are usually activity-dependent, also occur in more mature spines and are associated with synaptic plasticity.[28] Synaptic plasticity, which entails the strengthening or weakening of synapses over time as well as synapse formation and elimination (structural plasticity), is widely believed to be the cellular basis of learning and memory.[28–30] In vivo imaging in the cerebral cortex of mice has shown that spine dynamics/remodeling is associated with different forms of learning.[30–33] Synaptic plasticity is also thought to be necessary for the encoding and storage of memory.[34] The foundation of this theory dates back to Donald Hebb, who postulated a link between alterations in synaptic activity and memory storage.[35]

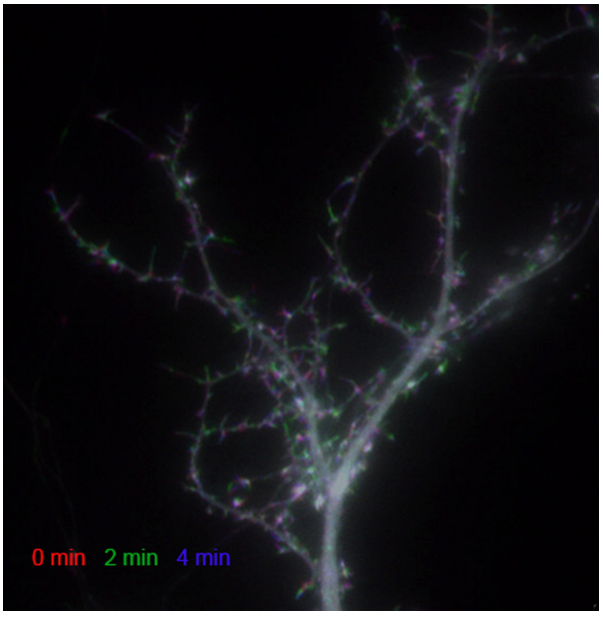

Figure 1 Dendritic spines are dynamic structures. A three-color temporal overlap of a hippocampal neuron expressing green fluorescent protein-tagged β-actin.
Notes: In general, green and magenta indicate dynamic spines whereas white depicts more stable spines.

Experimental attempts to model Hebb's theory led to the discovery of long-term potentiation (LTP), which typically uses high frequency stimulation to increase synaptic transmission.[28] In order to encode information efficiently, an increase in synaptic strength must be counterbalanced by a weakening of synapses by a process termed long-term depression (LTD). LTD can be provoked experimentally with low frequency stimulation, causing a prolonged decrease in synaptic transmission.[29,36] These experimental models, LTP and LTD, have been invaluable in generating a wealth of data showing the essential function that synaptic plasticity has in learning and memory. Another line of evidence that supports this link is the well-documented association between abnormalities in dendritic spine/synapse formation and plasticity and numerous neurological disorders, including autism, Alzheimer's disease (AD), schizophrenia, and intellectual disability.[37,38]

This review focuses on the function and regulation of dendritic spines and excitatory synapses, and their role in human health and disease. We discuss the molecular mechanisms modulating dendritic spine development, morphology, and function, as well as the defects associated with these structures in certain neurological disorders.

Actin regulation in dendritic spine development and plasticity

Actin is the major cytoskeletal element in dendritic spines where filamentous actin (F-actin), which results from the polymerization of monomeric actin (G-actin), is found at high concentrations. F-actin within spine heads is organized into a branched network that is highly dynamic and regulated by neuronal activity.[39–41] Fluorescence recovery after photobleaching experiments with green fluorescent protein-tagged β-actin showed that 85% of the actin turned over in less than 1 minute, and LTD stabilized a significant portion of the dynamic actin.[39] Super-resolution imaging of spines also showed fast actin turnover (ie, on a time scale of seconds to minutes) and suggested that the F-actin network comprises

mostly short filaments that undergo both retrograde and anterograde actin flow.[40] Actin turnover does, however, vary within regions of spines; spine tips have a higher turnover rate than at the base where actin seems to be more stable.[42] A dynamic actin cytoskeleton is critical for the morphological malleability of spines, which underlies the formation and plasticity of these structures. Microtubules are also found in at least a subset of spines where they modulate spine morphology and maturation, most likely through their interplay with the actin cytoskeleton.[43] However, a detailed discussion of the role of microtubules in regulating dendritic spine function is beyond the scope of this review.

Actin remodeling is regulated by the Rho family of small GTPases that includes Rho, Rac, and Cdc42. These small GTPases are molecular switches that exist in an active (guanosine-5′-triphosphate-bound) and an inactive (guanosine-5′-diphosphate-bound) state. The cycling of the GTPases between the active and inactive states is regulated by three types of proteins, ie, guanine nucleotide exchange factors (GEFs), GTPase activating proteins (GAPs), and guanine dissociation inhibitors. GEFs promote the exchange of GDP for GTP, activating the GTPase; GAPs increase intrinsic GTP hydrolysis, returning these proteins to an inactive state; and guanine dissociation inhibitors form soluble complexes with the GTPases and sequester them in an inactive state.[44]

Rac and Cdc42 induce dendritic spine formation, whereas Rho promotes the retraction and loss of spines.[45–47] Rac can promote spine formation through its downstream effector, p21-activated kinase (PAK).[48] Cdc42 stimulates spinogenesis and enlargement of spine heads via activation of the actin-binding protein neural Wiskott-Aldrich syndrome protein (N-WASP) and the Arp2/3 complex, which localizes to the postsynaptic density (PSD) and mediates the formation of branched actin filaments.[46,49] Moreover, loss of Cdc42 in mice results in deficits in synaptic plasticity and remote memory recall.[50] Rho family GEFs and GAPs also have important roles in spine development and function. Mice lacking the Rac GEF karilin-7 exhibit defects in cortical spine density and in working memory.[51] The Rac GEF Tiam1 is required for dendritic spine formation, and knockdown of Tiam1 causes a decrease in spine and synapse density.[52,53] β-PIX, another GEF, regulates spine formation through activation of Rac and subsequently PAK.[48] GEF-H1, a Rho family GEF, inhibits spine formation and negatively regulates spine length through a Rho pathway.[54] Rho family GAPs also contribute to the development of dendritic spines and synapses. Expression of the Rac GAP α1-chimaerin leads to a loss of spines by inhibiting new spine formation and by mediating the pruning of existing spines.[55,56] Oligophrenin-1, a Rho-GAP, regulates the maturation and plasticity of excitatory synapses by inhibiting Rho activity.[57] Furthermore, p190 RhoGAP modulates spine morphogenesis by regulating Rho GTPase activity.[58] The function of guanine dissociation inhibitors in regulating spine development and plasticity is currently unknown and represents an exciting avenue for future investigation.

Contribution of ABPs to dendritic spine formation and plasticity

Actin binding proteins (ABPs) also play a large role in modulating actin dynamics. Therefore, a number of ABPs, which can localize to the PSD, are known to regulate spine/synapse formation and plasticity via their ability to modulate actin. As already discussed, N-WASP, which promotes polymerization of branched actin filaments through activation of the Arp2/3 complex, induces spine formation and enlargements of spine heads.[46] Knockout of ArpC3, a subunit of the Arp2/3 complex, in forebrain excitatory neurons in mice led to a loss of spines and defects in synaptic plasticity and episodic memory.[59] WAVE1, another WASP family member and an effector of Rac, regulates spine morphology and density as well as synaptic plasticity, and loss of this protein results in deficits in learning and memory.[60,61] Knockdown of cortactin, which also activates the Arp2/3 complex, similarly led to alterations in spine number and morphology.[62] Formins are another class of actin nucleators that are implicated in spine regulation. Formins can be activated by Rho GTPases, but unlike the Arp2/3 complex, formins produce unbranched actin filaments.[63,64] One study demonstrated that mammalian diaphanous-related formin 2 promotes filopodia formation;[65] however, future studies are needed to further explore the role of formins in spine formation and plasticity. Proteins containing WASP homology 2 actin binding domains are a third class of actin nucleators that were most recently identified.[66] Mice lacking Spir-1, the founding member of the WASP homology 2 protein family, have reduced spine density on cortical neurons and exhibit increased fear memory.[67]

Actin remodeling is mediated by other proteins, such as profilin, cofilin, and gelsolin. Profilin promotes actin polymerization by acting as a nucleotide exchange factor, catalyzing ADP to ATP exchange on G-actin, and by binding G-actin and increasing its incorporation into actin filaments.[68,69] Profilin II, a brain-enriched isoform, is associated with stabilization of spine morphology, and blockade of profilin targeting to spines leads to destabilization of spine structure.[70] Interestingly, fear conditioning in rats resulted in profilin redistribution into spines in the lateral

amygdala, which corresponded with an increase in the size of their postsynaptic densities.[71] Mice deficient in profilin II unexpectedly do not have defects in LTP/LTD or learning and memory; however, the number of perforated synapses is increased in the striatum of these mice when compared with wild-type controls.[72] Moreover, conditional knockout of profilin I in the mouse forebrain did not result in significant defects in excitatory synaptic transmission or in spine density or morphology.[73] Because profilin I and II could have overlapping functions, a double knockout will be necessary to decipher the functions of profilin in regulating spine/synapse development and plasticity. Cofilin, which localizes to the PSD,[74] is another key regulator of actin dynamics that binds to and severs actin filaments.[75] Cofilin-mediated actin turnover is important for controlling spine length and morphology.[65] Furthermore, suppression of cofilin activity is important for the stabilization of mature spines.[76] Cofilin localization and activity in spines is modulated by synaptic plasticity.[77,78] In addition, cofilin-mediated actin turnover regulates the size of spine heads during LTP and LTD, and loss of cofilin impairs synaptic plasticity and associative learning.[77,79–81] The activity of gelsolin, which also severs actin filaments, is important for regulating actin turnover during LTD.[39]

Neurabins and developmentally regulated brain protein (drebrin) are additional ABPs that contribute to spine development and plasticity. Two neurabins have been identified to date, ie, neurabin I (NrbI) and neurabin II (NrbII), which is also called spinophilin. NrbI is only expressed in the brain whereas NrbII is expressed in a variety of mammalian tissues, including the brain.[82,83] NrbI regulates dendritic filopodia length, spine formation and maturation, and synaptic plasticity.[84–86] Mice deficient in NrbI have defects in contextual fear memory and LTP, but not in LTD, and display an increase in synaptic transmission.[87,88] In contrast, NrbII-deficient mice have defects in LTD, but not LTP.[87,89] These mice also exhibit a transient increase in spine density during development, resistance to kainate-induced seizures, and an impairment in conditioned taste aversion learning.[89,90] Drebrin is an F-actin binding protein, the expression of which changes from an embryonic (E) isoform to an adult (A) isoform via an alternative splicing mechanism during postnatal development.[91] Drebrin A is highly enriched within dendritic spines in the adult brain where it regulates synaptic transmission.[92] Drebrin is also an important regulator of spine morphology and development.[91,93,94] Drebrin modulates actin dynamics by influencing the interaction of other ABPs, such as cofilin and α-actinin, with actin and by impeding actin-myosin interactions.[95–97] Indeed, controlling the balance between drebrin and cofilin is proposed to be essential for regulating actin dynamics in spines.[98] Other ABPs and regulators also play important roles in dendritic spine development and plasticity, and we refer the reader to other reviews to gain additional insight into their function in spine formation and plasticity.[99–101]

Key receptors and intracellular signaling pathways that modulate dendritic spine morphology and development

Glutamate receptors are key regulators of excitatory synaptic transmission and synaptic plasticity in the brain and have critical functions in learning and memory.[102] Most excitatory synaptic transmission is mediated by two types of ionotropic glutamate receptors, ie, the *N*-methyl-*D*-aspartate receptor (NMDAR) and the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR). Activation of the NMDAR leads to activation of downstream effectors, such as calcium-calmodulin-dependent protein kinase II (CaMKII), reorganization of the actin cytoskeleton, and phosphorylation and insertion of AMPARs into the plasma membrane.[103–105] AMPAR membrane insertion and removal as well as AMPAR trafficking are regulated by the actin cytoskeleton via myosin motors and ABPs, such as cofilin and PICK1, indicating the important role that actin plays in modulating AMPAR localization and function.[80,106–108] AMPAR insertion into the plasma membrane occurs during synaptic strengthening, such as during LTP, whereas AMPAR removal results in weakening of synapses during LTD.[105] Interestingly, LTP promotes the expansion of spine heads whereas LTD leads to spine shrinkage,[109] suggesting a link between spine morphology and synaptic efficacy.

A second class of glutamate receptors, metabotropic glutamate receptors (mGluRs), also contribute to spine morphology and development. The mGluRs are G-protein coupled and subdivided in three groups: group 1 includes mGluR1 and 5, group 2 consists of mGluR 2 and 3, and group 3 contains mGluR 4, 6, 7, and 8.[110] PSD scaffolding proteins, including Homer and Shank, interact and regulate the activity of group 1 mGluRs.[111,112] Moreover, stimulation of group 1 mGluRs results in a significant increase in dendritic spine length, indicating these receptors regulate spine morphology.[113] The role of mGluRs in spine formation is currently not clear. In one study, mGluR5 knockout mice exhibited a decrease in spine density in cortical layer IV neurons whereas in another study mGluR5 knockout mice

had an increased number of spines.[114,115] Future studies are needed to determine the function of mGluRs in modulating spine formation.

Calcium signaling within dendritic spines is an important mechanism for regulating spine morphology as well as synaptic plasticity and function.[116] Spines can maintain different concentrations of free intracellular calcium than those found in dendritic shafts, indicating that they can serve as individual calcium compartments.[117,118] The calcium concentration in dendritic spines can be regulated by NMDAR channels, by voltage-gated calcium channels, and by release of calcium from internal stores.[6] Intracellular calcium can transduce a signal by activating a number of calcium-dependent kinases, including CaMKII. CaMKII is a major component of the PSD within spines and has a central role in synaptic plasticity as well as learning and memory.[119] Moreover, a CaMKII isoform, CaMKIIβ, can bind directly to F-actin within spines,[120] providing a link between CaMKII signaling and the actin cytoskeleton.

Other membrane receptors are found in spines and influence their morphology and development. Plexin B1 and its ligand semaphorin 4D promote spine formation and changes in spine morphology through a RhoA/Rho-associated kinase pathway.[121] Semaphorin 3F, and its receptors neuropilin-2 and Plexin A4, regulate spine morphogenesis and spine size.[122] EphB receptor signaling is also critical for spine formation. Mice deficient in EphB1, EphB2, and EphB3 have decreased spine density, abnormal spine morphology (ie, very small or no spine heads), and reduced dendritic filopodia motility.[123,124] EphB receptors regulate spine development through a kalirin (GEF)/Rac/PAK pathway and an intersectin (GEF)/Cdc42/N-WASP pathway.[125,126] The neuregulin (Nrg)-1 receptor ErbB4 regulates spine size and AMPA-mediated synaptic transmission.[127] Loss of ErbB2/B4 in mice causes defects in spine maturation and behavioral abnormalities that include increased aggression and decreased prepulse inhibition, which are observed in schizophrenic patients.[128] These phenotypes are rescued by treatment with clozapine, an antipsychotic drug used to treat schizophrenia.[128] Nrg-1/ErbB4 signaling also modulates spine formation by a kalirin-dependent mechanism.[129]

Dendritic spine and synapse defects associated with neurological disorders

A number of neurological disorders, including schizophrenia, AD, autism spectrum disorder, and Down syndrome, are associated with abnormalities in the number, morphology, and plasticity of dendritic spines and synapses. Schizophrenia is a spectrum disorder, which usually develops in late adolescence or early adulthood, and is characterized by impairments in cognition, perception, and motivation.[130] In patients with schizophrenia, a reduction in spine density is observed within various brain regions such as the prefrontal cortex, the temporal cortex, the striatum, and pyramidal neurons in the hippocampus.[131–135] On the other hand, an increase in spine density is seen in the caudate and putamen patch of patients with schizophrenia.[136] Interestingly, alterations in some of the genes/proteins that regulate spine morphology and development, as discussed above, are associated with schizophrenia. *NRG1* and *ErbB4* are susceptibility genes for schizophrenia, and multiple postmortem studies show aberrant Nrg-1/ErbB4 signaling in the brains of schizophrenic patients.[137–139] Disrupted in schizophrenia 1, which regulates Rac activity through its interaction with the GEF kalirin-7, is also a schizophrenia susceptibility gene (Figure 2).[140,141] Moreover, patients with schizophrenia have reduced kalirin messenger (m)RNA levels in their dorsolateral prefrontal cortex, and missense mutations in kalirin have been identified in schizophrenic patients.[142,143] Cdc42 mRNA levels are lower in patients with schizophrenia, whereas mRNA levels of the Cdc42 effector protein 3 (Cdc42EP3) are increased.[142,144] Cdc42EP3 binds septins and regulates septin organization, and Cdc42 inhibits this interaction.[145] Therefore, the aberrant expression of Cdc42 and Cdc42EP3 in schizophrenia is proposed to affect opening of the septin barrier in spine necks, in response to glutamate stimulation, which alters molecular diffusion and trafficking between spines and the parent dendrites and leads to impaired synaptic plasticity and spine loss.[144] The expression of PSD95, an important scaffolding protein in spines, is also altered in schizophrenic patients.[146] Intriguingly, dysbindin, a schizophrenia susceptibility gene, was recently reported to modulate spine dynamics and maturation.[147]

AD is a neurodegenerative disease that results in cognitive decline, and usually begins at around 65 years of age. In patients with AD, a significant loss of spines and synapses is seen in the hippocampus and cortex, which are areas of the brain that are significantly affected by AD pathology.[38,148] Current data indicate that spine and synapse loss is an early event in AD that precedes neuronal death.[38,149] As with schizophrenia, actin regulators and binding proteins are linked to AD. Cofilin aggregates and actin-cofilin rods are found in the brains of AD patients; these abnormal structures could hinder molecular transport and trafficking in neurons, which could contribute to synaptic loss.[97,150] Moreover, AD patients have

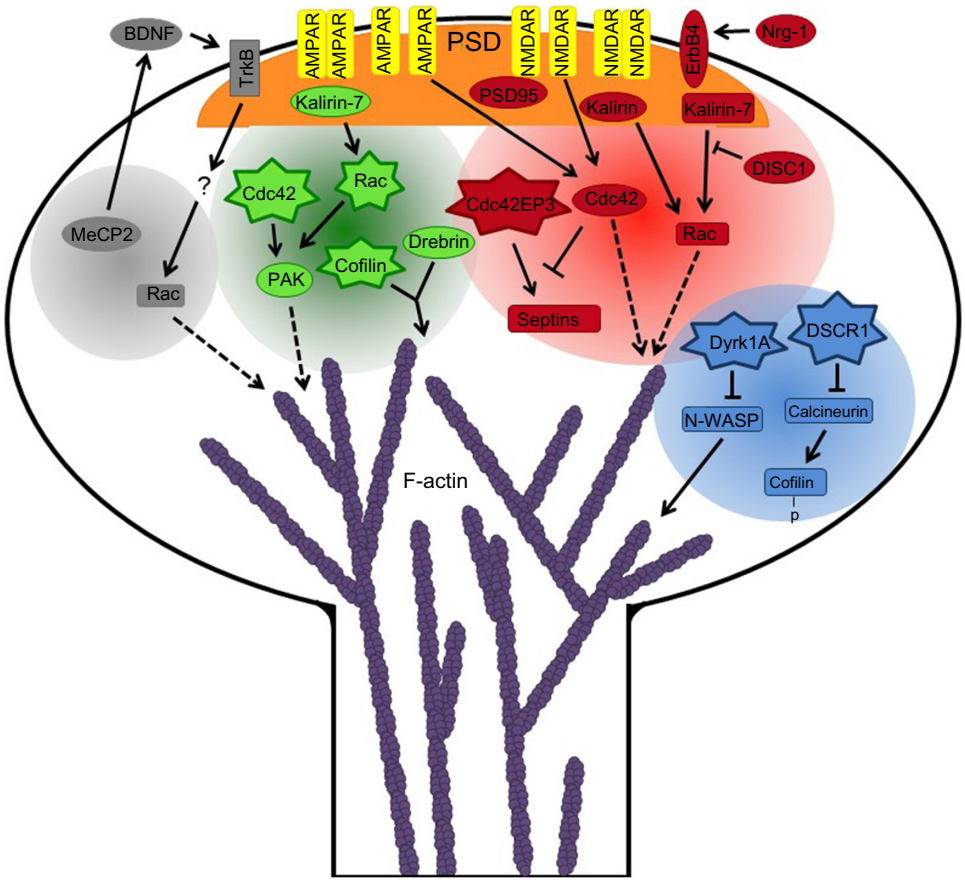

Figure 2 Schematic of molecular pathways underlying spine defects in several neurological disorders. The neurological disorders include Down syndrome (blue circle), schizophrenia (red circle), Alzheimer's disease (green circle), and Rett's syndrome (gray circle). Star shapes indicate upregulation of mRNA and/or protein levels or increased activation of proteins. Ovals represent susceptibility genes (Nrg-1, ErbB4, and DISC1), downregulation of mRNA and/or protein levels, loss-of-function mutations (MeCP2), or mislocalization/dysregulation (PAK). Dashed lines show proteins that regulate actin dynamics through downstream effectors. p-cofilin indicates phosphorylated-cofilin (inactive cofilin).

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; DISC1, disrupted in schizophrenia 1; Dyrk1A, dual-specificity tyrosine-phosphorylation-regulated kinase 1A; MeCP2, methyl CpG binding protein 2; NMDAR, *N*-methyl-*D*-aspartate receptor; N-WASP, neural Wiskott-Aldrich syndrome protein; PAK, p21-activated kinase; Nrg-1, neuregulin-1; Cdc42EP3, Cdc42 effector protein 3; PSD, postsynaptic density; PSD95, postsynaptic density protein 95; DSCR1, Down syndrome critical region 1.

reduced hippocampal levels of drebrin, which could disrupt the balance between drebrin and cofilin and lead to aberrant actin dynamics and synaptic dysfunction.[93,151] In AD, Rac and Cdc42 are upregulated, and their effector PAK is mislocalized or dysregulated in AD patients (Figure 2).[97,152,153] Furthermore, kalirin-7 expression is altered in the hippocampus of AD patients, which could also contribute to the aberrant spine and synapse phenotype.[154]

Rett syndrome (RTT) is an X-linked autism spectrum disorder associated with intellectual disability that affects neurodevelopment beginning in early childhood.[155] RTT is caused by loss-of-function mutations in *MeCP2*, which encodes the transcriptional regulator methyl CpG binding protein 2 (MeCP2), as many patients with RTT harbor *MeCP2* mutations.[156,157] Moreover, deletion of MeCP2 in central nervous system neurons results in an RTT-like phenotype in mice.[158] Defects in spines may contribute to RTT, as a decrease in spine number is observed in cortical regions of the brains of RTT patients.[159] In addition, a significant decrease in spine density is seen in hippocampal pyramidal neurons in RTT patients.[160] The aberrant spine development in RTT may be linked to MeCP2, because mice lacking MeCP2 exhibit a reduction in spine density in the motor cortex and hippocampus.[161] One of the transcriptional targets of MeCP2, brain-derived neurotrophic factor (BDNF), and its receptor TrkB, also regulate spine development and plasticity.[162,163] Furthermore, RTT patients have decreased levels of BDNF mRNA, and overexpression of BDNF can rescue some of the neuronal and behavioral phenotypes seen in MeCP2 knockout mice, suggesting a function for BDNF signaling in RTT.[164,165] Although the specific mechanisms by which BDNF signaling contributes to RTT are currently unknown, it is tempting to speculate that Rho GTPases are involved (Figure 2). BDNF modulates spine formation and plasticity

by a Rac-dependent mechanism, and regulation of the activity of the Rho GTPases by bacterial cytotoxic necrotizing factor 1 dramatically improves the behavioral phenotypes, including cognitive defects, in a mouse model of RTT.[166,167] However, future investigation will be necessary to determine if Rac or other Rho family GTPases are involved in RTT.

Down syndrome is an intellectual disorder that results from a partial or full additional copy of chromosome 21. A region within chromosome 21, termed the Down syndrome critical region (DSCR), is thought to be responsible for some or possibly all of the features associated with Down syndrome.[168] Two genes, *DSCR1* and *DYRK1A*, within this region are of particular interest because their increased expression in mice can recapitulate some Down syndrome phenotypes.[169] *DYRK1A* encodes dual-specificity tyrosine-phosphorylation-regulated kinase 1A (Dyrk1A), which regulates spine formation and actin dynamics (Figure 2). Overexpression of Dyrk1A in hippocampal neurons causes a significant decrease in spine density by inhibiting N-WASP-mediated actin polymerization.[170] Furthermore, cortical neurons from Dyrk1A transgenic mice exhibit a reduction in spine density and aberrant spine morphology due to altered actin dynamics.[171] This is consistent with the reduction in spine number and altered spine morphology seen in patients with Down syndrome.[172,173] *DSCR1* encodes DSCR1 protein (also termed RCAN1), which interacts with Fragile X mental retardation protein to regulate spine morphogenesis.[174] In addition, DSCR1 inhibits the calmodulin-dependent phosphatase calcineurin, and DSCR1 knockout mice have increased calcineurin activity and defects in spine density, synaptic plasticity, and learning and memory.[175] DSCR1 transgenic mice display Down syndrome-like defects in learning and memory, impaired synaptic plasticity, and reduced spine density.[176] Alterations in actin dynamics may underlie the spine defects as calcineurin dephosphorylates and activates cofilin, which severs actin filaments.[75,177]

Remaining knowledge gaps and ongoing research

Although progress has been made over the last few decades in understanding spine development, function, and plasticity, many questions remain. For example, what are the molecular mechanisms that designate a spine to be maintained or pruned? Are the signaling cascades in individual spines that modulate their remodeling and plasticity conserved or unique? What are the key players that regulate spine dynamics as synapses are forming and maturing? Much of our knowledge regarding spine development has been obtained using fixed samples; however, to answer these and other important questions, spine development must be investigated as a real-time process. Moreover, the importance and potential difference in individual spines is increasingly being recognized, making it essential to study spines on an individual basis to understand how they integrate to form circuits. As imaging and other technologies advance, the possibility of investigating individual spines is becoming more feasible. Optogenetic approaches, for instance, may permit selective spine activation to study individual spine dynamics.[178] Hopefully, these and other technological developments will pave the way to understanding how individual spines contribute to complex neuronal circuits and ultimately behavior.

Conclusion

In this review, we have summarized some recent insights into spine formation, function, and plasticity. We have highlighted the significance of actin remodeling in these processes and discussed some key actin regulators in dendritic spines. We have also discussed the contribution of crucial synaptic receptors and intracellular signaling pathways to spine development and plasticity. Because of the central role that spines play in cognitive function, defects in their development are associated with a number of neurological disorders, such as schizophrenia, AD, autism spectrum disorder, and Down syndrome. We have outlined the spine/synapse defects associated with these disorders and what is known about the underlying molecular mechanisms that contribute to them. Finally, we have provided insight into some important unanswered questions regarding spines and how addressing these questions will shape the future of dendritic spine research.

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Disclosure

The authors report no conflicts of interest in this work.

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