Regulation of Dendrite and Spine Morphogenesis and Plasticity by Catenins

Jyothi Arikkath

Abstract The appropriate regulation of dendrite, spine, and synapse morphogenesis in neurons both during and after development is critical for the formation and maintenance of neural circuits. It is becomingly increasingly clear that the cadherin–catenin cell adhesion complex, a complex that has been widely studied in epithelia, regulates neuronal morphogenesis. More interestingly, the catenins, cytosolic proteins that bind to cadherins, regulate multiple aspects of neuronal morphogenesis including dendrite, spine, and synapse morphogenesis and plasticity, both independent of and dependent on their ability to bind cadherins. In this review, we examine some of the more recent and exciting studies that implicate individual catenins in various aspects of neuronal morphogenesis and plasticity.

Keywords Catenins · Neurons · Dendrite · Spine · Synapse · Plasticity

Introduction

Neurons in the various regions of the brain are morphologically distinct, a property that correlates their physiological functional roles. Most neurons have elaborate dendritic arbors. Appropriate dendritic arborization is necessary to ensure accurate information input and transfer, since dendrites are electrochemical compartments that serve integral roles in neuronal computation [1]. In the hippocampus, mushroom-shaped protrusions arise on dendrites.

These are spines and are the sites of excitatory synapse formation. Moreover, spines are not static structures, but are plastic and respond by changes in structure to a variety of physiological cues [2].

The pattern of dendritic arborization is critical, since it regulates the composition of neurotransmitter receptors and ion channels and the density of synapses. Dendritic patterns influence the synaptic inputs that a neuron can receive and affect the processing of synaptic input. A neuron receives multiple inputs and only once the integrated input brings the membrane potential to the threshold is an action potential fired resulting in neurotransmitter release. This integration is determined by the pattern of dendritic arborization, the history of neuronal excitability, and the synaptic inputs. Consequently, alterations in dendritic branching can perturb neural network organization and lead to neural circuit dysfunction. The formation of dendritic arbors and synapses are hence tightly regulated by both intrinsic and extrinsic cues. Our understanding of the pathways by which neurons respond to these cues and convert them to structural and functional alterations remains incomplete.

Synapses are highly specialized cell–cell contact sites and mediate directional information transfer. The presynaptic terminal, formed on axons, includes the machinery for neurotransmitter release, while the postsynaptic sites include neurotransmitter receptors, scaffolding proteins, and signaling proteins that promote response to the released neurotransmitter and hence allow the flow of information.

Spines and synapses are not static structures but are capable of altering synaptic communication in response to synaptic activity. This is a key property that underlies the balance of neural networks and also learning and memory. Clearly, our ability to understand the molecular basis of learning and memory requires an understanding of the structure and plasticity of synapses and spines.

J. Arikkath (✉)
University of California San Francisco,
San Francisco, CA 94143, USA
e-mail: Jyothi.arikkath@ucsf.edu

Structural and functional abnormalities in dendrites and synapses are associated with a number of human neurological disorders including Alzheimer's disease [3], mental retardation syndromes [4], and autism.

The cadherin–catenin cell adhesion complex mediates cell adhesion in epithelial cells where their functions have been extensively investigated [5]. It is now clear that the components of the complex are expressed in neurons and are critical in regulating dendritic and synaptic architecture and plasticity. Components of the cadherin–catenin complex play vital roles in both dendritic arborization and in the structure and function of spines and synapses. Some of these functional roles are independent of their ability to bind cadherins and depend on their ability to regulate other intracellular proteins. Although catenins regulate both dendrite and spine morphogenesis, which ultimately requires the regulation of the actin cytoskeleton, the underlying mechanisms are presumably different. We do not yet have a clear understanding of the entire pathways that link the catenins to the actin cytoskeleton, although several studies implicating a number of intermediate effectors are beginning to emerge. Moreover, recent studies have implicated roles for microtubules in spine morphogenesis [6–8]; however, the role of catenins in microtubule mediated spine morphogenesis remains unclear. In this review, we discuss some of the new and exciting data that demonstrate crucial roles for the cytosolic catenins in dendrite, spine, and synapse morphogenesis, in particular in hippocampal neurons.

The Cadherin–Catenin Cell Adhesion Complex at Synapses

The cadherin–catenin cell adhesion complex is expressed in neurons and the roles of the components of the complex are beginning to be understood. This complex includes the transmembrane domain containing cadherins and the catenins. The catenins are cytosolic proteins that bind to the intracellular domains of classical cadherins (Fig. 1). Through interactions of the catenins with multiple intracellular effectors, this complex controls a variety of intracellular signaling pathways. Since the cadherins and their roles in neuronal morphogenesis have been extensively reviewed [9, 10], this review is restricted to the functional roles of the catenins in neuronal morphogenesis and plasticity.

The cadherins include multiple family members with distinct expression patterns in central neurons [11]. The family comprises of more than 80 members and have been classified into several subfamilies including classical cadherins, protocadherins, Fat cadherins, cadherin-related neuronal receptors, and seven-pass transmembrane cadherins [12]. Various cadherins have been implicated in multiple
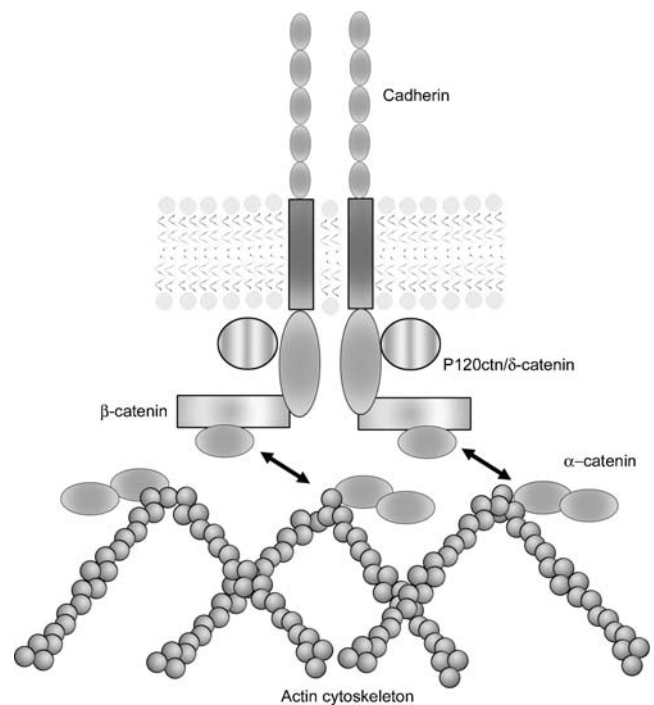
Fig. 1 Schematic of the cadherin–catenin cell adhesion complex: Cadherins are transmembrane domain containing proteins that mediate homophilic adhesion. Intracellularly, they are linked to a variety of catenins, α-catenin, β-catenin, and members of the p120ctn of proteins, which also provide a link to the actin cytoskeleton

aspects of neuronal development and morphogenesis [13–17]. N-Cadherin, a member of the classical cadherin family, is the most widely distributed cadherin in neurons with a distinct pattern of expression during development. At nascent synapses, N-cadherin is evenly distributed along the synapse while in mature synapses, it is clustered at the active zone in vitro. At mature hippocampal mossy fiber CA3 synapses, N-cadherin is localized to *puncta adherentia*, distinct regions bordering the active zone [18].

The Catenins

Catenins are cytosolic binding partners of the cadherins. Catenins are classified into three distinct families. The α-catenin family including three members (αN-catenin, αE-catenin, and αT-catenin), the β-catenin family including β-catenin and plakoglobin, and the p120ctn family of catenins. The p120ctn family consists of four distinct family members—δ-catenin (also known as neurojungin/neural plakophilin-related arm protein), p120ctn, Armadillo repeat gene deleted in velocardiofacial syndrome (ARVCF), and p0071.

In addition to cadherins, the catenins bind to a variety of proteins, including PDZ domain containing proteins,

effectors of the actin cytoskeleton, protein kinases, and protein phosphatases. This increases the repertoire of interactions that the complex is capable of and hence, the complex can modulate multiple signaling pathways.

At the cellular level in neurons, the distribution of αN-catenin and β-catenin [19] is similar to that observed for N-cadherin. P120ctn is localized to both membrane and cytosolic fractions in neurons and associated with N-cadherin [20], although there are alterations in this association during development. δ-Catenin is expressed almost exclusively in the nervous system [21] and at the cellular level is observed in both dendrites and synapses in hippocampal neurons [22, 23]. The distribution of ARVCF and p0071 in the nervous system remains unexplored.

Catenins modulate cadherin-based adhesion [24, 25], trafficking of cadherin [26], surface stability of cadherin [27], and modulation of intracellular signaling pathways [28, 29].

α-Catenin

The α-catenins are encoded by three different genes. The products of these genes include αN-catenin which shows a neural specific expression pattern, αE-catenin that is predominantly expressed in epithelia and αT-catenin that is expressed in the heart. Structurally, the N-terminal region of α-catenin includes the β-catenin binding domain and a dimerization domain, while the C terminus includes an actin binding site. In addition to binding actin, α-catenin binds multiple actin-binding proteins including eplin, vinculin, and formins; thus, it is capable of regulating the actin cytoskeleton by a variety of different pathways.

In contrast to the classical model of the cadherin–catenin cell adhesion complex, in which α-catenin was postulated to bind to the actin cytoskeleton and β-catenin simultaneously, recent studies [30, 31] indicate that the binding of α-catenin to the actin cytoskeleton and β-catenin are mutually exclusive. The monomeric form of α-catenin binds to β-catenin while the dimeric form has preferential affinity for actin. However, since αN-catenin can bind to a number of actin-binding proteins, including α-actinin, spectrin, vezatin, and vinculin, it can still link to and regulate the actin cytoskeleton in association with the cadherin–catenin complex.

In hippocampal neurons, the genetic loss of αN-catenin enhances spine mobility leading to the formation of immature filopodial-like spines with reduced stability [32]. In contrast, the overexpression of αN-catenin promotes an increase in the spine density and stability, concomitant with an increase in synapse density. Overexpression of α-catenin also promotes an increase in the spine headwidth [32]. Mechanistically, the ability of αN-catenin to regulate

spine dynamics and stability requires the presence of domains required for binding to β-catenin and various cytoskeletal proteins [32]. Surprisingly, at the ultrastructural level, hippocampal synapses in the cdf/cdf mice, a spontaneous mouse mutation that has a genetic deletion that includes the αN-catenin gene, appear normal [33].

αN-Catenin is relocalized in response to synaptic activity. In hippocampal neurons, tetrodotoxin (a blocker of the voltage gated sodium channels) promotes the removal of αN-catenin from synapses while bicuculline (a gamma-aminobutyric acid receptor antagonist) promotes its synaptic accumulation. In addition to promoting spine stability, overexpression of αN-catenin also inhibits tetrodotoxin-induced spine lengthening, suggesting that αN-catenin may function as a mediator for converting activity-dependent signals to structural plasticity of spines [32].

In contrast to its effects on spine dynamics, the effects of overexpression of αN-catenin on dendritic branching are less clear. In one case, it was reported that overexpression of αN-catenin does not lead to any obvious changes in dendritic architecture or branching [32, 34]; however, other reports indicate that overexpression of αN-catenin promotes dendritic branching [35]. The reason for this discrepancy is unclear, but might reflect differences in the stages of development.

Given the compromise in spine stability in the absence of αN-catenin, one might predict that hippocampal learning might be compromised in mice that lack αN-catenin. In the cdf/cdf mice, fear conditioning and prepulse inhibition of the startle response are perturbed [33].

In summary, although α-catenin links to the actin cytoskeleton and β-catenin and hence the cadherin–catenin cell adhesion complex, independently it does bind to a number of effectors of the actin cytoskeleton. The identity and roles of these effectors on the ability of α-catenin to regulate dendrite and spine morphogenesis in neurons remains unclear.

β-Catenin

β-Catenin is a multifunctional protein required for cadherin-based adhesion and regulation of transcription via the Tcf/Lef and additional transcription factor-mediated pathways. Although well studied in epithelia, the functional roles of β-catenin in neurons is only beginning to be understood. Structurally, β-catenin includes N- and C-terminal regions that flank a series of 12-arm repeats. The C-terminal region of β-catenin includes a PDZ binding motif that enables it to interact with a variety of synaptic scaffolding proteins, including synaptic scaffolding molecule (S-SCAM) [36].

β-Catenin regulates multiple aspects of neuronal morphogenesis including dendritic arborization, spine structure, and synaptic function. Conditional deletion of β-catenin in newborn neurons in the postnatal dentate gyrus results in their failure to develop extensive dendritic trees and the resulting neurons have short dendritic arbors and do not mature into granule neurons [37]. It is not entirely clear how β-catenin mediates this functional role.

The effects of β-catenin on dendritic arborization vary during development. In hippocampal neurons, overexpression of a stabilized form of β-catenin that is resistant to degradation promotes dendritic branching [35] (DIV 7–9). Although a similar effect is seen at later stages (DIV 10–12), the increase in branching is not as dramatic as observed in the earlier stages [38]. Similar effects are observed in neurons expressing an intracellular domain of cadherin, which is capable of sequestering β-catenin. This functional role of β-catenin in promoting dendritic morphogenesis is independent of its ability to regulate transcription via the Tcf/Lef pathway. Activity-dependent enhancement of dendritic growth is dependent on β-catenin and Wnt signaling.

In addition to its effects on dendritic arborization, overexpression of the stabilized form of β-catenin at DIV 10–12 increases the density of dendritic spines and filopodia [38].

Postsynaptic deletion of β-catenin, using the cre-loxP removal of β-catenin in cultured hippocampal neurons, results in alterations in spine morphology with the spines becoming thin and elongated. Functionally, postsynaptic deletion of δ-catenin also results in a reduction in the amplitude of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated miniature excitatory postsynaptic currents (mEPSCs) and inhibition of activity dependent bidirectional scaling of mEPSC amplitude. These changes are not accompanied by any changes in the frequency of the mEPSCs or synapse density [39]. The reduction in the amplitude of the glutamatergic response requires the ability of β-catenin to mediate interactions via its central arm repeats with cadherin and with PDZ domain containing proteins via its C-terminal region.

Overexpression of β-catenin reduces the amplitude of mEPSCs. Synaptic activity results in a reduction of mEPSC amplitude and this effect is reversed by the postsynaptic expression of a construct that sequesters β-catenin [40].

β-Catenin is also an important mediator of presynaptic assembly. Deletion of β-catenin from hippocampal neurons results in a decrease in the number of reserve pool vesicles at the synapse and impairments in response to prolonged repetitive stimulation. In in vitro studies using cultured hippocampal neurons, loss of β-catenin leads to a dispersion of vesicles along the axon. Mechanistically, this functional role of β-catenin requires both the domains that mediate its association with cadherins and PDZ-containing proteins [41].

Activity induces the relocalization of β-catenin from dendritic shafts to spines and increases its association with cadherins [42]. The association with cadherins and the activity-dependent phosphorylation are dependent on the phosphorylation of β-catenin at residue tyrosine-654, in a cdk5-dependent manner [43], since a mutation in β-catenin that prevents it from being phosphorylated is concentrated in spines while a constitutively phosphorylated form is distributed in the shaft. Concentration of β-catenin in spines leads to an increase in the size of synaptic clusters and an increase in synaptic activity.

Brain-derived neurotrophic factor (BDNF), a neurotrophin, is critical for synaptic plasticity and mice that lack BDNF have impairments in the induction of long term potentiation [44]. Using synaptophysin green fluorescent protein (GFP) as a marker for presynaptic vesicles, recent studies have shown that BDNF promotes the mobility of synaptic clusters and an increase in synaptic numbers [45]. Interestingly, BDNF promotes the phosphorylation of β-catenin and its subsequent dissociation from cadherin. Preventing the phosphorylation of β-catenin inhibits the increased mobility of vesicles and increased synaptic density in response to BDNF. These results point to a potentially critical role for β-catenin in the regulation of synaptic morphology in response to synaptic activity.

Activity-dependent gene expression is an important component of synaptic plasticity [46]. In response to synaptic activity, β-catenin is cleaved by calpain at the N terminus and the resulting fragment including the more C-terminal region of β-catenin is resistant to degradation mediated by the GSK3 β/ubiquitin/proteosome pathway [47]. This fragment translocates to the nucleus and is able to activate Tcf-dependent gene transcription and upregulate the Fosl1 gene. In vivo, Fosl1 is upregulated in response to learning behavior, suggesting that β-catenin can transcriptionally regulate genes involved in learning. Clearly, other genes must be regulated by β-catenin in this manner and remain to be identified.

Recent studies implicate a role for β-catenin in amygdala-dependent learning and memory [48]. Fear conditioning in mice leads to an increase in the transcription, but not total protein levels, of β-catenin in the amygdala. Although the total protein level of β-catenin remains unaltered under these conditions, there is a GSK-3β-dependent increase in its phosphorylation at Tyr654, which in turn leads to a decrease in affinity for cadherin. Physiologically, β-catenin is necessary for the consolidation of fear memory, but is not necessary for its acquisition.

The effectors that allow β-catenin to link to the actin cytoskeleton in neurons is not entirely clear, although several such effectors are known in nonneuronal cells. One obvious candidate is α-catenin. Although α-catenin binds mutually exclusively to β-catenin and the actin cytoskeleton directly, it interacts with a variety of actin binding

proteins and could link β-catenin to the actin cytoskeleton via these proteins. The mechanisms that regulate the ability of β-catenin to modulate the actin cytoskeleton and dendrite and spine morphogenesis remain to be dissected.

p120ctn

Multiple isoforms of p120ctn are known to exist; however, their relative distributions in central neurons and contributions to physiological functions in neurons is not entirely clear [49]. Structurally p120ctn has N- and C-termini that flank a series of armadillo repeats. A putative nuclear localization signal is localized within the arm repeats. In neurons, p120ctn is localized at synaptic contacts during development. In chick ciliary neurons, p120ctn is colocalized with N-cadherin and β-catenin during development. However, in more mature contacts, p120ctn and β-catenin were replaced by presenilin and γ-catenin [50]. It is unclear how these alterations in associations translate to physiological function.

In cultured hippocampal neurons, p120ctn is localized to both membrane and cytosolic fractions. During the initial stages of development, p120ctn is localized to cell bodies and growth cones [20]. As development proceeds, a proportion of the p120ctn is colocalized with the presynaptic marker, synaptophysin at synaptic structures (DIV 7), and this proportion slightly reduces as development proceeds (DIV 14). Similarly, p120ctn is partially colocalized with synaptophysin in the mouse hippocampus. Interestingly, the localization of p120ctn appears to be both at presynaptic and postsynaptic sites.

In addition to its interaction with cadherin, p120ctn interacts with a number of proteins including fer [51], fyn [52], kinesin [53], PTP-μ, and cortactin [54]. The roles of some of these interactions, including Fer [55], in neurons are beginning to be understood; however, much remain to be explored.

Functionally, the loss of p120ctn in a murine model leads to a severe reduction in dendritic branching in vitro [56]. In addition, loss of p120ctn leads to a severe reduction in spine and synapse density, with accompanying changes in spine morphology, both in vivo and in vitro. In the hippocampus of mice that lack p120ctn, there is a severe reduction in the density of psd95 and synaptophysin puncta indicating a severe reduction in synaptic number. In hippocampal neurons from mice that lack p120ctn, there is a 50% reduction in spine density. This functional role of p120ctn in regulating spine density appears to be independent of its ability to bind cadherin, at least in vitro, since a construct of p120ctn that lacks the ability to bind cadherin is effective in restoring spine density in cultured neurons that lack p120ctn. However, a mutant form of p120ctn that lacks the ability to regulate Rho is unable to restore the spine density. Consistent with this, hippocampal lysates from p120ctn deleted neurons have reduced Rac1 and increased RhoA activity [56]. In addition to spine density, loss of p120ctn from cultured neurons also results in a reduction in the spine headwidth and spine length. The ability of p120ctn to regulate spine headwidth requires its ability to regulate Rho and cadherin, while the ability to regulate Rho is sufficient to influence spine length.

Recent studies indicate that in addition to its effects on spines and dendrites, p120ctn also regulates presynaptic assembly [55]. Cre-mediated knockdown of p120ctn in hippocampal cultures from p120ctn flox/flox mice leads to perturbations in presynaptic assembly as indicated by diffused localization of synaptophysin–GFP (a presynaptic marker) puncta. Interestingly, this functional role of p120ctn is mediated by its ability to be associated with the nonreceptor tryrosine kinase Fer, since either peptide mediated perturbation of the interaction between p120ctn and fer or overexpression of a mutant form of p120ctn that lacks the fer binding site leads to a similar diffused localization of synaptophysin–GFP.

Considering the ability of p120ctn to regulate dendrite morphogenesis, spine and synapse density and morphogenesis, and presynaptic assembly, it is highly conceivable that loss of p120ctn in the murine model might lead to deficits in plasticity with learning and cognitive abnormalities. This hypothesis remains to be examined.

In summary, the ability of p120ctn to regulate both dendrite and spine morphogenesis is consistent with its ability to influence the activity of the small GTPases. P120ctn is also known to regulate microtubule dynamics [57]; however, the contribution of this regulation to spine dynamics remains unclear.

δ-Catenin

The distribution of δ-catenin is predominantly restricted to the nervous system [21]. The structure of δ-catenin is similar to that of p120ctn. Unlike p120ctn, δ-catenin includes a PDZ-binding motif at the C terminus that permits it to associate with a variety of PDZ domain containing proteins including erbin, densin-180, plakophilin-related armadillo-repeat protein-interacting protein, S-SCAM, AMPA receptor binding protein (ABP), and GluR-interacting protein (GRIP) [23, 58–61].

δ-Catenin was originally identified by virtue of its association with presenillin, a gene that has been widely associated with Alzheimer's disease [62, 63]. δ-Catenin is one of the genes lost in the genetic deletion associated with the Cri-du-chat mental retardation syndrome. Interestingly, the loss of δ-catenin correlates with the severity of mental retardation [64,

65]. Recent studies indicating roles for δ-catenin in dendrite [22, 66], spine, and synapse [67] morphogenesis suggests that loss of δ-catenin may perturb neural circuit formation and/or maintenance and may contribute to the pathology of the mental retardation phenotype.

Similar to some of the other catenins, δ-catenin influences dendritic morphology, spine and synaptic structure and plasticity. Overexpression of δ-catenin leads to an increase in dendritic branching [66, 68]. Conversely, loss of δ-catenin in a murine model leads to a reduction in dendritic branching [22]. Erbin, a member of the leucine-rich and PDZ family of proteins, is upstream of δ-catenin in regulating dendritic branching and δ-catenin mediates its effects on the actin cytoskeleton via its C-terminal region. The C-terminal region of δ-catenin binds cortactin, a protein that is known to regulate the actin cytoskeleton; however, it is not entirely clear if this functional effect is mediated by cortactin. Unlike p120ctn, loss of δ-catenin does not lead to global alterations in the levels of active Rac and Rho in neurons from δ-catenin null mice [22], suggesting that p120ctn and δ-catenin may regulate dendritic morphogenesis via different mechanisms.

Overexpression of δ-catenin in hippocampal neurons (DIV21) leads to an increase in the number of protrusions along the dendrite [68, 69] and siRNA mediated inhibition of δ-catenin leads to a decrease in the spine and synapse density [69]. However, this effect is probably stage specific, since shRNA knockdown of δ-catenin at earlier stages (DIV 11–17) leads to an increase in spine and synapse density [70]. In Chinese hamster ovary cells, overexpression of δ-catenin leads to an increase in the activation of Rac and Cdc42 with a concomitant decrease in the activation of Rho [69]. However, slightly different results have been observed upon overexpression of δ-catenin in mouse embryonic fibroblasts in which there was an increase in the level of active RhoA with no effect on the activity of Rac and Cdc42 [71]. It is unclear how Rac and Rho exactly contribute to the alterations in dendritic and spine morphogenesis in hippocampal neurons, since loss of δ-catenin in the δ-catenin null mice does not lead to global alterations in the levels of active Rac and Rho [22]. However, since this murine model does not represent a complete null and still retains an N terminal fragment, which has been suggested to be important in the interaction of δ-catenin with p190RhoGEF and subsequent regulation of Rho, it is possible that the retained fragment is still functional. Since dendritic deficits are observed in neurons from δ-catenin null mice [22], this suggests that δ-catenin can regulate dendritic branching independent of alterations in the global levels of active Rac and Rho, but it does not exclude local effects on Rac and Rho activity at synapses.

In addition to its effects on dendritic and spine morphogenesis, δ-catenin has been implicated in the trafficking of AMPA receptor subunits [23, 67]. δ-Catenin interacts with the ABP and the GRIP through PDZ-mediated interactions. Overexpression of δ-catenin in organotypic hippocampal slices increases AMPA receptor mediated EPSCs, but not those mediated by N-methyl D-aspartate (NMDA) [67]. In association with GRIP, over-expression of δ-catenin promotes the surface expression of GluR2 in neurons. Conversely, RNAi-mediated suppression of the expression of δ-catenin leads to a decrease in the levels of surface GluR2, however, this does not lead to any alterations in the AMPA/NMDA ratio.

δ-Catenin is associated in a complex with a number of synaptic scaffolding proteins. δ-Catenin can also regulate the surface expression of GluR via its ability to bind ABP/GRIP and be anchored to the membrane via its interaction with cadherin. The ability of δ-catenin to bind to cadherin promotes its association with synaptic sites where it can then recruit ABP and GRIP which then regulate the localization of the GluR2 subunits [23].

Mice that lack δ-catenin have severe deficiencies in spatial learning and impairments in cognitive function [72]. Although these mice have normal baseline synaptic transmission at CA3–CA1 synapses, they have reduced short-term potentiation and nonlinear responses to protocols that induce long-term potentiation. However, these changes are not accompanied by any obvious structural changes at synapses. This mouse model still retains an N-terminal fragment of δ-catenin, so it is not entirely clear if similar or more severe deficits would be observed with mice that are completely devoid of expression of δ-catenin.

In summary, although δ-catenin can regulate the activity of the small GTPases, it remains unclear if this is the primary mechanism by which δ-catenin influences the actin cytoskeleton and dendrite and spine morphogenesis (Table 1).

ARVCF and p0071

ARVCF and p0071 are the least understood catenins, although expression of each has been detected in the nervous system. Similar to δ-catenin, both of these family members include a PDZ binding motif and have been shown to interact with synaptic PDZ containing proteins [58, 61, 73–75]; however, the functional relevance of these interactions and their contributions to neuronal morphogenesis remains unclear.

Future Directions

It is clear that the catenins are important mediators of neuronal morphology and function. It is becomingly increasingly clear that they have functional roles in

Table 1 Effects of loss of function or overexpression of catenin on dendrites, spines, and synapses

Catenin	Dendrite	Spine	Synapse	Plasticity
α-catenin	O/E: (1) No effect [29] (2) Enhanced branching [35]	LOF: Reduced spine stability; O/E: Increased spine stability [29]	O/E: Increase in synapse density [29]	LOF: Impairment in fear conditioning and prepulse inhibition of the startle response [30]
β-catenin	LOF: Conditional deletion in newborn neurons (postnatal dentate gyrus) results in a failure to develop extensive dendritic trees [34]; O/E: Increase in dendritic branching	O/E: (DIV 10–12) Increase in density of spines and filopodia [35]; LOF: Thin and elongated spines [36]	LOF: Dispersion of synaptic vesicles along the axon, decrease in the number of reserve pool vesicles at the synapse, and impairments in response to prolonged repetitive stimulation [37]	LOF: Decrease in BDNF-induced synaptic mobility and increase in synaptic density [41]; LOF: Compromise in amygdala-dependent consolidation of fear memory [44]
P120ctn	LOF: Reduced branching [52]	O/E: Filopodia-like structures with no mature spine heads [52]; LOF: Reduced spine density [52]	LOF: Reduced synapse density [52]; LOF: Perturbations in synaptic assembly [51]	Unknown
δ-catenin	LOF: Reduced branching [19]; O/E: Increase in branching [61]	O/E: Increase in protrusions [64]; LOF: siRNA knockdown—decrease in spine density [64] (DIV 21); shRNA knockdown (DIV 11–17)—increase in spine density [70]	LOF: siRNA knockdown—decrease in synapse density [64]	LOF: Reduced short-term potentiation, nonlinear response to protocols that induce long-term potentiation
ARVCF	Unknown	Unknown	Unknown	Unknown
P0071	Unknown	Unknown	Unknown	Unknown

O/E overexpression, *LOF* loss of function

neurons, in particular in dendrite and synapse morphogenesis and plasticity that are both dependent and independent of their ability to bind cadherin.

Although we have made remarkable progress in understanding the physiological roles of the catenins in neurons, much remain to be done. The contribution of catenins to higher order neural functions remain to be defined. The contribution of the catenins to activity-dependent regulation of neuronal morphology and function, particularly in vivo, remains relatively unexplored. It is also unclear how the pathways regulated by catenins fit into the larger network of proteins that regulate neuronal morphogenesis. Clearly, a large repertoire of protein interactions for the catenins and their contributions to neuronal physiology remain to be identified. With the technological advances in genomics and proteomics, the future holds promise for identifying the multitude of pathways that the catenins potentially interact with to regulate multiple aspects of neuronal physiology and function.

References

1. Spruston N (2008) Pyramidal neurons: dendritic structure and synaptic integration. Nat Rev Neurosci 9:206–221
2. Bourne JN, Harris KM (2008) Balancing structure and function at hippocampal dendritic spines. Annu Rev Neurosci 31:47–67
3. Knobloch M, Mansuy IM (2008) Dendritic spine loss and synaptic alterations in Alzheimer's disease. Mol Neurobiol 37:73–82
4. Bassell GJ, Warren ST (2008) Fragile X syndrome: loss of local mRNA regulation alters synaptic development and function. Neuron 60:201–214
5. Nelson WJ (2008) Regulation of cell–cell adhesion by the cadherin–catenin complex. Biochem Soc Trans 36:149–155
6. Hu X et al (2008) Activity-dependent dynamic microtubule invasion of dendritic spines. J Neurosci 28:13094–13105
7. Jaworski J et al (2009) Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. Neuron 61:85–100
8. Gu J et al (2008) Microtubules in dendritic spine development. J Neurosci 28:12120–12124
9. Suzuki SC, Takeichi M (2008) Cadherins in neuronal morphogenesis and function. Dev Growth Differ 50(Suppl 1):S119–S130
10. Takeichi M (2007) The cadherin superfamily in neuronal connections and interactions. Nat Rev Neurosci 8:11–20
11. Bekirov IH et al (2002) Identification and localization of multiple classic cadherins in developing rat limbic system. Neuroscience 115:213–227
12. Yagi T, Takeichi M (2000) Cadherin superfamily genes: functions, genomic organization, and neurologic diversity. Genes Dev 14:1169–1180
13. Uemura M et al (2007) OL-Protocadherin is essential for growth of striatal axons and thalamocortical projections. Nat Neurosci 10:1151–1159
14. Suzuki SC et al (2007) Cadherin-8 is required for the first relay synapses to receive functional inputs from primary sensory afferents for cold sensation. J Neurosci 27:3466–3476
15. Kadowaki M et al (2007) N-Cadherin mediates cortical organization in the mouse brain. Dev Biol 304:22–33
16. Tanabe K et al (2006) Cadherin is required for dendritic morphogenesis and synaptic terminal organization of retinal horizontal cells. Development 133:4085–4096
17. Togashi H et al (2002) Cadherin regulates dendritic spine morphogenesis. Neuron 35:77–89
18. Uchida N et al (1996) The catenin/cadherin adhesion system is localized in synaptic junctions bordering transmitter release zones. J Cell Biol 135:767–779
19. Benson DL, Tanaka H (1998) N-Cadherin redistribution during synaptogenesis in hippocampal neurons. J Neurosci 18:6892–6904
20. Chauvet N et al (2003) Distribution of p120 catenin during rat brain development: potential role in regulation of cadherin-mediated adhesion and actin cytoskeleton organization. Mol Cell Neurosci 22:467–486
21. Ho C et al (2000) delta-Catenin is a nervous system-specific adherens junction protein which undergoes dynamic relocalization during development. J Comp Neurol 420:261–276
22. Arikkath J et al (2008) Erbin controls dendritic morphogenesis by regulating localization of delta-catenin. J Neurosci 28:7047–7056
23. Silverman JB et al (2007) Synaptic anchorage of AMPA receptors by cadherins through neural plakophilin-related arm protein AMPA receptor-binding protein complexes. J Neurosci 27:8505–8516
24. Thoreson MA et al (2000) Selective uncoupling of p120(ctn) from E-cadherin disrupts strong adhesion. J Cell Biol 148:189–202
25. Ireton RC et al (2002) A novel role for p120 catenin in E-cadherin function. J Cell Biol 159:465–476
26. Liu H et al (2007) Involvement of p120 carboxy-terminal domain in cadherin trafficking. Cell Struct Funct 32:127–137
27. Davis MA et al (2003) A core function for p120-catenin in cadherin turnover. J Cell Biol 163:525–534
28. Nelson WJ, Nusse R (2004) Convergence of Wnt, beta-catenin, and cadherin pathways. Science 303:1483–1487
29. Hartsock A, Nelson WJ (2008) Adherens and tight junctions: structure, function and connections to the actin cytoskeleton. Biochim Biophys Acta 1778:660–669
30. Yamada S et al (2005) Deconstructing the cadherin–catenin–actin complex. Cell 123:889–901
31. Drees F et al (2005) Alpha-catenin is a molecular switch that binds E-cadherin–beta-catenin and regulates actin-filament assembly. Cell 123:903–915
32. Abe K et al (2004) Stability of dendritic spines and synaptic contacts is controlled by alpha N-catenin. Nat Neurosci 7:357–363
33. Park C et al (2002) Deletion in Catna2, encoding alpha N-catenin, causes cerebellar and hippocampal lamination defects and impaired startle modulation. Nat Genet 31:279–284
34. Takeichi M, Abe K (2005) Synaptic contact dynamics controlled by cadherin and catenins. Trends Cell Biol 15:216–221
35. Yu X, Malenka RC (2003) Beta-catenin is critical for dendritic morphogenesis. Nat Neurosci 6:1169–1177
36. Nishimura W et al (2002) Interaction of synaptic scaffolding molecule and beta-catenin. J Neurosci 22:757–765
37. Gao X et al (2007) Conditional knock-out of beta-catenin in postnatal-born dentate gyrus granule neurons results in dendritic malformation. J Neurosci 27:14317–14325
38. Yu X, Malenka RC (2004) Multiple functions for the cadherin/catenin complex during neuronal development. Neuropharmacology 47:779–786

39. Okuda T et al (2007) beta-Catenin regulates excitatory postsynaptic strength at hippocampal synapses. Proc Natl Acad Sci U S A 104:13479–13484

40. Peng YR et al (2009) Coordinated changes in dendritic arborization and synaptic strength during neural circuit development. Neuron 61:71–84

41. Bamji SX et al (2003) Role of beta-catenin in synaptic vesicle localization and presynaptic assembly. Neuron 40:719–731

42. Murase S et al (2002) Depolarization drives beta-catenin into neuronal spines promoting changes in synaptic structure and function. Neuron 35:91–105

43. Schuman EM, Murase S (2003) Cadherins and synaptic plasticity: activity-dependent cyclin-dependent kinase 5 regulation of synaptic beta-catenin–cadherin interactions. Philos Trans R Soc Lond B Biol Sci 358:749–756

44. Zakharenko SS et al (2003) Presynaptic BDNF required for a presynaptic but not postsynaptic component of LTP at hippocampal CA1–CA3 synapses. Neuron 39:975–990

45. Bamji SX et al (2006) BDNF mobilizes synaptic vesicles and enhances synapse formation by disrupting cadherin–beta-catenin interactions. J Cell Biol 174:289–299

46. Cohen S, Greenberg ME (2008) Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. Annu Rev Cell Dev Biol 24:183–209

47. Abe K, Takeichi M (2007) NMDA-receptor activation induces calpain-mediated beta-catenin cleavages for triggering gene expression. Neuron 53:387–397

48. Maguschak KA, Ressler KJ (2008) Beta-catenin is required for memory consolidation. Nat Neurosci 11:1319–1326

49. Keirsebilck A et al (1998) Molecular cloning of the human p120ctn catenin gene (CTNND1): expression of multiple alternatively spliced isoforms. Genomics 50:129–146

50. Rubio ME et al (2005) Assembly of the N-cadherin complex during synapse formation involves uncoupling of p120-catenin and association with presenilin 1. Mol Cell Neurosci 30:611–623

51. Xu G et al (2004) Continuous association of cadherin with beta-catenin requires the non-receptor tyrosine-kinase Fer. J Cell Sci 117:3207–3219

52. Piedra J et al (2003) p120 Catenin-associated Fer and Fyn tyrosine kinases regulate beta-catenin Tyr-142 phosphorylation and beta-catenin–alpha-catenin interaction. Mol Cell Biol 23:2287–2297

53. Chen X et al (2003) p120 catenin associates with kinesin and facilitates the transport of cadherin–catenin complexes to intercellular junctions. J Cell Biol 163:547–557

54. Boguslavsky S et al (2007) p120 catenin regulates lamellipodial dynamics and cell adhesion in cooperation with cortactin. Proc Natl Acad Sci U S A 104:10882–10887

55. Lee SH et al (2008) Synapses are regulated by the cytoplasmic tyrosine kinase Fer in a pathway mediated by p120catenin, Fer, SHP-2, and beta-catenin. J Cell Biol 183:893–908

56. Elia LP et al (2006) p120 catenin regulates dendritic spine and synapse development through Rho-family GTPases and cadherins. Neuron 51:43–56

57. Ichii T, Takeichi M (2007) p120-catenin regulates microtubule dynamics and cell migration in a cadherin-independent manner. Genes Cells 12:827–839

58. Deguchi M et al (2000) PAPIN. A novel multiple PSD-95/Dlg-A/ZO-1 protein interacting with neural plakophilin-related armadillo repeat protein/delta-catenin and p0071. J Biol Chem 275:29875–29880

59. Ide N et al (1999) Interaction of S-SCAM with neural plakophilin-related Armadillo-repeat protein/delta-catenin. Biochem Biophys Res Commun 256:456–461

60. Izawa I et al (2002) Densin-180 interacts with delta-catenin/neural plakophilin-related armadillo repeat protein at synapses. J Biol Chem 277:5345–5350

61. Laura RP et al (2002) The Erbin PDZ domain binds with high affinity and specificity to the carboxyl termini of delta-catenin and ARVCF. J Biol Chem 277:12906–12914

62. Zhou J et al (1997) Presenilin 1 interaction in the brain with a novel member of the Armadillo family. NeuroReport 8:2085–2090

63. Paffenholz R et al (1999) The arm-repeat protein NPRAP (neurojungin) is a constituent of the plaques of the outer limiting zone in the retina, defining a novel type of adhering junction. Exp Cell Res 250:452–464

64. Cerruti Mainardi P (2006) Cri du Chat syndrome. Orphanet J Rare Dis 1:33

65. Medina M et al (2000) Hemizygosity of delta-catenin (CTNND2) is associated with severe mental retardation in cri-du-chat syndrome. Genomics 63:157–164

66. Martinez MC et al (2003) Dual regulation of neuronal morphogenesis by a delta-catenin–cortactin complex and Rho. J Cell Biol 162:99–111

67. Ochiishi T et al (2008) Regulation of AMPA receptor trafficking by delta-catenin. Mol Cell Neurosci 39:499–507

68. Kim K et al (2002) Dendrite-like process formation and cytoskeletal remodeling regulated by delta-catenin expression. Exp Cell Res 275:171–184

69. Abu-Elneel K et al (2008) A {delta}-catenin signaling pathway leading to dendritic protrusions. J Biol Chem 283:32781–32791

70. Arikkath J, Peng I, Ng YG, Israely I, Liu X, Ullian EM, Reichardt LF (2009) δ-catenin regulates spine and synapse morphogenesis and function in hippocampal neurons during development. J Neurosci (in press)

71. Kim H et al (2008) Delta-catenin-induced dendritic morphogenesis. An essential role of p190RhoGEF interaction through Akt1-mediated phosphorylation. J Biol Chem 283:977–987

72. Israely I et al (2004) Deletion of the neuron-specific protein delta-catenin leads to severe cognitive and synaptic dysfunction. Curr Biol 14:1657–1663

73. Ohno H et al (2002) Localization of p0071-interacting proteins, plakophilin-related armadillo-repeat protein-interacting protein (PAPIN) and ERBIN, in epithelial cells. Oncogene 21:7042–7049

74. Izawa I et al (2002) ERBIN associates with p0071, an armadillo protein, at cell–cell junctions of epithelial cells. Genes Cells 7:475–485

75. Jaulin-Bastard F et al (2002) Interaction between Erbin and a catenin-related protein in epithelial cells. J Biol Chem 277:2869–2875