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Catenins: Playing Both Sides of the Synapse

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Abstract

Synapses of the central nervous system (CNS) are specialized cell-cell junctions that mediate intercellular signal transmission from one neuron to another. The directional nature of signal relay requires that synaptic contacts are morphologically asymmetric with distinct protein components, while changes in synaptic communication during neural network formation require synapses to be plastic. Synapse morphology and plasticity require a dynamic actin cytoskeleton. Classical cadherins, which are junctional proteins associated with the actin cytoskeleton, localize to synapses and regulate synaptic adhesion, stability and remodeling. The major intracellular components of cadherin junctions are the catenin proteins, and increasing evidence suggests that cadherin-catenin complexes modulate an array of synaptic processes. Here we review the role of catenins in regulating the development of pre- and postsynaptic compartments and function in synaptic plasticity, with particular focus on their role in regulating the actin cytoskeleton.

Introduction

Excitatory synapses of the CNS are asymmetric cellular junctions formed between neurons. Structurally, they are divided into two specialized domains: the presynaptic bouton on the axon side of the contact, and the postsynaptic compartment on the dendrite (see Figure 1 for a more detailed description of synaptic organization). Proper apposition of pre- and postsynaptic membranes and organization of pre- and post-synaptic compartments is paramount to synaptic function. Specific partnering between axon and dendrite, followed by domain specialization at points of contact, initiates neuronal synaptogenesis[1]. Synaptic target recognition and intercellular reorganization are believed to be driven in large part by synaptically located transmembrane cell adhesion proteins and their cytoplasmic ligands[2], including the cadherin/catenin adhesion system of proteins[3].

Classical cadherins are single pass transmembrane proteins characterized by an extracellular domain containing five cadherin repeat sequences that mediates specific calcium-dependent homotypic interactions. The cytoplasmic tail is strikingly similar between cadherins, and binds members of the armadillo repeat family of proteins, p120-catenin and β -catenin. p120-catenin and β -catenin bind distinct regions of the cadherin cytoplasmic tail: p120-catenin binds to the membrane proximal or juxta-membrane domain and β -catenin binds to the distal part of the tail [4]. p120-catenin regulates lateral clustering and stabilization of cadherins at the membrane

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[5]. β -catenin binding to cadherin recruits α -catenin, an unrelated catenin that can also bind directly to F-actin and a number of actin-binding proteins [6]. Binding and recruitment of catenins to cadherins promotes cadherin-mediated adhesion and regulates multiple signaling pathways [4,7].

Classical cadherins have well established roles in epithelial cell-cell adhesion, and multiple lines of evidence indicate a role for cadherins in synaptogenesis[3]. Cadherins are expressed in neurons and are among the first proteins concentrated at nascent excitatory synapses in cultured hippocampal neurons[8]. N-cadherin is transported with early components of the active zone in precursor vesicle packets that initiate synapse formation[9], and N-cadherin colocalizes with early synaptic markers along extending axons *in vivo*[10]. These observations suggest that cadherins could function in early stages of synapse formation and presynapse assembly. Consistent with this, disruption of cadherin function inhibits synapse formation [11]. Interfering with cadherin function also disrupts postsynaptic spine morphology[11], and cadherins are required for activity-induced spine remodeling[12]. Although these data indicate that cadherins are necessary for synapse development, they do not appear to be sufficient since cadherin-mediated adhesion alone does not induce synapse formation *in vitro*[13].

Like cadherins, catenins are expressed in neurons and localize to synaptic contacts. p120-catenin and the highly related δ -catenin localize to synapses and dendritic spines[14,15]. Endogenous β -catenin is enriched at synapses[8,11], and EGFP-tagged β -catenin localizes robustly to dendrites and dendritic spines, though less so to axons[16]. Finally, endogenous α -N-catenin, the neuronal form of α -catenin, is found at synapses[11], and EGFP-tagged α -N-catenin localizes to dendritic spines and weakly to axons[17] similar to that of EGFP-tagged β -catenin. Like other cell-cell junctions, catenin localization at synapses is believed to be largely cadherin-driven[11], and evidence suggests that cadherin-catenin complexes are formed on both sides of the synapse[11,16-19] (a model for catenin function in synapses is shown in Figure 2). However, as described earlier, there are clear structural and functional differences between the presynaptic and postsynaptic compartment. In this review, we will discuss how catenins function on both sides of the synapse to regulate aspects of synaptic organization and plasticity.

Catenins and the Presynapse

Current data strongly suggest that targeted delivery of proteins plays a critical role during presynapse assembly. Preassembled packets of presynaptic proteins are thought to move along the axon in transport vesicles, and docking and fusion of these vesicles at nascent contacts permits rapid assembly of presynaptic domains[20]. N-cadherin was shown to be a component of these presynaptic packets[9], and is transported along extending axons[10]. Although in epithelial cells β -catenin binding to E-cadherin is required to facilitate E-cadherin targeting to the plasma membrane[21], deletion of the β -catenin binding region in N-cadherin does not inhibit membrane targeting or packet formation *in vivo*[10]. This result suggests that β -catenin is not required for N-cadherin trafficking, and that cadherins may function independently of catenins in this initial stage of presynapse formation. It is not known, however, if loss of β -catenin affects the kinetics of N-cadherin trafficking or stability at synaptic contacts.

Cadherin-catenin complexes have an important role in presynaptic organization. Proper localization and organization of synaptic vesicles along the presynaptic active zone is critical for synaptic function[1]. Loss of cadherin function[11] or loss of β -catenin[19] disrupts synaptic vesicle localization in cultured neurons, indicating that cadherin-catenin complexes function in presynaptic organization. Disruption of cadherin-catenin association with the actin cytoskeleton is not the primary cause of the defect in vesicle clustering in the absence of β -catenin. Instead, the PDZ binding domain of β -catenin is required for clustering of synaptic

vesicles at presynaptic terminals [19]. Thus, the primary role of β -catenin in presynaptic organization might be to promote molecular complexes that bind and cluster synaptic vesicles at the active zone.

Disassembly of cadherin- β -catenin interactions at the presynapse is critical for synapse formation induced by brain-derived neurotrophic factor (BDNF). Application of BDNF to neurons enhances synaptic transmission and induces synapse sprouting. It was recently discovered that BDNF promotes splitting of synaptic vesicle clusters, and this activity depends on dissociation of cadherin- β -catenin complexes[18]. Tyrosine phosphorylation of β -catenin is required for dissociation from cadherins[22], and when this is blocked BDNF-mediated vesicle cluster splitting and synapse formation is prevented. Interestingly, tyrosine phosphorylation of β -catenin also regulates cadherin interactions in the postsynaptic compartment and influences synaptic structure[16]. How breaking cadherin-catenin interactions promotes reorganization of the presynaptic compartment remains unclear.

α -N-catenin functions in postsynaptic organization (discussed below), but its role in presynaptic organization is less clear. Loss of α -N-catenin does not disrupt synaptic vesicle clustering, consistent with the finding that cadherin-catenin association with the actin cytoskeleton is not required for β -catenin-mediated vesicle organization, though a slight reduction in cluster size occurs[17]. It is possible that little α -N-catenin is present in axons; alternatively, F-actin could be limited at the presynapse. Nonetheless, although most of the actin at the synapse is concentrated in the postsynaptic dendritic spine, F-actin is present in the presynapse and is believed to play an important role in presynaptic function[23]. Actin filaments are distributed throughout the presynaptic terminal[24], and GFP-actin is enriched at synaptic vesicle clusters and surrounding regions[25]. It has been proposed that this F-actin network functions as a scaffold for vesicle clusters[23]. Given the importance of β -catenin in synaptic vesicle clustering and a new model for α -catenin in regulating actin assembly (discussed below), it is possible that α -N-catenin, if present, could modulate presynaptic actin network formation.

Catenins and the Postsynapse

Postsynaptic domains of excitatory synapses are formed on dendritic spines — small, dynamic protrusions that extend from dendritic shafts. Dendritic spines contain all the molecules required for postsynaptic signaling and typically possess a single synapse. Dendritic spines vary in shape and size and are traditionally classified as thin, stubby, or mushroom. Spine morphology is correlated with synaptic strength: the larger the spine head, the stronger the synapse. Neuronal activity modifies spine shape and size, and spines may provide a morphological basis for synaptic plasticity[26-28].

Actin filaments form the main structural component of the spine cytoskeleton, and spine morphology and motility are regulated by actin dynamics. Actin within spines is highly dynamic, and drugs that induce actin depolymerization cause spine loss in cultured neurons [29,30]. Not much is known about the ultrastructure of the actin network in spines, though EM data suggests that spine heads possess two discrete populations of actin filaments: a set of filaments that forms a stable core in the central region of the spine, and a set of dynamic filaments at the periphery[31]. Not surprisingly, a number of proteins that bind actin or regulate actin dynamics are present in dendritic spines and regulate spine formation and motility. They include the motor protein myosin II; the actin crosslinker α -actinin; cortactin, an Arp2/3 actin nucleation complex; and the actin binding protein derbrin[32]. In addition, Rho GTPases — modulators of the actin cytoskeleton — regulate spine morphogenesis[26]. Cadherin-catenin protein complexes regulate actin dynamics and Rho GTPase signaling in epithelial cells, and evidence suggests a similar role in dendritic spines.

Disruption of endogenous cadherin function causes a robust defect in spine morphology. Inhibiting cadherin function at early stages of synapse development in neuronal cultures causes normal mushroom-shaped spines to be replaced by filopodia or thin spines, suggesting that spine maturation is blocked[11]. Under these conditions, β -catenin is no longer concentrated at synapses; presumably α -N-catenin localization is lost as well. Given the importance of actin assembly in spine morphogenesis and the link between cadherin adhesion and the actin cytoskeleton, these results suggest that classical cadherins could be regulating spine development through catenins. Mounting evidence suggests that cadherin-catenin complexes regulate actin organization and concomitant spine morphogenesis in at least two ways: directly through α -N-catenin, and through p120-catenin and Rho GTPase signaling.

α -N-catenin and postsynaptic organization

In α -N-catenin null neurons, synapses form and N-cadherin and β -catenin localize normally to synaptic contacts. However, spine shape and motility is affected: spines are often long and thin and more dynamic, with aberrant filopodia extensions emanating from spine heads[17]. This phenotype is similar to when cadherin function is blocked[11], though less severe. In contrast, overexpression of α -N-catenin stabilizes spines and increases spine number. Both the N-terminus of α -N-catenin which binds β -catenin and contains the homodimerization domain, and the C-terminus which is required for actin association are required for increasing spine stability. This suggests that cadherin-catenin complex formation and association with the actin cytoskeleton is essential for spine morphogenesis[17].

Alpha-catenin binds and bundles F-actin, and was long considered to be a direct link between cadherin and the actin cytoskeleton by binding to β -catenin and actin simultaneously. However, recent biochemical and cell biological data indicate otherwise[33,34]. It was discovered that α -catenin cannot bind to β -catenin and actin simultaneously. Instead, the oligomeric state of α -catenin dictates binding partner: as a monomer, α -catenin forms a ternary complex with β -catenin and E-cadherin; as a dimer, it binds to and bundles F-actin. In addition, α -catenin dimers inhibit Arp2/3-mediated actin polymerization. These data indicate that α -catenin does not directly link the cadherin-catenin complex to the actin cytoskeleton. Instead, cadherin-catenin complexes may increase the concentration of α -catenin at cadherin contacts, promoting dimer formation and regulating local actin geometry and dynamics[33,34]. Could α -N-catenin be functioning similarly at synapses? Though not tested directly, current observations are largely consistent with this model. Loss of α -N-catenin reduces spine stability and causes filopodia to aberrantly project from spine heads[17], a possible consequence of reduced actin bundling and increased Arp2/3 activity. Dominant negative cadherins that function by sequestering endogenous catenins away from native cadherin contacts also cause spines to become more filopodiallike[11], again consistent with a role for α -N-catenin regulating local actin dynamics within the dendritic spine, particularly along the synaptic cleft where cadherins are concentrated.

Neuronal activity promotes actin-driven changes in spine size and strength, and cadherins, β -catenin and α -N-catenin regulate activity-induced remodeling. Cadherin function is required for activity-driven spine expansion[12] and, interestingly, activity increases spine localization of both β -catenin and α -N-catenin[16,17]. Adhering to the new model of α -catenin function, increasing levels of the β -catenin- α -N-catenin complex within the spine would cause a raise in α -N-catenin concentration at the synapse, promoting its dimerization. Alpha-N-catenin dimers would suppress branched actin polymerization and promote actin bundling, favoring a more stable actin cytoskeleton. Consistent with this, α -N-catenin overexpression increase spine head width and stabilize spines [17].

The new model for α -catenin function would predict that the loss of β -catenin, required for recruiting and concentrating α -catenin to the cadherin contacts, would cause a similar spine phenotype to that observed in the absence of α -N-catenin. However, no spine phenotype was noted in neurons lacking β -catenin[19]. One possible explanation for this is that the highly-related protein plakoglobin can compensate for the absence of β -catenin in spines, as has been reported in other systems. Another possibility is that α -N-catenin is recruited to dendritic spines independently of β -catenin. Alpha-catenin binds to a number of proteins that localize to dendritic spines and regulate spine morphogenesis, including formins and α -actinin[6]. Future work is needed to understand how α -N-catenin, dependent or independent of cadherin adhesion, regulates actin dynamics in spines.

p120-catenin and postsynaptic organization

p120-catenin regulates cadherin function by promoting cadherin trafficking and stability[5], and provides an additional link between cadherin engagement and actin dynamics by signaling through Rho-family GTPases[35]. In neurons, p120-catenin and the related δ -catenin are expressed in neurons and localize to synapses[14,15,36]. δ -catenin is restricted to the postsynaptic compartment and loss of δ -catenin in mice disrupts normal synaptic plasticity [38], though the effects on postsynaptic organization at the molecular level remain unknown. Loss of p120-catenin in mice reduces synapse density, lowers N-cadherin levels and alters Rho GTPase activity in the hippocampus[37]. Cultured hippocampal neurons lacking p120-catenin have reduced spine density, and the spines formed are significantly shorter and thinner than those of controls. Interestingly, the spine density phenotype can be rescued by expressing a p120-catenin construct that lacks binding sites for cadherin but can regulate Rho, indicating that association between p120-catenin and cadherin is not required for control of spine density. In contrast, defects in spine morphology are rescued by a mutant p120-catenin that can bind cadherins but not regulate Rho, indicating that p120-catenin regulates spine maturation primarily through its association with cadherins[37]. Thus, p120-catenin appears to regulate the spine cytoskeleton in two ways: 1) through stabilization of cadherins by promoting cadherin-catenin complex formation and catenin-mediated effects on the actin cytoskeleton, and 2) through Rho GTPase signaling by regulating actin assembly in the spine. While these are two independent functions of p120-catenin, they almost certainly cooperate during normal spine morphogenesis. For example, Rho GTPase signaling within the spine regulates assembly of the actin network, which is likely bound and organized by α -N-catenin. Future work is needed to understand how these two properties of p120-catenin function to regulate the actin cytoskeleton in dendritic spines.

Synapse biology places unique requirements on proteins required for the formation, maintenance and remodeling of this specialized cell-cell contact. Catenins clearly play a prominent role in synapse formation, though much remains unknown about the mechanisms underlying catenin action. Future work is expected to elucidate how catenins, bridged through cadherin adhesion, function to organize and potentially coordinate pre- and postsynaptic organization.

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Figure 1. Model of an excitatory synapse

Synapses are divided into two specialized domains: the presynaptic bouton on the axon side of the contact, and the postsynaptic compartment on the dendrite. The presynaptic bouton is filled with synaptic vesicles carrying neurotransmitter. Actin is associated with vesicles in the presynapse, possibly functioning as a scaffold. Upon depolarization, synaptic vesicles fuse within a specialized region of the plasma membrane known as the active zone and release neurotransmitter into the synaptic cleft. Directly apposed to the presynaptic active zone lies the postsynaptic region, characterized by an electron-dense meshwork of proteins known as the postsynaptic density (PSD). Neurotransmitter receptors — including the ionotropic glutamate receptors NMDAR (N-methyl-D-aspartate receptor) and AMPAR (alpha-amino-3-

hydroxy-5-methyl-4-isoxazole propionic acid receptor) — and signaling molecules are concentrated in the PSD. The majority of excitatory PSDs are found on top of dendritic spines, specialized structures protruding from dendritic shafts. Spines are actin-rich, and spine morphology and motility are regulated by actin dynamics. Pre- and post-synaptic membranes are connected by transmembrane cell adhesion proteins, including classical cadherins.

Figure 2. Schematic illustration of catenin function in pre- and postsynaptic compartments
 Cadherin adhesion at synapses recruits available catenins to pre and postsynaptic compartments. In the presynapse, β-catenin association with PDZ-domain containing proteins is required for synaptic vesicle clustering. Roles for p120-catenin and α-N-catenin in presynaptic organization are less well defined. In the postsynapse, p120-catenin regulates both cadherin stability and Rho GTPase signaling to the actin cytoskeleton, affecting synapse formation and spine development. Neuronal activity promotes β-catenin localization into spines, influencing synaptic structure, possibly by recruiting α-N-catenin to sites of cadherin adhesion. Alpha-N-catenin controls spine morphology and stability, possibly by regulating the

actin cytoskeleton when present at high enough concentrations to form a dimer, the only state in which α -catenin binds F-actin.