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Synapse adhesion: a dynamic equilibrium conferring both stability and flexibility

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Abstract

Cell adhesion molecules linked to cytoskeleton generate stable cell-cell junctions. Cadherins provide a canonical example, but paradoxically, they participate in a multitude of transient and regulatable interactions. Their extracellular binding generates weak adhesion that is modified by clustering; interactions with F-actin are regulated, can be transient, and can alter F-actin dynamics. Additionally, cadherin recycling from the cell surface can modify the size and location of junctions and strength of adhesion. In epithelial cells, this ongoing dynamic behavior is important for maintaining stable junctions. Recent work supports that cadherins act similarly at synapses where their actions are likely to be shared by integrins and other actin-linked cell adhesion molecules (CAMs). Together the collaborative activities of such CAMs provide a stable, but flexible structure that can promote and support changes in synapse shape and size while maintaining stable junctions to permit information flow.

Indexing Terms

cadherins; synapse adhesion; F-actin

Introduction

Synapses evolved in order to transfer information within networks of neurons and other cells. Information flows principally by a sequence of presynaptic membrane depolarization, neurotransmitter release and diffusion, and postsynaptic activation of neurotransmitter receptors, but can also occur through the exchange of growth factors, peptides and by cell-to-cell contact-mediated signals. Out of the recognition of this primary function grew the concept that synapse adhesive structure evolved mostly to provide a passive support, perhaps more sophisticated than glue, but nevertheless a relatively simple strut-like scaffold maintaining a constant gap separating rigidly parallel synaptic membranes. Here, the synapse, with its adhesive struts, can be viewed as two shore-lines separated by a one-way bridge that allows vehicles (information) to travel across.

Synapses also store information over long periods, and they do this, in part, by changes in overall size or shape of postsynaptic dendritic spines, or by incorporating perforations or evaginations [1–4]**. This makes a bridge analogy insufficient. In order to change shape while maintaining information transfer, a stable, but flexible structure is required in which proteins, membranes, and cytoskeletal support networks can be added or removed without jeopardizing communication. Here, we propose that this basic structure can be provided by cell adhesion molecules (CAMs) linked to F-actin cytoskeleton.

A variety of adhesion proteins are found at synapses. Many of those identified can initiate synapse formation, customarily demonstrated by an ability to generate artificial synapses between CAM-expressing non-neuronal cells or CAM-coated beads and neurons [5].

Synaptogenic CAMs include presynaptic neuroligins which can bind to postsynaptic neuroligins, LRRTMs, or a complex of cerebellin1 and gluDdelta2, presynaptic netrin Gs and LAR protein tyrosine phosphatase receptors which bind to postsynaptic netrin G ligands, presynaptic latrophilin 1 and postsynaptic teneurin-2, ephB interactions with ephrin-Bs, homophilic binding between synCAMs, and interactions between as yet unidentified presynaptic partners and postsynaptic SALMs. It is not known how many of each of these families are co-expressed at synapses, whether they act competitively, or cooperatively. However, in-depth analyses indicate that particular pairs impart unique synaptic features, supporting the idea that CAMs can act cooperatively. Synaptogenic CAMs typically bind PDZ proteins rather than F-actin. Because these have been the subjects of several recent reviews [6–10], they will not be discussed in depth here. Instead, in this review, we focus on the nature of synapse adhesion and the contributions of non-synaptogenic, actin-linked CAMs to the generation and maintenance of synapse adhesive structure (Fig. 1). The focus is on cadherins, but much of what is covered is equally applicable to the integrin family.

An Overview of Actin-Linked Adhesion

Neither cadherins nor integrins appear to be able to trigger synaptogenesis, but they both can confer synapse stability [11–14]. Cadherins and integrins are bona fide adhesion proteins that are tethered in the plasma membrane by links to the F-actin cytoskeleton, and they both can generate junctions. Adherens junctions between epithelial cells assemble on a foundation of E-cadherin transcellular homophilic binding [15,16], where they contribute to cell polarity and to the organization and stabilization of F-actin [17,18]. Epithelial cells form asymmetric adhesive junctions with the basal lamina via hemi-desmosomes generated by integrins binding to laminin, an interaction that is anchored by intermediate filaments [19,20]. Integrins are also the basis for focal adhesions which are restricted adhesive interactions with extracellular matrix anchored by F-actin [21]. Cadherins and integrins were essential for the generation of multicellular organisms and as such, they are highly conserved evolutionarily. Even the earliest metazoans express members of the cadherin and integrin superfamilies [22–25]. In vertebrates, cadherins and integrins are not unique to the nervous system, and are deployed over and over again during development to sort, organize, and provide structural support for the genesis of tissues and organs. After development, they continue to be expressed where they play essential roles in maintaining cellular polarity and tissue integrity. These essential roles are underscored by their dysregulation in a variety of metastatic cancers [26,27].

The lineage of cadherins extends back to the closest single cell relatives of metazoans, and the presence of cadherins distinguishes animals from plants and fungi [23]. Among a variety of embryonic events, cadherins mediate cell and tissue sorting, events that illustrate both the stable and dynamic properties of F-actin linked adhesion. Cell type specific cadherin expression coupled with homophilic binding serves to sort cells into germ layers during the earliest phases of embryogenesis. In a series of classic experiments, Takeichi and colleagues demonstrated that E-cadherin expressing endoderm segregated from N-cadherin expressing ectoderm by homophilic binding in a calcium-dependent fashion [28–30]*. At later stages, similar actions serve to organize cells into nuclear groups, such as the sorting of motor neuron pools in the ventral spinal cord (e.g. [31]). Cadherin actions in cell sorting exemplify concurrent and seemingly conflicting roles in generating a stable and dynamic environment. Cell sorting is an active process in which adhesive bonds are made and broken as cells migrate and organize into sheets or groups. At the same time, the bonds that are made maintain cell contact while helping to generate the forces that permit developing sheets to migrate, undulate, and fold.

Dynamic Adhesion Based on Structure

The cadherin superfamily encompasses over 100 members. All are Type I transmembrane proteins with a variable number of cadherin repeats in the extracellular domain, but with respect to a role in junction development and maintenance, we will focus on the classic (or Type I and Type II) cadherins. In vertebrates, they have 5 extracellular cadherin (EC) repeat domains and a highly conserved intracellular domain that can bind members of the p120 catenin family in the juxtamembrane region and β -catenin over an extended C-terminal region. Structural studies indicate that calcium ions bind at sites lying between EC domains and this serves to rigidify the extracellular structure such that it forms an elongated crescent [32*,33]. In this extended conformation, molecules engage in both within (*cis*) and cross-membrane (*trans*) interactions [32]*. For Type I cadherins binding occurs between EC domains in which a conserved Trp side chain in one molecule interacts with a hydrophobic binding pocket in another. A similar interaction involving two conserved Trps is observed in Type II cadherins [34]. Binding is unstable and suggests that cadherins are continually making and breaking bonds so that stable adhesion involves interactions between multiple cadherins [35,36]. There is some disagreement among structural studies regarding the extent of overlap between adhering extracellular domains [32*,37], but all agree that relatively weak binding between single partners become strengthened and stabilized considerably when multiple partners are engaged in clusters or as a series of dimers [38,39].

Dynamic and Stable Interactions with Actin

Extracellular binding is stabilized by interactions of the intracellular C-terminal domain with F-actin. Cadherins engage F-actin indirectly and can influence its organization or promote its assembly via a variety of mechanisms. The best studied is via β -catenin interactions with α -catenin. Alpha-catenin can bind F-actin via several different partners, including, α -actinin, afadin, and formin [40–42]. It can also bind F-actin directly, but α -catenin interactions with β -catenin or F-actin are mutually exclusive [43]**, indicating that this is probably not the principal anchor for adhesion. In fact, α -catenin may delineate dynamic cadherins. High resolution FRAP studies in developing *Drosophila* epithelial cells show that α -catenin defines a dynamic E-cadherin pool [44,45], while in the absence of α -catenin, clusters of stable F-actin form at sites of cadherin stability[44]. However, the decreased dendritic spine stability observed in neurons lacking α N-catenin suggests that α -catenin may stabilize synaptic cadherins [12]. At this time, the F-actin binding interactions that serve to anchor adhesion in any cell are not known, but there are several possibilities. Mutant cadherins lacking β -catenin binding domains are poorly adhesive [46,47], suggesting stable actions are mediated via β -catenin partners. Cadherin interactions with β -catenin and its residence time on the cell surface are negatively regulated by tyrosine phosphorylation of β -catenin [48,49]. Near the membrane, δ -catenin can bind to cortactin [50] and p120 catenin can regulate actin via its effects on RhoGTPases [51–53], an interaction that may influence synapse assembly [54]. In epithelial cells cadherin actions are functionally joined to those of other transmembrane adhesive receptors, such as nectins, vezatin, and a synaptotagmin like molecule, each of which may provide the principal links to F-actin [55–57]. Together the structural properties and binding interactions of cadherins paint a picture of a highly dynamic process that supports adhesion.

Recycling and Renewal

Cadherins at both adherens and synaptic junctions are also recycled. They are removed from the surface via clathrin-dependent endocytosis [48,58], and in epithelia, they are trafficked to the plasma membrane using components of the exocyst complex [59]. Internalization requires breaking interactions with the actin cytoskeleton, but is most likely regulated by

interactions at the intracellular, juxtamembrane domain of cadherins, which binds p120 catenin family members. In non-neuronal cells, when p120-catenin is bound to the juxtamembrane domain of either E- or VE-cadherin, clathrin dependent endocytosis is prevented by a mechanism that has been postulated to be competition [60–63]. In neurons, N-cadherin is recycled [48,64], but interestingly, an N-cadherin mutant incapable of binding p120 catenin family members (but able to be internalized) has been shown to be more *stable* on the surface of growth cones, countering the idea that cadherin surface expression is governed by a simple competition between p120-catenin and clathrin adapters [64]. Adding to the complexity, N-cadherin internalization motifs are atypical and not concentrated at the p120 binding domain [48], and E-cadherin has been shown to employ alternate internalization modes (e.g. [65]).

Cadherin internalization decreases adhesion. This can be detrimental to tissue integrity. Enhanced internalization of desmosomal cadherins is suspected to contribute to the epidermal fragility and blister formation observed in the autoimmune disease pemphigus [66], but coupled with balanced exocytosis, targeted internalization is essential for motility [64]. Additionally, a recent imaging study that utilized photoswitchable tags on various cadherin mutants shows that at stable non-neuronal junctions, cadherins are continually added and this action is counterbalanced by continual removal, driven in part by endocytosis [45]. Other studies in developing *Drosophila* neuroepithelia have shown that endocytic removal of surface, nonjunctional cadherins helps to maintain the position and stability of adherens junctions [67,68]. Similar analyses of synapses have not been carried out, but it is likely that there will be parallels. These data underscore the dynamic nature of a seemingly stable junction. They also support the idea that information storage at synapses is unlikely to be encoded in the conformation or organization of individual proteins.

Supporting and Stabilizing Junctional Morphing

It is easy to see why dynamic adhesion and cadherin recycling may be important to developing synapses. Developing synapses change their size and shape constantly over the first few weeks. Several studies have shown that developing dendritic spines are highly motile and while they dance relative to their anchorage sites on dendritic shafts, and morph in length and head-size, they maintain contact with their presynaptic terminals [69–71]*. Such movement demands that developing junctions are both strong and flexible, a quality that permits cadherin-mediated junctions to support tissue morphogenesis during development. This quality also permits easy disassembly, for during development, many of the synapses that are made are only temporary. That cadherin-mediated adhesion contributes to early synaptic properties is consistent with several lines of data. Developing, but not mature, junctions are readily disassembled by actin depolymerizing agents [72]**, indicating that they are actin-linked. Overexpression of dominant negative-acting cadherins, which disrupt β -catenin localization and impair function of all cadherins generally prevents synaptogenesis in young neurons [13,14]; and the synapse-triggering actions of neuroligins require cadherins [73]*. Additionally, cadherin-mediated adhesion is likely to contribute to molecular matching between pre- and postsynaptic partners [74–79]*. However, it should also be noted that a sustained disruption of cadherins appears to permit the engagement of alternate mechanisms in that synapses can eventually form without them [13,14]. It would be interesting to test whether integrins can substitute for cadherins. Cell lines used in artificial synapse assays also express integrins, and integrins possess many of the junction-forming attributes of cadherins, suggesting they could play similar roles. Whether or not integrins could be recruited this way has not been tested directly, but data from knockout mice better support that integrins principally regulate synapse maturation and synapse plasticity [80,81].

Time lapse imaging experiments show that synapses, particularly those on dendritic shafts, can move laterally [82–84]. Pre- and postsynaptic sites of both excitatory and inhibitory synapses can move in unison for distances that can exceed ten microns [83]. Such movement is promoted by F-actin [84]. While the function of lateral synapse movement is not known, it may be relevant for adjusting synapse position, such as what is observed in the systematic migration of cerebellar basket cell projections from Purkinje cell bodies to axon initial segments. This targeted synapse movement is guided by a standing gradient of neurofascin anchored by ankyrinG to F-actin [85]. In an interesting parallel, cadherin- α -catenin complexes engaged in *trans* between epithelial cells flow apically utilizing F-actin [86]. Movement that maintains adhesion and includes the base of an adhesive contact also occurs at the specialized cadherin/protocadherin-mediated contacts that generate tip links between stereocilia on cochlear hair cells. The tip links form a critical element of hair cell mechanotransduction by setting the tension on a channel gating spring. In order to maintain responsiveness to an ongoing stimulus, tension on the gating spring is adjusted by raising or lowering tip link position on a stereocilium using a myosin/actin driven motor. Significantly mutations in either of the tip link components results in hearing loss [87].

Cadherin adhesion can be readily modified by virtue of relatively weak extracellular interactions, changes in calcium levels, flexible interactions with the cytoskeleton that can be regulated by phosphorylation, and by internalization. Notably missing as a major mechanism for dynamic regulation is synthesis. Several studies indicate that within the first postnatal week in chicks and rodents—as synaptogenesis is just beginning—mRNA levels for classic cadherins in CNS diminish dramatically and are expressed at very low levels in adults [88–90]. In contrast, protein levels are maintained at readily detected levels throughout adulthood (e.g. [77,79]). Consistent with this observation, cadherin turnover appears to be very slow. While direct measurements of cadherin half-life are lacking, shRNA-mediated N-cadherin knockdown or its loss following Cre-mediated deletion requires weeks [91,92]. Thus, cadherins appear to be recycled and reutilized rather than degraded and synthesized.

Maintaining Stable Synapse Structure

In contrast to developing synapses, mature synaptic structure is stable. Time-lapse imaging studies show that the vast majority of dendritic spines do not turn over or even move very much [93–96], and biochemical studies indicate that the proteinaceous networks that form postsynaptic densities are coherent and readily purified [97–99]. Actin-linked adhesion is present, but no longer necessary to maintain appositions [72]. The maintained expression of actin-linked CAMs at synapses likely regulates the stability of junctions, much as they do in epithelial cells. Because mature appositions do not depend on F-actin [72], the actin organizing actions of cadherins and integrins can be recruited to generate changes in spine shape. Consistent with this idea, mice having a conditional deletion of N-cadherin in hippocampus have normal synapse appositions, but cannot maintain LTP or the increase in dendritic spine size that occurs at potentiated synapses [100]*. β 1-integrin adhesion has also been linked to activity-dependent changes in actin cytoskeleton [101–103] and regulation of LTP [80,81,104]. Whether cadherins and integrins act coordinately in this respect has not been tested.

Synapse size is generally stable and observations of epithelial junctions suggest this is likely to be an active process of CAM recycling at the edges of junctions. Imaging studies in cultured hippocampal neurons and electron microscopy in mature hippocampus support the view that there are zones of more concentrated endocytosis and exocytosis that lie immediately adjacent to synapses [105**,106*]. For example, AMPA-type glutamate receptors are inserted into the plasmalemma at these zones, where they can then migrate to

the synaptic membrane in order to maintain persistent synaptic potentiation or, alternatively, are internalized here as part of the mechanism leading to synaptic depression [107–109]. Additionally, synaptic vesicles utilizing clathrin-mediated internalization tend to be internalized more commonly adjacent to active zones [110]. It is likely then, that other synaptic proteins like cadherins are also internalized and externalized via these domains, and this may be utilized to maintain synapse size and position. Interestingly, many mature synapses are discontinuous or perforated [111], and stimuli that produce LTP have been associated with the generation of synapse perforations [4,112]. Such perforations appear to be negatively regulated by NCAM, and significantly, display endocytic zones [113], thus creating additional domains where proteins (and membrane) can be readily exo- and endocytosed.

Thus, at mature synapses, actin linked CAMs are unlikely to generate the pre- to postsynaptic grid, but they still confer stability by regulating sites of endocytosis, and by providing a readily assembled matrix on which changes in synapse size, shape, and content can be effected without jeopardizing a synaptic contact. Additionally, it is likely that actin-linked CAMs are recruited to generate new synapses as newly born dentate gyrus granule cells integrate into networks, as changes in estrogen levels promote new synapse formation in hippocampus and in the context of learning and memory.

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Figure 1.

Cartoon illustrates some of the dynamic aspects of cadherin localization and interactions with actin cytoskeleton at developing (left) and mature (right) synapses. Arrows indicate transient interactions: extracellular domain swapping in *cis* and in *trans* and intracellular clustering. Actin is represented as stable condensations as well as elongated, more dynamic filaments. Alpha-actinin also has a dynamic relationship with actin and cadherin that is not well understood, but α -catenin promotes cadherin mobility [44]. The precise binding relationship between cadherins and actin is not known, but may involve *cis* interactions with nectins, vezatin or synaptotagmin-like proteins, or β -catenin binding to actin binding proteins [55–57].