

Synaptic adhesion molecules

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Synopsis

The chemical synapse is a specialized asymmetric adhesion site between the axon of a neuron and its target cell. Synapse formation is a multi-step process involving target recognition followed by reciprocal inductive interactions that result in recruitment of proteins, such as receptors, and organelles, such as synaptic vesicles, to both the presynaptic and postsynaptic compartments. Synaptic cell adhesion molecules are believed to mediate initial inductive interactions, stabilize connections, and function as nucleation sites for signaling events that promote synapse development and regulate synaptic activity.

Introduction

The structures and major intracellular interactions of several different synaptic adhesion molecules believed to play important roles at synapses are shown in figure 1. One large class is the cadherin superfamily with more than 100 members which are defined by the presence of one or more ~110 amino acid cadherin repeats in their extracellular domains. The cadherin superfamily is subdivided into classical or type I cadherins, atypical or type II cadherins, desmosomal cadherins, protocadherins, seven-pass transmembrane cadherins, Fat cadherins, plus others. A second large group of adhesion molecules is the immunoglobulin (Ig) superfamily, members of which contain varying number of extracellular Ig domains. In some Ig superfamily members fibronectin type III (FNIII) repeats are inserted between the Ig and transmembrane domains. N(neural)CAM, SynCAM, L1, the nectins, Sidekicks, SYG/nephrin, Dasm1, SALM, LAR-RPTPs, and many other members of this family have been reported to play roles in synapse development in both vertebrates and invertebrates. The neuroligins and neuexins are heterophilic adhesion molecules characterized by the presence of an acetylcholine esterase-like domain in the former and one to six LNS (laminin A, neuexin, sex hormone-binding protein) domains in the latter. Multiple genes and extensive splicing generate many isoforms of these proteins that promote differentiation of both excitatory and inhibitory synapses. Interactions mediated through constituents of the extracellular matrix (ECM) are essential for synapse development at the neuromuscular junction, and also appear to be important modulators of CNS synapse development and function. Both classical ECM receptors, including integrins and the dystroglycan complex, and novel receptors, such as the receptor tyrosine kinase MUSK, mediate synapse development through ligation to ECM constituents. Virtually all of the synaptic adhesion molecules described above interact with scaffolds and other proteins within the cytoplasm. These interactions function to localize synaptic adhesion molecules at synapses and to permit efficient activation of intracellular signaling cascades after synaptic adhesion molecule ligation. Many synaptic adhesion molecules contain PDZ domain-binding, poly-proline and other motifs which interact with PDZ, SH3 and other domains of scaffold proteins. Scaffold proteins act as key organizers to control localization of SNAREs, receptors, other synaptic proteins and organelles on both sides of the synapse.

Classical cadherins

Classic cadherins are a family of calcium-dependent, homophilic, cell-cell adhesion molecules that have been implicated in many developmental processes. Several studies indicate that N-cadherin functions as a synaptic recognition molecule. In *Drosophila*, absence of N-cadherin prevents synapse formation by the axons of photoreceptors in the medulla. The axons from the individual photoreceptors fail to establish stable connections with their target neurons in the medulla. Although analyzed in less detail, inhibition of cadherin function in the chick optic tectum also disrupts synapse formation by the axons of retinal ganglion cells. Extrapolating from these observations, it seems highly likely that a large number of cadherin members expressed in the vertebrate CNS also affect synapse formation with many having overlapping and redundant functions. Mutation of cadherin 11 has been shown to result in enhanced synaptic plasticity (LTP) in the hippocampus through unknown mechanisms.

Much of the progress in understanding the roles of cadherins in forming adhesive junctions has been made in studies of epithelial adherens junctions that share many molecular components with neuronal synapses. These discoveries have provided important insights into the pathways regulating synapse formation. The 'core' cadherin complex is composed of a cadherin bound through its

cytoplasmic domain to β -catenin which is bound in turn to α -catenin. In addition, the membrane-proximal portion of the cadherin cytoplasmic domain interacts less strongly with members of the p120 catenin family (p120 catenin, δ -catenin, p0071 and ARVCF). p120 catenins have been shown to regulate cadherin surface stability and clustering as well as regulate Rho family GTPases. Cadherin adhesion regulates organization of the actin cytoskeleton via several pathways: (1) through direct interaction of α -catenin with actin or actin-binding proteins, including α -actinin, vinculin, spectrin, afadin, ZO-1 and formin-1; (2) through regulation by p120 catenins of Rho GTPases and cortactin. Numerous kinases and phosphatases regulate the properties, stability, and interactions of the cadherin complex, including the protein kinases Cdk5, casein kinase I, Fyn, Yes, and Fer, and the protein tyrosine phosphatases PTP- μ , LAR, SHP1/2, and PTP1B. In addition to regulators of the actin cytoskeleton, the proteins in the cadherin complex interact with many additional proteins that control intracellular signaling pathways, including transcriptional regulators like Kaiso and TCFs, scaffold proteins, such as AKAP, and cytoplasmic enzymes including PI3 kinase, Cdk5, and receptor tyrosine kinases, plus cytoplasmic motor proteins and other proteins including presenillin. In addition, β -catenin and δ -catenin interact with PDZ-containing scaffold proteins that also mediate their synaptic functions.

Several of the catenins appear to function as effectors of cadherins in controlling synapse development. β -catenin functions as a scaffold to localize synaptic vesicle pools to synaptic sites. The presence of α N-catenin is required for normal spine maturation and stability. The absence of either δ -catenin or p120 catenin severely perturbs central synapses. Absence of p120 catenin reduces dramatically the density of dendritic spines and synapses. Absence of δ -catenin results in gross abnormalities in synaptic function and plasticity. In part, these proteins may function through regulation of the small G proteins, Rac and Rho. They may also function through stabilization of surface cadherins or through regulation of tyrosine phosphorylation and control of cortactin activity.

Protocadherins

Protocadherins are characterized by the presence of four to seven extracellular cadherin (EC) motifs, which are distinguishable from those present in other cadherin members, and absence of the conserved motifs in the classic cadherins that mediate interactions with β -catenin and p120 catenin family members. About 80 different protocadherins have been identified and genes of nearly 60 members are tandemly arrayed in three clusters, the α -, β -, γ -protocadherin genes (*Pcdh- α* , *- β* , and *- γ*) on a single chromosome in mammals. (α -protocadherins are also known as CNRs, cadherin-related neuronal receptors). Recent phylogenetic analysis has characterized several conserved motifs shared by an additional subfamily of protocadherins, the δ -protocadherins, whose genes are located on several different chromosomes. These include Pch1, Pch7, Pch8 (aracadin), Pch9 and Pch11. The *Pcdh- α* and *Pch- γ* clusters contain two large genomic regions, with tandem arrays of large exons expressing the variable extracellular domains followed by a set of common exons, each encoding a small portion of the shared C-terminal cytoplasmic domain. *Pch- β* lacks a shared constant region. Protocadherins are highly expressed in the central nervous system with individual members differentially expressed in subsets of neurons, suggesting they help generate specific synaptic connections within the CNS. Genetic deletion of the *Pch- γ* locus results in a reduction of inhibitory synapse density in the spinal cord. The mechanisms through which the protocadherins regulate synaptogenesis are not well understood. The strength of homophilic adhesion mediated by the extracellular domains of the protocadherins appears to be weaker than adhesion mediated by classic cadherin interactions. Recent evidence suggests that some protocadherins function through

regulation of classic cadherin adhesion. Protocadherins may also have non-cadherin proteins as ligands. For example, at least one of the Pch- α isoforms, Pch- α 4, interacts through its RGD motif with β 1 integrins. Protocadherin-7 interacts with PP1, a protein tyrosine phosphatase that dephosphorylates AMPA receptors and CAM kinase II.

NCAM (Neural cell adhesion molecule)

Neural cell adhesion molecule (NCAM) was the first Ig superfamily member reported to function at the synapse. NCAM is encoded by a single gene with three isoforms of 180k, 140k, and 120kDa produced by alternative splicing. The two larger isoforms are transmembrane proteins, differing in the presence of a differentially spliced exon that encodes an insert in the cytoplasmic domain, whereas NCAM-120 is a GPI (glycophosphatidyl inositol)-linked protein that lacks a transmembrane and cytoplasmic domain. All isoforms have five Ig domains followed by two FNIII repeats. The NCAMs are believed to mediate both homophilic and heterophilic interactions. Recently identified interacting partners include the Ig-family cell adhesion molecule L1, the FGF receptor, laminin and some integrins. Intracellular partners include the protein tyrosine phosphatase RPTP α , the tyrosine kinase p59Fyn and spectrin. The most remarkable feature of NCAM is that it is virtually the sole acceptor for long linear homopolymers of α 2, 8-linked sialic acid residues (polysialic acid, PSA). The major phenotypes of the NCAM knockout can be mimicked by the enzymatic removal of PSA, indicating that the major essential function of NCAM is to provide a substrate for PSA addition, which is highly charged, thereby increasing the volume of extracellular space and inhibiting adhesive interactions mediated through other cell adhesion molecules.

In vivo and *in vitro* results have demonstrated that NCAM regulates synaptic maturation at the neuromuscular junction and hippocampal synaptic plasticity (LTP), in part through associated PSA homopolymers. The NCAM homologues in invertebrates, *Drosophila* fasciclin II (FasII) and *Aplysia* apCAM, are involved in synapse growth, stability and plasticity and the expression of each is regulated by neuronal activity. Of particular interest, fasciclin II has been shown to function as both a permissive and restrictive regulator of synapse growth at the *Drosophila* neuromuscular junction, depending upon the comparative pre and post-synaptic levels of this protein. The ability of fasciclin II to promote new synapse formation requires the presence of the *Drosophila* orthologues of amyloid precursor protein and the scaffold protein Mint. Fasciclin II forms a complex with each of these proteins, the latter through its PDZ-interaction motif. In *Aplysia* sensory neurons, down-regulation of the NCAM homologue, apCAM, is required for the serotonin-induced enhancement of synaptic varicosity formation that accompanies synaptic facilitation. Normally, apCAM is downregulated following synaptic facilitation as a result of phosphorylation at a putative MAP kinase site. Overexpression of apCAM in sensory, but not motor neurons completely suppresses the formation of new varicosities without interfering with the activation by serotonin of CREB. Thus studies in both *Drosophila* and *Aplysia* indicate that NCAM homologues are important effectors of signaling pathways that control synaptic structural plasticity.

L1-family CAMs

The L1-type cell adhesion molecules are glycoproteins with six Ig, five FNIII, a single transmembrane and a cytoplasmic domain. Four members, L1-CAM, Neurofascin, Nr-CAM and CHL-1, have been identified in vertebrates while *Drosophila* has only one homologue, Neuroglian.

L1-type CAMs mediate several aspects of neuronal development, including neuronal migration, neurite extension, axon pathfinding, myelination, fasciculation, synapse targeting and LTP. Among these family members, the role and function of L1 has been particularly intensely studied. In addition to binding L1 molecules present on other cells, L1 associates with additional ligands, including the proteoglycan neurocan, several RGD-binding integrins, and the CAMs axonin-1/TAG and contactin/F3/F11. L1 also interact with the axon guidance receptor neuropilin in both cis- and trans to form a receptor for Semaphorin 3A.

Of particular interest, localization of neurofascin at the initial axon segment of cerebellar Purkinje neurons results in specific localization of GABAergic synapses to this same region of the axon. At early stages of development both GABAergic synapses and neurofascin are less well localized. Refinement of neurofascin localization precedes and is required for localization of the GABAergic synapses. Neurofascin binds with high affinity to an isoform of ankyrin, an intracellular adaptor protein which is localized also to the initial axon segment and provides a scaffold for association with β -spectrin and the F-actin cytoskeleton. These interactions are required to localize both neurofascin and the GABAergic synapses. Observations in other CNS regions indicate that other L1 CAM family members are also preferentially localized to sub-domains of neurons. It seems likely that they also help localize synapse formation. A number of human brain disorders have been linked to mutations in the L1 gene and L1 knockout mice reproduce several aspects of these phenotypes. It will be interesting to determine whether any aspects of the phenotypes associated with these disorders result from mis-targeting of synapses.

Other synaptic immunoglobulin superfamily members

SYG-1 is a member of the Ig superfamily identified in a genetic screen for synapse mutants in *C. elegans* that contains four Ig, a single transmembrane, and a cytoplasmic domain with a PDZ interaction motif. SYG-1 regulates the position of presynaptic terminal differentiation by HSNL axons which innervate the vulval muscles. It is related to *Drosophila* Duf/Kirre and the three vertebrate NEPH proteins that are important for organization of the slit diaphragm in the kidney glomerulus. SYG-1 binds to SYG-2, which has six Ig domains and one FNIII domain and is expressed transiently by primary vulval epithelial cells during synapse formation. SYG-2 provides an intermediate target that focuses accumulation of SYG-1 and synaptic vesicles. The mammalian homologue of SYG-2 is nephrin whose presence in podocytes is also essential for organization of the slit diaphragm in the kidney. The roles of the NEPH family and nephrin in vertebrate synapses are not yet known, but recent work, stimulated by the observations in *C. elegans* has documented their expression patterns in the CNS. In addition, the NEPH proteins have been shown to interact with CASK, a constituent of the CASK/MINT/Veli complex, which is thought to participate in pre and post-synaptic organization. Since both nephrin and the NEPH proteins are expressed in the CNS, it will not be surprising if they prove to have important functions there.

The Sidekick (Sdk) CAMS, Sdk-1 and Sdk-2, contain six Ig domains, thirteen FNIII repeats, a single transmembrane domain and a cytoplasmic domain terminated by a PDZ interaction motif. Interestingly, in the retina the Sdk-1 and Sdk-2 proteins are found in non-overlapping subsets of presynaptic (amacrine and bipolar) and postsynaptic (ganglion) cells that project to common inner plexiform (synaptic) sublaminae. Sdk-positive synapses are confined to specific sublaminae, and ectopic expression of Sdk in Sdk-negative cells redirects their arbors to Sdk-positive sublaminae, implying that the Sdks may control laminar specificity within the retina. The interactions and signaling mechanisms controlled by the Sdks that regulate synapse location are not known.

Dasm (Dendrite arborization and synaptic maturation)¹ is a recently reported Ig family member

with five Ig-like domains, two FNIII domains and a cytoplasmic domain with a C-terminal PDZ domain-binding motif. Dasm has been shown to promote dendritic elongation and branching as well as the maturation of excitatory glutamatergic synapses. Dasm interacts with PDZ-containing scaffold proteins, including Shank and S-SCAM. In its absence, AMPAR-mediated, but not NMDAR-mediated, synaptic transmission is severely impaired in cultured hippocampal neurons. A Dasm mutant lacking the PDZ-interaction motif does not promote AMPA receptor-mediated synaptic transmission. The extracellular ligands for Dasm have not been identified.

The SALMs (synaptic adhesion-like molecules) are another recently characterized family of five synaptic adhesion molecules (SALM1-5) that contain six leucine-rich repeats plus single Ig and FNIII repeats in their extracellular domains. The SALMs are transmembrane proteins with cytoplasmic domains terminated by a PDZ-interaction motif. Some members of the SALM family have been shown to promote excitatory synapse formation through interactions with PSD-95 and other cytoplasmic scaffold proteins. Members have also been shown to interact with NMDA and AMPA receptors. It is not clear whether they function as typical cell adhesion molecules by mediating adhesion with other cells.

The four nectins (nectin 1-4) are transmembrane proteins containing three extracellular Ig-like repeats and a cytoplasmic domain terminated by a PDZ-interacting motif. While each of the nectins mediates homophilic adhesion, they promote stronger heterophilic adhesion with other family members. Several nectins also interact with the integrin $\alpha_v\beta_3$. Each of the nectins interacts with the F-actin-binding protein afadin, thereby anchoring the nectins directly to the F-actin cytoskeleton. Through afadin-mediated interactions with α -catenin, the nectins recruit and collaborate with the cadherins to promote formation of adherens junctions in epithelial cells. Afadin also binds the small G protein Rap1. The Rap1-Afadin complex has been shown to interact with p120 catenin and through p120 catenin to activate cadherin-mediated adhesion. Active (GTP-bound) Rap promotes maturation of dendritic spines in the CNS and it seems possible that this is, in part, through regulation of the afadin-nectin-cadherin complex. Nectin-1 is preferentially expressed in axons. Preferential engagement of heterophilic adhesion between axonal nectin1 and dendritic nectin3 may provide a basis for the preferential interactions of axons with dendrites vs. other axons.

Members of the LAR (Leukocyte common antigen-related) family of receptor protein tyrosine phosphatases are transmembrane proteins with each containing three Ig and eight FNIII domains plus two cytoplasmic tyrosine phosphatase motifs. The cytoplasmic domains of these proteins interact with liprin- α /SYD-2, which binds to the PDZ-containing scaffold protein GRIP. This interaction promotes the surface expression and clustering of receptors at postsynaptic sites. In *Drosophila* and *C. elegans*, LAR and liprin- α have been also implicated in presynaptic terminal differentiation. In *Drosophila*, LAR-mediated synaptic differentiation is regulated by interactions of LAR with the cell surface-associated proteoglycans syndecan and dally-like. In cultured hippocampal neurons, LAR is concentrated at mature excitatory synapses where it promotes their development and maintenance through enhanced spine formation and surface AMPA receptor expression.

Finally, the four members of the SynCAM family (also known as Nectin-like proteins) constitute a small subset of the Ig superfamily, each member of which contains three extracellular Ig domains and a PDZ-interacting motif in its short cytoplasmic domain. They were identified in a genomic search for members of the Ig superfamily capable of interacting with PDZ-domain-containing scaffolds. Similar to many other Ig family members, the SynCAMs mediate homophilic cell-cell adhesion. SynCAM1 is highly enriched in both presynaptic and postsynaptic membranes of neurons, whereas SynCAM3 is found in non-junctional contact sites of presynaptic nerve terminals, axons and glia cell processes. Clustering of SynCAM1 is sufficient to trigger differentiation of functional presynaptic terminals. SynCAM1 overexpression also increases synaptic function in

immature excitatory neurons. Interactions mediated through association with PDZ-domain containing scaffolds are essential for its synapse-inducing activities. The PDZ-interaction motif in SynCAM binds to the PDZ domains present in CASK and syntenin.

Neurexins and Neuroligins

Neuroligins are composed of a cholinesterase-like domain, an O-glycosylation region, a single transmembrane domain and a short C-terminal cytoplasmic tail containing a PDZ-binding motif. Three genes encoding neuroligins are present in the rat and mouse while five are present in the human genome. The first neurexin to be characterized was identified as a receptor for the spider venom constituent α -latrotoxin. There are three Neurexin genes, each of which encodes two neurexin isoforms with one promoter initiating transcription of a long mRNA encoding α -neurexin isoforms while a second promoter located within an intron initiates transcription of a shorter mRNA encoding β -neurexin isoforms. The extracellular domain of α -neurexin contains three EGF-like domains, each of which is flanked by a pair of LNS domains. Instead of six LNS domains, only one is present in the β -neurexins, which lack all of the EGF repeats. The extracellular domains of both α - and β -neurexins are followed by a transmembrane domain and a cytoplasmic domain containing a C-terminal PDZ-interacting site. Differential splicing of the transcripts from each of the neurexin and neuroligin genes generates a tremendous number of variants of each protein family. Recent results have demonstrated that splicing controls the specificity of neurexin-neuroligin interactions as well as their activities in promoting excitatory and inhibitory synapse formation. In addition to binding neuroligins, some, but not all isoforms of neurexins interact with dystroglycan.

On cultured hippocampal neurons, clustering of the β -neurexins or neuroligins triggers pre- or postsynaptic differentiation, respectively. In contrast to SynCAM, however, neuroligin overexpression does not result in enhanced synaptic transmission in immature excitatory neurons. Similar to the SynCAMs, the synapse-promoting activities of these proteins are dependent on their interactions with PDZ-containing scaffold proteins. The PDZ-interacting motif in neuroligin interacts with PSD-95, which recruits AMPA and NMDA receptors as well as with S-SCAM, which interacts with AMPA receptors and β -catenin. β -neurexin interacts with the CASK/Mint/Veli complex, which is proposed to act as a scaffold for synaptic vesicle transport and localization. β -neurexin also interacts with syntenin, which has recently been shown to interact with the presynaptic cytomatrix active zone protein ELKS/ERC2/CAST1, which binds in turn several additional active zone proteins, including piccolo, bassoon and RIM. Interestingly, neuroligin1 is mainly localized to excitatory whereas neuroligin2 is localized at inhibitory synapses. Overexpression and knockdown experiments *in vitro* suggest that the expression levels and localization of different neuroligins may play a crucial role in controlling the ratio of excitatory and inhibitory synapses. Mutations in human neuroligin genes are associated with a small percentage of autistic individuals.

ECM (Extracellular matrix)-mediated interactions

ECM molecules regulate synapse development in both the central and peripheral nervous systems. At the neuromuscular junction (NMJ), several constituents of the basal lamina have been shown to be essential for normal synapse formation. Most importantly, the presence of nerve-derived agrin in the basal lamina and its receptor, the tyrosine kinase MUSK, in muscle are absolutely required for synapse formation and maintenance. In addition, several subunits of laminin also play important roles. The presence of the laminin β 2 subunit in the laminin trimer within the

synaptic basal lamina appears to play two distinct roles. First, this subunit prevents invasion of the synaptic cleft by Schwann cells, thereby preserving communication between the motor axon terminal and the muscle surface. Second, this subunit directly binds to N-type calcium channels. In its absence few active zones are seen at neuromuscular junctions, even at sites where Schwann cells have not invaded the synaptic cleft, and synaptic transmission is severely impaired. In contrast, although synaptic transmission is not impaired in its absence, the laminin $\alpha 4$ subunit functions to ensure proper alignment of active zones in the nerve terminal with folds in the postsynaptic muscle membrane. In laminin $\alpha 4$ mutants, the active zones and folds are no longer aligned with each other. Laminin $\alpha 4$ is largely excluded from the small regions of basal lamina aligned with the active zones and muscle folds, suggesting that it may inhibit the formation of these specializations. In addition to MUSK, the integrins and dystroglycan complex function as receptors for basal lamina proteins at the neuromuscular junction. Absence of $\beta 1$ integrins severely impairs neuromuscular junction formation. Mild deficits are observed in the absence of some constituents of the dystroglycan complex.

Although there have been many studies, there are less obvious roles for ECM constituents at synapses in the central nervous system. The ECM glycoprotein reelin, best known for its role in controlling neuronal migration in the cortex and cerebellum, also promotes maturation of many CNS synapses through the same signaling pathway important for its role in cell migration—Src-family kinase mediated phosphorylation of Dab, following engagement of the reelin receptors VLDLR and apoER2. Several additional ECM receptors also affect synapse maturation. For example, the cell surface proteoglycan syndecan-2 is enriched in the mammalian hippocampus and promotes morphological maturation of dendritic spines in cooperation with the receptor tyrosine kinase EphB2. Syndecan-2 is a transmembrane glycoprotein with a cytoplasmic PDZ-interacting motif, which interacts with CASK, syntenin and synbindin. As described previously, syndecan regulates LAR in *Drosophila*.

In *Drosophila*, elegant studies have demonstrated a crucial role for integrins in memory formation in the mushroom body. In hippocampal neuron cultures, several studies have demonstrated important roles for integrins in promoting synapse maturation. *In vivo* studies have shown that inhibition of RGD binding or $\beta 1$ integrin function through genetic or pharmacological techniques impairs long-term plasticity. Ligand engagement by integrins results in activation of several intracellular signaling cascades including those initiated by Src-family, focal adhesion kinase, and integrin-linked kinases, plus recruitment of scaffolds and adaptor proteins, such as talin and paxillin that lead to reorganization of actin cytoskeleton.

Concluding remarks

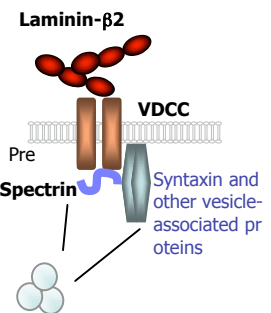
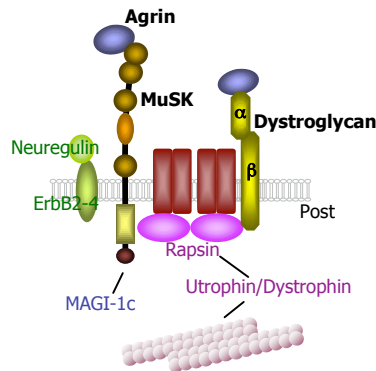
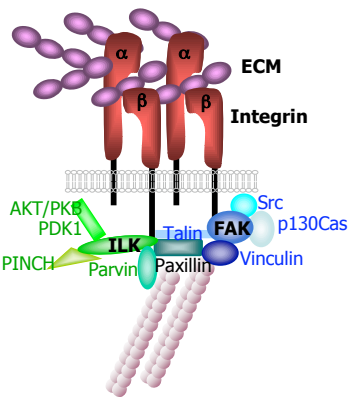
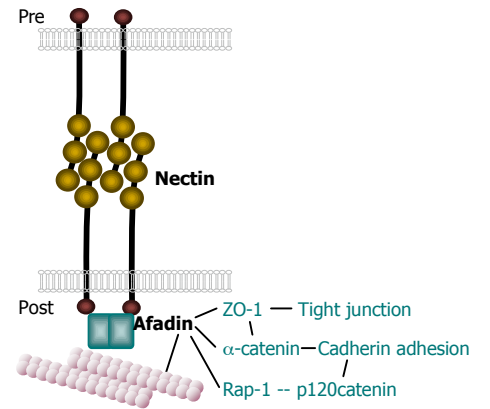
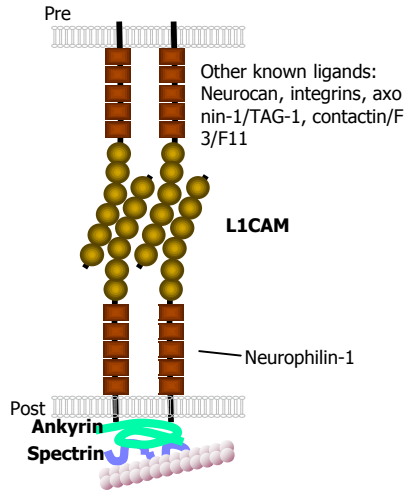
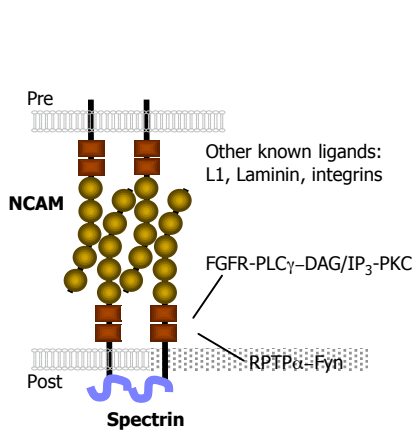
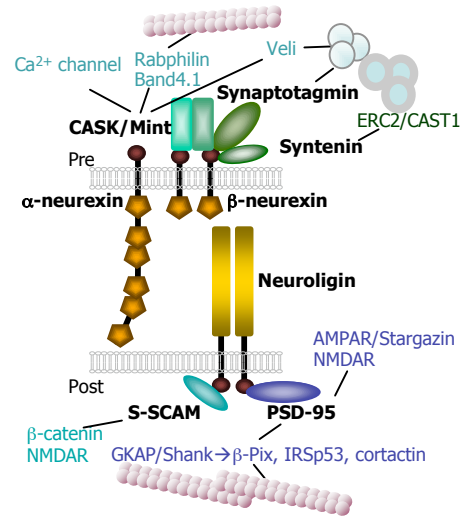
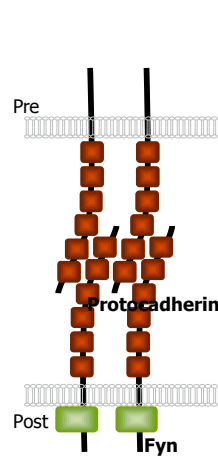
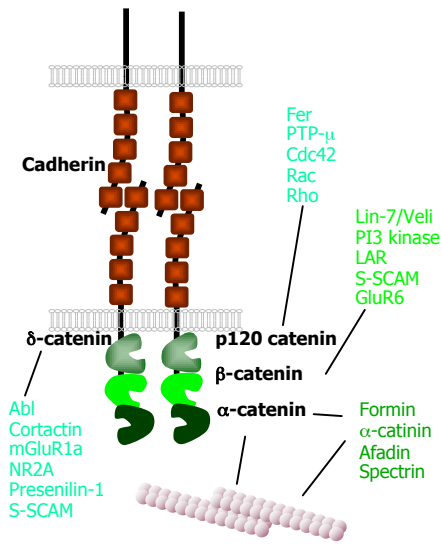
Much exciting evidence demonstrating important roles of synaptic adhesion molecules has been accumulated recently in both *in vivo* and *in vitro* model systems. We anticipate that future studies focusing on the crosstalk between different adhesion molecules will further illuminate our understand of synapse development and function.

Further Reading

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Table 1. Roles of adhesion molecules at the synapse

Function	Molecule	Class	Place of action	Comment
Target recognition	N-cadherin	Cadherin	Chick optic tectum <i>Drosophila</i> visual system	Synaptic recognition
	Protocadherins	Cadherin	CNS?, spinal cord	Determination of synaptic connectivity
	Flamingo	Cadherin	<i>Drosophila</i> visual system	Interactions of R-cell growth cones with target neurons
	Neurofascin	Ig	Mouse GABAergic cerebellar Purkinje cells	Subcellular specification of GABAergic synapses
	Sidekick	Ig	Mouse retina	Lamina-specific synaptic connectivity in inner plexiform layer
	Nectin	Ig	Hippocampal pyramidal	Regulation of axon-dendrite interactions
Induction and maturation of synapse	SynCAM	Ig	Hippocampal pyramidal neurons	Induction of synaptic differentiation
	Dasm, SALM	Ig	Hippocampal pyramidal neurons	Promotion of surface AMPA receptor expression and synaptic maturation
	LAR-RPTP	Ig	Hippocampal pyramidal neurons	Promotion of surface AMPA receptor expression and synaptic maturation
	Neuroigin/ β -neurexin		Hippocampal pyramidal neurons	Induction of synaptic differentiation
	Laminin β 2 Laminin β 4	ECM	Neuromuscular junction (NMJ) in <i>Drosophila</i> and mouse	Organization of active zone, alignment and maintenance of NMJ
	Reelin	ECM	Mouse cortex and cerebellum	Maturation of CNS synapses
	Syndecan-2	Proteoglycan	<i>Drosophila</i> NMJ Hippocampal pyramidal neurons	Postsynaptic maturation
	Versican	ECM proteoglycan	Chick optic tectum.	Lamina-specific cue for presynaptic maturation of retinal ganglion axons
	CPG15 (neuritin)	GPI-linked surface protein	Motor neuron	Regulation of axonal branching and synapse maturation
Synaptic plasticity	Cadherin-11	Cadherin	Hippocampal pyramidal neurons	Regulation of hippocampal LTP
	NCAM, FasII, apCAM	Ig	Vertebrate CNS, <i>Drosophila</i> NMJ and <i>Aplysia</i> sensory neurons	Regulation of new synapse formation and structural synaptic plasticity
	Integrins	ECM receptor	Central excitatory synapse	Modulation of NMDA-mediated synaptic currents and synaptic plasticity



	Cadherin extracellular domain		Synaptic vesicle
	LNS (lamininA, neurexin, sex hormone-binding protein) domain		Cytomatrix active zone vesicle
	Immunoglobulin domain		Actin cytoskeleton
	Fibronectin III domain		Plasma membrane
	PDZ-binding motif		Lipid raft
	Acetylcholine receptor		Basal lamina

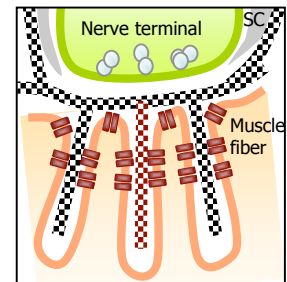


Figure 1. Structures and interactions of synaptic adhesion molecules

Top row of three diagrams illustrate interactions of the classical cadherin complex (left), protocadherin complex (middle), and neuroligin/neurexin complex (right). The second row depicts complexes formed by N(neural)CAM (left), L1-family CAMs (middle), and nectins (right). The bottom row illustrates interactions mediated as a result of integrin-ECM interactions (left), agrin/MuSK/dystroglycan interactions (middle), and laminin β 2-calcium channel association (right). A lower power schematic of the neuromuscular junction is depicted at the lower right corner of this figure. Agrin, laminin β 2 and laminin α 4 chain-containing laminin trimers reside in the basal lamina depicted in this figure, while the agrin receptor MUSK is localized to the muscle plasma membrane. The three EGF-like repeats are not depicted in the β -neurexin structure. Pre: presynaptic compartment; Post: postsynaptic compartment; VDCC: voltage-dependent calcium channel; SC: Schwann cells. See text for details.

Suggested cross-references to other articles

- MS 335 Extracellular matrix (laminin, fibronectin, cadherin, integrin)
- MS 343 Ephrins and Eph Receptors
- MS 347 Dendritic development (Activity, Wnt, & Rho GTPases)
- MS 348 Developmental synaptic plasticity: LTP, LTD, and synapse formation and elimination
- MS 349 Presynaptic development & active zones
- MS 351 Retrograde transsynaptic influences
- MS 356 β -Catenin: localization of synaptic vesicles
- MS 357 Postsynaptic development, muscle (agrin, MuSK, rapsyn, neuregulin)
- MS 358 Synaptogenic molecules (neuroligin, synCAM)
- MS 360 Postsynaptic development, neuronal (molecular scaffolds)
- MS 364 SYG
- MS 371 Sidekick
- MS372 DsCAM and Flamingo
- MS1250 Development of vertebrate neuromuscular junctions
- MS1253 Agrin
- MS1352 SynCAM
- MS1365 Neurexins
- MS1375 Neuroligins
- MS1784 Neuroligins and neurexins
- MS1785 NCAM and synapse regulation
- MS1786 Cadherins and synapse organization
- MS1788 Assembly of postsynaptic specialization