Cell adhesion molecules in the central nervous system

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Key words: synapses, cell adhesion molecules, cadherin superfamily, immunoglobulin superfamily, nerve tissue proteins, axons

Cell-cell adhesion molecules play key roles at the intercellular junctions of a wide variety of cells, including interneuronal synapses and neuron-glia contacts. Functional studies suggest that adhesion molecules are implicated in many aspects of neural network formation, such as axon-guidance, synapse formation, regulation of synaptic structure and astrocyte-synapse contacts. Some basic cell biological aspects of the assembly of junctional complexes of neurons and glial cells resemble those of epithelial cells. However, the neuron specific junctional machineries are required to exert neuronal functions, such as synaptic transmission and plasticity. In this review, we describe the distribution and function of cell adhesion molecules at synapses and at contacts between synapses and astrocytes.

Introduction

The cell-cell adhesion system is involved in many aspects of neuronal development, including neuronal cell migration, axon-bundle formation, synapse formation and formation of complex of glial networks which surround axons and synapses. These adhesion systems are important for brain morphology and highly coordinated brain functions, such as memory and learning.1-3 Like epithelial junctions, cell-cell junctions in the nervous systems contain a variety of transmembrane proteins, cytoskeletal elements and signaling complexes.

During early development of the nervous systems, differentiated neurons migrate to their proper positions and elongate their axons towards their targets. Growing axons are guided by various attractive or repulsive target-derived cues.4 After reaching their target areas, axonal growth cones still need to recognize their appropriate target cells for the formation of synapses. Then, initial contacts are formed between axons and dendrites, and signaling through homophilic and heterophilic receptors induces differentiation of the synaptic specialization.5 Most of these interactions and recognitions have been shown to be mediated by cell surface proteins. Various cell surface proteins have been identified and characterized as important regulators of axon-guidance and synapse formation (Table 1). These molecules interact with each other between the cells to activate various signaling pathways and bring the apposed cell membranes into contact. Some of these molecules are defined as adhesion molecules and others as signaling molecules. However, as certain adhesion molecules are known to have signaling functions and the signaling molecules often promote cell-cell adhesion, it might not be so easy to distinguish these membrane proteins specifically involved in adhesion or signaling.

In addition to neuron-neuron interactions, astrocyte-synapse interactions are also known to play important roles in the formation of neural networks. Astrocyte-synapse communication participates in synapse formation, synaptic transmission and axonal conduction, and perhaps modulates the activity of neuronal networks during development and throughout adult life.6 Recent advances have clarified the molecular compositions of astrocyte-synapse interfaces, and have provided new insight into astrocyte-synapse communication. To date, a few adhesion molecules have been identified at the astrocyte-synapse contacts. Here, we briefly summarize the key cell adhesion molecules involved in the synapse formation and in the astrocyte-synapse interactions.

Synapses

Synapses are a specialized form of intercellular junctions where the axon terminal of a neuron comes into functional contact with a target cell (Fig. 1A and B). Specificity and plasticity of synapses provide neurons with a structural and functional basis for the formation of the neuronal network system. Synapses are highly asymmetrical junctions formed between two different neurons, and early ultrastructural studies showed that the synaptic junctional areas contain at least two types of adhesion structure (Fig. 1C).7,8 One type of adhesion structure is the transmitter release zone associated with synaptic vesicles, termed synaptic junctions (SJs), and the other is a symmetrical junction, termed puncta adherentia junctions (PAJs), defined by the two criteria of symmetric paramembranous dense materials and the lack of association with synaptic vesicles (Fig. 1B). SJs are regarded as sites for neurotransmission. They are associated with presynaptic active zones containing Ca2+ channels and numerous neurotransmitter-filled synaptic vesicles which are docked on the presynaptic membrane by a complex of proteins, and postsynaptic densities where the specific neurotransmitter receptors and structural scaffolding and signaling proteins are localized. PAJs are regarded as mechanical adhesion sites between axon...
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Diagram of cell adhesion molecules in synapses:

A. Neuron structure with labels:
   - Synapses
   - Axon
   - Dendrites
   - Neuron Cell Bodies

B. Presynaptic Axon-side and Postsynaptic Dendrite-side:
   - Neurotransmitter Receptors
   - Synaptic Vesicles
   - Synaptic junction
   - Puncta Adherentia Junctions

C. Microscopic image of synapses.

D. Presynapse Axon-side and Postsynapse Dendrite-side:
   - Cadherin repeats
   - Ig repeats
   - Fibronectin type III
   - PDZ-binding motif
   - Catenins
   - Afadin
   - Spectrin
   - PSD-95/58/SCI

Intra-cellular binding proteins

E. Astrocyte, Axon terminal, Dendrite:
   - Neutrophin Receptors
   - Synaptic Vesicles
   - Necl-1
   - AMOG
   - Integrins
   - Homophilic

Microscopic image of astrocyte and Necl-1 binding.
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Figure 1 (see previous page). (A) Synapses are formed at the contact points between axons and dendrites of their target neurons. (B) At synapses, at least two types of intercellular junctions, synaptic and puncta adherentia junctions, have been recognized. Synaptic junctions are regarded as sites of neurotransmission, associated with synaptic vesicles at the presynaptic active zone where Ca^2+ channels localize, and postsynaptic densities (PSDs), where neurotransmitter receptors localize. Puncta adherentia junctions, which are not associated with synaptic vesicles or PSDs, appear to be ultrastructurally similar to adherence junctions of epithelial cells. (C) Electron microscopic morphology of the synapses between the mossy fiber terminals and the dendrites of pyramidal cells in the CA3 area of the hippocampus. Arrows indicate PAJs. Arrow heads indicate SJs. D: dendrite. S: dendritic spine. MT: mossy fiber terminal. Scale bar, 200 nm. (D) Molecular composition of the synapse. Many of these adhesion molecules possess a binding motif that binds to PDZ proteins. These interactions associate with each other and lead to the formation of a multi-molecular scaffold beneath both the pre- and post-synaptic membranes. (E) Astrocytes have many characteristic features and ensheath synaptic junctions in the brain, but do not form myelin. Necl-1 localizes at the contact sites between axon terminals and glia cell processes and interacts homophilically.

Table 1  Lists of the neuron-neuron and neuron-glia interactions in the nervous systems

| Classification | Adhesion molecules | Localization |
|----------------|--------------------|--------------|
| Cadherin Super Family | Classic cadherins | Synapse (PAJs), Neuron-Glia |
|                | Proto-cadherins | Synapse (PAJs), Neuron-Glia |
| Iglike Molecules | Nectins | Synapse (PAJs), Neuron-Glia |
|                | Nectin-like molecules (Necls) | Neuron-Glia |
|                | NCAM | Synapse |
|                | Syg-1, Syg-2 | Synapse |
|                | Sidekicks | Synapse |
|                | Integrins | Synapse, Neuron-Glia |
| Others | Neurilogs, neurexins | Synapse (SJs) |
|                | Eph receptors, ephrins | Synapse (SJs) |

Terminals and their targets, although their exact functions remain unknown. However, PAJs are morphologically similar to adherent junctions (AJs) formed in epithelia, and several important molecular constituents of neuronal synapses are common to both neurons and epithelial cells. Thus, some basic cellular aspects of the assembly of junctional complexes may be shared between these two cell types. During development, specific neuronal circuits are assembly of junctional complexes may be shared between these two and epithelial cells. Thus, some basic cell biological aspects of the constituents of neuronal synapses are common to both neurons and epithelial cells. Thus, some basic cell biological aspects of the synthesis, associated with synaptic vesicles at the presynaptic active zone where Ca^2+ channels localize, and postsynaptic densities (PSDs), where neurotransmitter receptors localize. Puncta adherentia junctions, which are not associated with synaptic vesicles or PSDs, appear to be ultrastructurally similar to adherence junctions of epithelial cells. Thus, some basic cell biological aspects of the contents of neuronal synapses are common to both neurons and epithelial cells. Thus, some basic cell biological aspects of the

Cadherins

Cadherins are Ca^2+-dependent cell-cell adhesion molecules that constitute a superfamily comprised of more than 100 members in vertebrates, and are grouped into subfamilies that are designated as classic cadherins and protocadherins. Classic cadherins are single-pass transmembrane proteins and have five extracellular cadherin repeat (EC) domains (EC1 to EC5). All classic cadherins are homophilic adhesion molecules that function with their cytoplasmic (CP) partners, catenins (Fig. 1D). Catenins are cadherin-binding proteins that connect cadherins to the actin cytoskeleton. These include α-catenin, β-catenin and p120 catenin. The cadherin-catenin complexes are known to regulate actin polymerization, a property important for maintaining the cell-cell adhesion. Catenins and their associated catenins have been observed in many neuronal populations in the central nervous systems (CNS). At the ultrastructural level, these proteins were found in synaptic junctions of most regions of the nervous systems, forming a symmetrical adhesion structure in the PAJs. During development, the cadherin-catenin complexes accumulate at early axo-dendritic filopodial contacts, and are retained in many of the mature synapses. A fragment of N-cadherin lacking its extracellular region serves as a dominant negative mutant of cadherin and inhibits their cell-cell adhesion activity. Expression of this mutant results in the appearance of filopodia-like spines, an increase in the spine length, and a decrease in the spine head width, and effects the organization of synapses in the cultured hippocampal neurons. Despite the evidence that cadherins are involved in the formation of synapses, they are not sufficient to form them in vitro, because expression of N-cadherin in non-neuronal cells fails to induce pre-synaptic differentiation in axons at the sites of contact. Recent studies also implicate catenins in the control of spine structure and synaptic organization in cultured hippocampal neurons. Deletion of β-catenin affects localization of synaptic vesicles along the axon, and loss of p120 catenin affects Rho-family small G-protein signaling, which results in a reduced spine density. A remarkable feature of classic cadherins is its binding specificity and region-specific distribution. In the brain, many subtypes of classic cadherins are expressed by restricted groups of functionally connected nuclei and laminas. Whether cadherin-mediated adhesion contributes to the formation of selective inter-neuronal connections during neural network formation remains unknown.

Protocadherins

Protocadherins are a group of transmembrane proteins that belong to the cadherin superfamily, and have varying numbers of the EC domains but divergent cytoplasmic domains that do not appear to signal through catenins. Various protocadherins are expressed in the nervous systems, and some of them are localized at synapses. Multiple α- and γ-protocadherin isoforms are highly expressed in distinct, although partially overlapping, sets of neurons and concentrated at synapses. The complex genomic organization and alternative splicing of protocadherins have led to the speculation that their diversity underlies synaptic specificity. γ-protocadherins are required for survival of specific neuronal types and arcadlin is required for activity-dependent synaptic morphogenesis. However, the biological functions of most protocadherins are unknown.

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Nectins

Nectins represent a family of Ca\(^{2+}\)-independent immunoglobulin (Ig)-like cell-cell adhesion molecules, which consist of four members (Fig. 1D).\(^{29}\) At the CA3 region of hippocampus, nectin-1 and nectin-3 asymmetrically localize at the pre- and post-synaptic sides, respectively, of the PAs, but not at SJs.\(^{10}\) Nectins form homo- or hetero-trans-dimers in a Ca\(^{2+}\)-independent manner, where heterotypic binding leads to stronger adhesion than homotypic binding.\(^{30-32}\) In epithelial cells in culture, nectins first form cell-cell adhesion and then recruit cadherin to the nectin-based cell-cell adhesion sites to cooperatively form AJs.\(^{33,34}\) Araf, an actin-filament binding protein that connects nectins to the actin cytoskeleton, is also present at PAs. Disruption of nectin-based cell-cell adhesion in cultured hippocampal neurons decreases the size of synapses but increases their number,\(^{10}\) and a nectin-1 mutant causes human cleft lip/palate, syndactyly and ectodermal dysplasia.\(^{35}\) In both nectin-1 and -3-deficient mice, the number of PAs at the synapses between the mossy fiber terminals and the dendrites of the CA3 pyramidal cells in the hippocampus is reduced. In addition, the abnormal mossy fiber trajectory is observed, suggesting that nectins are involved in the formation of PAs, which maintain the proper mossy fiber trajectory in the CA3 region of the hippocampus.\(^{36}\) In afadin-deficient mice, perforated synapses in the hippocampus are observed. Reduction in the number of PAs is likely to be further enhanced in afadin-deficient mice than in nectin-1 or -3-deficient mice. The observation of loss of PAs in the nectin and afadin-deficient mice suggests the possibility that the localization of the cadherin/catenin complex is regulated by the nectin/afadin system, similar to epithelial adherens junctions. The recruitment of afadin (AF-6) to postsynapse is regulated by small G-protein Rap1, and is involved in spine formation.\(^{37}\)

The axon-biased localization of nectin-1 and its trans-interaction with nectin-3 in cooperation with the cadherin machinery is critical for the ordered association of axons and dendrites.\(^{38}\) However, the sorting signal of nectin-1 to axons has not been identified.\(^{39}\) The genetic deletion of nectin-1 loosens the contacts between axons and dendritic spines, while the overexpression of nectin-1, causing mislocalization of nectin-1 to dendrites, induces atypical dendro-dendritic contacts as well as excessive axo-dendritic contacts. These actions of nectins require cadherin-catenin complexes suggesting that the two adhesion systems cooperate.\(^{38}\) These data suggest that localized cadherin activity may be achieved by cooperative heterophilic nectin interactions. It is also likely that mechanisms work for restricting adhesion activity at specific cell-cell contact sites. These data are consistent with those obtained in epithelial cells, suggesting that nectins form initial cell-cell adhesion and recruit cadherins to the nectin-based cell-cell adhesion sites to form AJs, and suggest that nectins play similar roles in the formation of PAs.

Other Ig Superfamily CAMs

Other Ig superfamily CAMs, which have varying numbers of Ig-like domains, have been identified at synapses and have been shown to be involved in synaptic formation and plasticity. For example, neural cell adhesion molecule (NCAM), which contains five Ig-like domains and two fibronectin type III repeats, is engaged in homophilic and heterophilic interactions with a variety of ligands at synapses, such as fibroblast growth factor receptor (FGFR), L1, TAG-1/axonin-1 and heparan sulfate proteoglycans (Fig. 1D).\(^{40,41}\) NCAM is widely expressed in the developing and adult brains and plays crucial roles in migration, pathfinding of axons, and synaptic plasticity. It is involved in both early synaptogenesis and subsequent synaptic maturation.\(^{42,43}\) NCAM is unique among adhesion molecules in that it carries a large amount of the negatively charged sugar, polysialic acid (PSA) (Bonfanti et al., in this issue). Poor axonal fasciculation is observed in the hippocampus of NCAM-deficient mice, resulting in an impaired synapse formation in the CA3 region.\(^{44}\) Mossy fibers also appear defasciculated in mice with the NCAM-180 isoform.\(^{45}\) These functions of NCAM appear to be mediated by primarily by presence of the PSA moiety.\(^{46}\) Neurofascin 186 (NF186), an L1 family Ig-like cell adhesion molecule, is implicated in the subcellular organization of GABAergic synapses between basket interneurons and Purkinje cells in the cerebellum.\(^{47}\)

**SYG-1/SYG-2**

SYG-1/SYG-2 are specific adhesion molecules that determine synaptic specificity in a lock-and-key manner. SYG-1, a four Ig-like domain-containing protein, and SYG-2, a seven Ig-like domain- and one fibronectin type III repeat-containing protein, were isolated in a genetic screen for C. elegans mutants that exhibit defective synaptic positioning.\(^{48,49}\) Interactions between SYG-1 and SYG-2 induce formation of synapses at appropriate synaptic targets. The Drosophila orthologues of roughest (rst) have been implicated in axon fasciculation and layer targeting in the fly visual system.\(^{50}\) Moreover, SYG-1 and SYG-2 share significant homology with the mice and human proteins NEPH and Nephrin, which are expressed in the CNS, although their roles in the CNS remain unknown.

**Sidekicks**

Sidekicks, which have six Ig-like domains and thirteen fibronectin type III repeats, have been implicated in selective synapse formation in the chicken retina.\(^{52}\) Sidekick-1 and -2 are differentially expressed among subsets of retinal ganglion cells in a non-overlapping manner. Sidekicks act as homophilic adhesion molecules in vitro, and are highly concentrated at synapses of restricted regions in vivo. Ectopic expression of Sidekick in Sidekick-negative cells induces mis-targeting. These data suggest that sidekick interactions may promote lamina-specific connectivity.

**Neuroligin**

Neuroligin is an esterase-like domain-containing protein and localizes at the post-synaptic side of SJs, whereas β-neurexin is a laminin-globular-domain-containing protein and localizes at the pre-synaptic side of SJs. These two molecules interact with one another and this interaction induces the formation of synapses in vitro (Fig. 1D). The neurexin family was first identified as receptors for alpha-latrotoxin, which acts presynaptically to release neurotransmitters from sensory and motor neurons.\(^{53}\) More than 1,000 neurexin isoforms are generated by alternative splicing, which are differentially expressed in the nervous systems.\(^{54}\) Neuroligins is a β-neurexin binding partner.\(^{55,56}\) β-Neurexin binds neuroligins trans-synaptically and induces formation of glutamatergic and GABAergic presynaptic specializations in vitro.\(^{20,57,58}\) However, neuroligins are
indispensable for synapse maturation and synaptic transmission, but not for triggering initial synapse formation from the phenotypes of knockout mice.  

**Necl-2**

Necl-2 was previously characterized as a tumor suppressor gene, and is also termed TSLC1/SgiGSF/RA175/IGSF4/SynCAM1. Necl-2 is a homophilic adhesion molecule, but also shows heterophilic cell-cell adhesion activity with Nect-1 and nectin-3. Necl-2 is widely expressed in various tissues and localizes at the basolateral plasma membrane in epithelial cells, not in the specialized cell–cell junctions such as AJs, TJs and desmosomes. Necl-2 localizes at synapses and induces pre-synaptic differentiation and stabilization, at least in vitro.  

**Eph Receptor**

Eph receptor tyrosine kinases and their ephrin ligands are grouped into two families: ephrinA ligands are tethered to the plasma membrane by a GPI linkage and bind to EphA receptors, whereas ephrinB ligands are transmembrane proteins that bind preferentially to EphB receptors (Fig. 1D). EphB receptors localize to synapses, where they can bind the NMDA-type glutamate receptor subunit NR1 via the extracellular domain. Stimulation of EphB receptors by ephrin ligands results in increased synaptic density and in NMDA receptor-mediated calcium influx and gene expression. EphBs multiple mutant mice develop abnormal spines in the hippocampus both in vitro and in vivo. However, the molecular mechanisms of many ephrin/Eph-related synaptic functions and their roles in the initial steps of synapse assembly are still largely unknown.  

**Axon-Astrocyte Contacts**

Astrocytes are characteristic star-shaped glial cells, and their many processes ensheath synaptic junctions in the brain, but do not form myelin (Fig. 1E). Astrocytes are also known to regulate synaptic transmission by uptake of neurotransmitters, such as glutamate, ATP and GABA, from the synaptic cleft through membrane transporters, and release of glutamate upon reversal of the transporter. Other substances released by astrocytes can strengthen synaptic transmission by co-activating NMDA receptors in the postsynaptic membrane (e.g., D-serine) or can reduce it by binding to neurotransmitters. Synapse formation may also be regulated by factors produced by astrocytes. The co-culture of purified neurons with astrocytes has been identified at contacts between neurons and astrocytes. The co-culture of purified neurons with astrocytes may be of interest to determine whether they act in a parallel or in a hierarchical manner. For most of the functions of neuron-glia contacts, we still lack sufficient information on their functions at both cellular and molecular levels. Future research on the mechanisms of neuron-glia interactions will lead to greater insight into the mechanisms underlying the formation of complex neural circuitries.  

**AMOG (Adhesion Molecule on Glia)**

AMOG (Adhesion molecule on glia), the β2-subunit of the Na⁺/K⁺ ATPase, is a membrane glycoprotein and localizes at contacts between neurons and astrocytes. AMOG is implicated in neurite outgrowth and neuronal migration. AMOG associates with the catalytic α-subunit of the Na⁺/K⁺ ATPase and forms a functional ion channel. This unique molecule serves as a cell adhesion molecule and a subunit of ion channel. AMOG is firstly expressed in the brain shortly before granule cell migration. The expression level of AMOG increases during early postnatal development and reaches the highest expression level in adult. AMOG-deficient mice present motor incoordination and paralysis in early postnatal life and die shortly after birth. The exact functions of AMOG still remain elusive.  

**Integrins**

Integrins are cell surface receptors that interact with the extracellular matrix (ECM) and transduce the signal from the ECM to the cell. Integrins consist of two distinct chains, α- and β-subunits. Integrins at contacts between neurons and astrocytes activate protein kinase C (PKC) signaling and promotes synaptogenesis in vitro. However, the involvement of the integrins-dependent PKC signaling in synaptogenesis still remains elusive in vivo.  

**Necl-1/TSSL1/SynCAM3**

Necl-1/TSSL1/SynCAM3, which has a domain structure similar to those of nectins, localizes at axon-astrocyte contacts (Fig. 1E). Necl-1 shows Ca²⁺-independent homophilic cell-cell adhesion activity and heterophilic cell-cell adhesion activity with Necl-2, nectin-1 and nectin-3, but not Necl-5 or nectin-2. Necl-1 does not bind afadin, but binds Dlg3/MPP3, a membrane-associated guanylate kinase family member, Pals2 and CASK. Necl-1 is specifically expressed in neural tissue, and localizes to contact sites along axons, nerve terminals, glial cell processes, axon bundles and myelinated axons. However, the exact functions of Necl-1 remain unknown.  

**Conclusions and Perspectives**

Herein, we described the roles of the various adhesion molecules in synapse formation, and neuron-glia interactions. Functional studies of individual cell adhesion molecules have provided a wealth of information on their roles in synapse assembly, spine morphogenesis and synaptic plasticity. Although the various adhesion systems can mediate adhesive interactions, individually, they probably control specific aspects of synapse formation. Because multiple systems appear to cooperate at individual synapse, it will be of great interest to determine whether they act in a parallel or in a hierarchical manner. For most of the functions of neuron-glia contacts, we still lack sufficient information on their functions at both cellular and molecular levels. Future research on the mechanisms of neuron-glia interactions will lead to greater insights into the mechanisms underlying the formation of complex neural circuitries.  

**Acknowledgements**

We are grateful to Dr. Yoshihisa Kudo at Tokyo University of Pharmacy and Life Sciences and colleagues at Kobe University for comments on the manuscript. This work was supported by grants-in-aid for Scientific Research and for Cancer Research from Ministry of Education, Culture, Sports, Science and Technology, Japan.
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