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Synaptic adhesion molecules and PSD-95

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Abstract

Synaptic adhesion molecules are known to participate in various steps of synapse development including initial contacts between dendrites and axons, formation of early synapses, and their maturation and plastic changes. Notably, a significant subset of synaptic adhesion molecules associates with synaptic scaffolding proteins, suggesting that they may act in concert to couple trans-synaptic adhesion to molecular organization of synaptic proteins. Here, we describe an emerging group of synaptic adhesion molecules that directly interact with the abundant postsynaptic scaffold PSD-95, which include neuroligins, NGLs, SALMs, and ADAM22, and discuss how these proteins and PSD-95 act together to regulate synaptic development. PSD-95 may be one of the central organizers of synaptic adhesion that recruits diverse proteins to sites of synaptic adhesion, promotes trans-synaptic signaling, and couples neuronal activity with changes in synaptic adhesion.

Keywords: PSD-95; Neuroligin; Neurexin; Netrin-G; NGL; SALM; ADAM22; Synapse

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Abbreviations: ADAM, a disintegrin and metalloprotease; ADPEAF, autosomal dominant partial epilepsy with auditory features; AKAP, a kinase-anchoring protein; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EPSC, excitatory postsynaptic current; GABA, gamma-aminobutyric acid; GK, guanylate kinase; GKAP, guanylate kinase-associated protein; GPI, glycosylphosphatidylinositol; LGI, leucine-rich, glioma inactivated; Lrfn, leucine-rich repeat and fibronectin III domain-containing; LRR, leucine-rich repeat; LTD, long-term depression; LTP, long-term potentiation; NGL, netrin-G ligand; NMDA, *N*-methyl-D-aspartic acid; NO, nitric oxide; NOS, nitric oxide synthase; PDZ, PSD-95/Dlg/ZO-1; PSD, postsynaptic density; PSD-95, postsynaptic density-95; SALM, synaptic adhesion-like molecule; SH3, Src homology 3; TARP, transmembrane AMPA receptor regulatory protein.

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1. Introduction

Synapse formation involves various molecular and cellular processes including contact between presynaptic and postsynaptic structures, formation of early synapses, and stabilization and differentiation of early synapses into mature synapses. Synaptic adhesion molecules are known to play pivotal roles in each of these processes, and some synaptic adhesion molecules likely regulate more than a single step of these developments. At the molecular level, the extracellular domains of synaptic adhesion molecules participate in trans-synaptic adhesion, while their cytoplasmic domains on the pre- and postsynaptic sides associate with intracellular proteins to couple synaptic adhesion to molecular organization of multiprotein complexes. Examples of such adhesion molecules include neuroligin, neurexin, SynCAM, NCAM, N-cadherin, protocadherin, Eph receptors, ephrin, and NGL. The functions of these molecules, along with the cell biological principles of synapse development, have recently been summarized in excellent reviews (Akins and Biederer, 2006; Craig et al., 2006; Craig and Kang, 2007; Dalva et al., 2007; Dean and Dresbach, 2006; Gerrow and El-Husseini, 2006; Ichtchenko et al., 1996; Li and Sheng, 2003; McAllister, 2007; Piechotta et al., 2006; Scheiffele, 2003; Waites et al., 2005; Washbourne et al., 2004; Yamagata et al., 2003).

Here, we focus on an emerging group of synaptic adhesion molecules that directly interact, through their cytoplasmic domains, with PSD-95, an abundant postsynaptic scaffolding protein regulating the formation, function, and plasticity of excitatory synapses. Electron microscopic studies have revealed that PSD-95 is localized very close to the postsynaptic membrane (Petersen et al., 2003; Valtschanoff and Weinberg, 2001), suggesting that PSD-95 is localized in an ideal position to link extrasynaptic adhesion to cytoplasmic protein organization.

Synaptic adhesion molecules that directly interact with PSD-95 include neuroligins, NGLs, SALMs, and ADAM22. In this review, we will summarize these adhesion molecules and describe aspects of PSD-95 that are relevant to synaptic adhesion. Another aim of this paper is to discuss possible functions of the interaction between PSD-95 and the adhesion molecules, taking into account the known functions of PSD-95.

2. PSD-95

PSD-95 (also known as SAP90) is a synaptic scaffolding protein with multiple protein–protein interaction domains that is enriched in the postsynaptic density (PSD), an electron-dense specialization of postsynaptic membrane that contains macromolecular protein complexes (Cho et al., 1992; Funke et al., 2004; Kim and Sheng, 2004; Kistner et al., 1993; Sheng and Hoogenraad, 2007). Recent studies indicate that PSD-95 is one of the most abundant proteins in the PSD (Chen et al., 2005; Cheng et al., 2006; Sheng and Hoogenraad, 2007; Sugiyama et al., 2005). Because the structural and functional characteristics of PSD-95 have recently been summarized (Funke et al., 2004; Kim and Sheng, 2004; Sheng and Hoogenraad, 2007), we will mainly focus on the characteristics of PSD-95 that are more relevant to its functional regulation of synaptic adhesion.

PSD-95 belongs to the PSD-95 family that has four known members: PSD-95/SAP90, PSD-93/chapsyn-110, SAP97, and SAP102. PSD-95 family proteins share similar domain structures. PSD-95 contains, from the N-terminus, three PDZ domains, an SH3 domain, and a GK domain (Fig. 1A). In addition, alternative splicing generates splice variants of PSD-95, PSD-93, and SAP97 (known as β splice variants for PSD-95 and SAP97) that contain an L27 domain at the N-terminus (Chetkovich et al., 2002; Parker et al., 2004); this domain mediates protein multimerization and regulates excitatory synaptic strength (Nakagawa et al., 2004; Schluter et al., 2006).

The PDZ domain is a 90-residue-long module that binds short peptide motifs at the extreme C-termini of other proteins. PDZ domains are found in a large number of proteins (ca. 400 proteins in the human genome), where tandem arrangements of PDZ domains are commonly observed. PDZ domains fall mainly into two classes based on the sequence of their peptide ligands. The class I ligand has a serine or threonine residue at the -2 position, whereas the class II ligand contains a hydrophobic residue at the same position (Hung and Sheng, 2002). The three PDZ domains of PSD-95, which belong to class I, interact with various neuronal proteins including membrane and signaling proteins.

The SH3 and GK domains of PSD-95, contained in the second half of the protein, also participate in protein interactions (Kim and Sheng, 2004). Of note, the SH3 domain of PSD-95 interacts with the GK domain in an intramolecular fashion (McGee and Bredt, 1999; Shin et al., 2000), which is thought to contribute to the structural stabilization of PSD-95. This interaction, when it occurs in an intermolecular fashion, may contribute a tail-to-tail multimerization of PSD-95 (McGee et al., 2001; Tavares et al., 2001). PSD-95 can also be multimerized in a head-to-head fashion through the interaction of N-terminal segments containing two critical cysteine residues (Christopherson et al., 2003; Hsueh et al., 1997; Hsueh and Sheng, 1999).

PSD-95 has diverse synaptic functions. One such function is to interact with membrane proteins and regulate their synaptic localization. PSD-95 seems to stabilize interacting membrane proteins at synapses by suppressing their lateral diffusion or internalization (Bats et al., 2007; Prybylowski et al., 2005; Roche et al., 2001). In addition to its role in protein trafficking, PSD-95 can regulate the functional properties of interacting membrane proteins, as shown by PSD-95-dependent changes in the gating of NMDA receptors (Lin et al., 2006), and the single-channel conductance of the inward rectifier potassium channel Kir2.3 (Nehring et al., 2000).

PSD-95 is an important regulator of synaptic strength and plasticity. PSD-95 overexpression in cultured neurons increases synaptic AMPA receptor clustering and currents (El-Husseini et al., 2000). In brain slices, PSD-95 overexpression increases the frequency of miniature excitatory postsynaptic currents (mEPSCs), enhances AMPA, but not NMDA, receptor-mediated EPSCs, promotes synaptic delivery of GluR1-containing AMPA receptors, occludes long-term potentiation