Journal of Neuroscience Research 85:2824–2832 (2007)

Mini-Review

Leucine-Rich Repeat Proteins of Synapses

Jaewon Ko and Eunjoon Kim*

National Creative Research Initiative Center for Synaptogenesis and Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST), Yuseong-Ku, Kuseong-Dong, Daejeon, Korea

Leucine-rich repeats (LRRs) are 20–29-aa motifs that mediate protein–protein interactions and are present in a variety of membrane and cytoplasmic proteins. Many LRR proteins with neuronal functions have been reported. Here, we summarize an emerging group of synaptic LRR proteins, which includes densin-180, Erbin, NGL, SALM, and LGI1. These proteins have been implicated in the formation, differentiation, maintenance, and plasticity of neuronal synapses.

Key words: LRR; cell adhesion molecule; densin-180; Erbin; NGL; SALM; LGI1

Neuronal development involves many events, including the outgrowth and migration of neuronal processes and the formation and differentiation of neuronal synapses. Neuronal proteins containing leucine-rich repeats (LRRs), such as the Nogo-66 receptor, Slit, AMIGO, LINGO, NGL, and NLRR, have been implicated in the regulation of neurite outgrowth and migration (Wong et al., 2002; Filbin, 2003; Chen et al., 2006), but relatively little is known about the role of LRR proteins in the regulation of neuronal synapses. Several recent studies have identified LRR proteins that regulate the structure and function of neuronal synapses. They include densin-180, Erbin, NGL, SALM, and LGI1.

LRRS

The LRR is a 20–29-aa motif that mediates protein–protein interactions and contains a conserved 11-aa sequence, LxxLxLxxN/CxL (where x is any amino acid; Kobe and Kajava, 2001). Analysis of the human genome reveals that there are ~330 LRR-containing proteins, indicating that LRRs are common. In proteins, LRRs usually occur in tandem arrays of a few to more than a dozen (2–52; Matsushima et al., 2005). Early X-ray crystallographic studies of ribonuclease inhibitor, which has 15 LRRs, revealed that each LRR contains a beta-strand and an alpha-helix connected by loops (Kobe and Deisenhofer, 1993). Multiple LRRs are arranged so that they form a nonglobular, horseshoe-shaped structure, wherein parallel beta-sheets line the inner circumference of the horseshoe (the concave side) and alpha-helices decorate the outer circumference (the convex side). Although the sequences and numbers of LRRs can differ, diverse LRRs share this overall horseshoe shape (Kobe and Kajava, 2001). Mutagenesis studies and structural analyses of LRR-ligand complexes have revealed that the concave surface of LRRs, which contains parallel beta-strands and adjacent loops, is involved mainly in ligand binding (Kobe and Deisenhofer, 1995; Papageorgiou et al., 1997; Kobe and Kajava, 2001).

DENSIN-180 AND ERBIN

Densin-180 was discovered as an LRR protein concentrated in the postsynaptic density (PSD; Apperson et al., 1996), a postsynaptic membrane specialization containing macromolecular complexes of membrane, signaling, and scaffolding proteins (Kennedy, 2000). Densin-180 contains, from the N-terminus, 16 LRRs, an LAPSD (LAP-specific domain), a mucin-like domain, a transmembrane domain, and a C-terminal PDZ domain (Fig. 1). Alternative splicing in the C-terminal region produces four variants of densin-180 that are differentially expressed during development (Strack et al., 2000). Based on its similarity to adhesion molecules, including GPIb-alpha, a surface membrane protein in platelets that binds to von Willebrand factor, densin-180 has been suggested to be a type I transmembrane protein mediating synaptic adhesion. This is further supported by the fact that densin-180 contains a predicted transmembrane domain and a site for glycosylation by sialic acid in its extracellular region. Studies in cultured hippocampal neurons, however, have shown that endogenous densin-180

Contract grant sponsor: Creative Research Initiatives Program of the Korean Ministry of Science and Technology (to E.K.).

*Correspondence to: Eunjoon Kim, National Creative Research Initiative Center for Synaptogenesis and Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST), Yuseong-Ku, Kuseong-Dong, Daejeon 305-701, Korea. E-mail: kime@kaist.ac.kr

Received 4 December 2006; Revised 29 January 2007; Accepted 1 February 2007

Published online 30 April 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jnr.21306

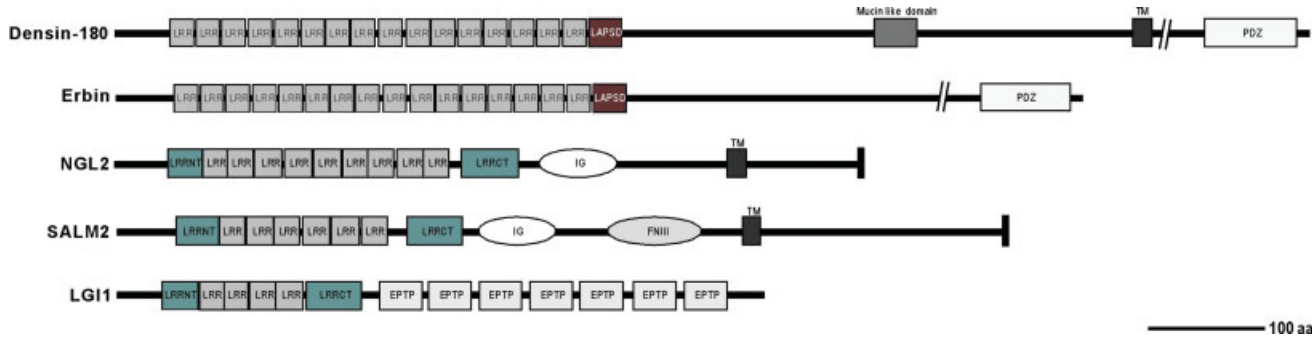

Fig. 1. Domain structures of synaptic LRR proteins. The five LRR proteins found at neuronal synapses are shown along with their domain structures. LRR, leucine-rich repeat; LAPSD, LAP-specific domain; TM, transmsmbrane segment; PDZ, PSD-95, Dlg, and ZO-1; LRRNT, N-terminal LRR; LRRCT, C-terminal LRR; Ig, immunoglobulin; FNIII, fibronectin type III; EPTP, Epitempin. Proteins: Erbin, ErbB2 interacting protein; NGL, netrin-G ligand; SALM, synaptic adhesion-like molecule; LGI1, leucine-rich, glioma-inactivated 1. Scale bar = 100 amino acids.

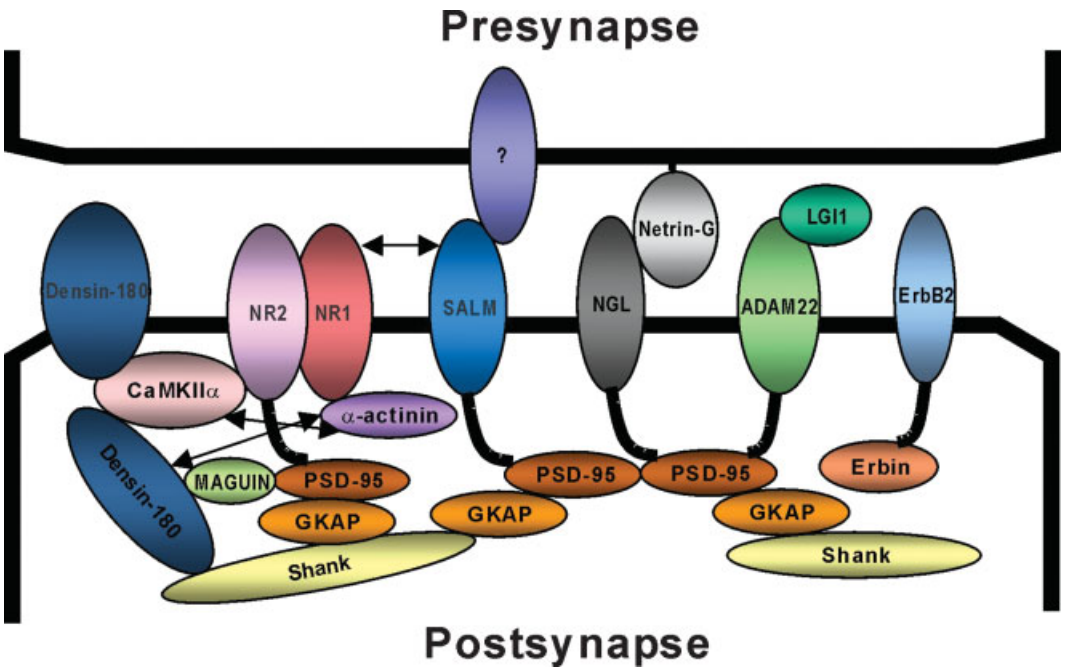

Fig. 2. Schematic diagram of the postsynaptic organization by LRR proteins. The C-terminal cytoplasmic tails of membrane proteins are indicated by black lines. Specific protein–protein interactions are indicated by direct contacts of the proteins or arrows. Netrin-G is tethered to the plasma membrane through a GPI anchor. Densin-180 may be either membrane or cytoplasmic protein. Proteins: CaMKIIα, the α subunit of calcium/calmodulin-dependent kinase II; ADAM22, a disintegrin and metalloprotease 22; PSD-95, postsynaptic density 95; GKAP, guanylate kinase-associated protein; Shank, SH3 and ankyrin repeat-containing protein; MAGUIN, membrane-associated guanylate kinase-interacting protein; NR1, NMDA receptor subunit 1; NR2, NMDA receptor subunit 2.

is not accessible to extracellular biotin labeling (Izawa et al., 2002), suggesting that it may not be a membrane protein.

Proteins interacting with densin-180 include α-actinin, the α subunit of calcium/calmodulin-dependent kinase II (CaMKIIα), δ-catenin, MAGUIN, and Shank (Fig. 2). The C-terminal region of densin-180 binds to CaMKIIα and α-actinin, and α-actinin binds to CaMKIIα, so that the three proteins form a ternary complex (Strack et al., 2000; Walikonis et al., 2001; Robison et al., 2005). Autophosphorylated CaMKIIα binds more strongly to densin-180, whereas densin-180 phosphorylation by CaMKIIα has little effect on their interaction, suggesting that densin-180 is involved in the synaptic localization of activated CaMKIIα (Walikonis et al., 2001); however, another study reported that autophosphorylation of CaMKIIα does not affect its binding to densin-180 (Strack et al., 2000). This discrepancy could be due to the use of different assay methods (Walikonis et al., 2001). In addition to densin-180,

CaMKIIα binds the NR2B subunit of N-methyl-D-aspartate (NMDA) receptors (Strack and Colbran, 1998; Gardoni et al., 1999; Leonard et al., 1999; Bayer et al., 2001), although densin-180 and NR2B do not compete for CaMKIIα binding (Strack et al., 2000). Together, these results suggest that synaptic localization of CaMKIIα requires binding to multiple synaptic proteins, including densin-180, α-actinin, and NR2B.

The C-terminal PDZ domain of densin-180 binds the C-terminus of δ-catenin (Izawa et al., 2002). Densin-180 forms a complex with δ-catenin and N-cadherin in the brain, suggesting that densin-180 may regulate N-cadherin-based synaptic adhesion and plasticity. The PDZ domain of densin-180 also associates with MAGUIN (Ohtakara et al., 2002), a mammalian homolog of *Drosophila* CNK and a multidomain adaptor that regulates the Ras-ERK/MAPK pathway (Kolch, 2005). Because MAGUIN interacts with PSD-95 (Yao et al., 1999), an abundant PDZ protein in the PSD (Funke et al., 2004; Kim and Sheng, 2004), and forms self-multimers (Ohtakara et al., 2002), MAGUIN multimers may link PSD-95 and densin-180, forming a ternary complex. The C-terminal region of densin-180 interacts with Shank (Quitsch et al., 2005), an abundant PDZ protein in the PSD that regulates the maturation of dendritic spines (Sala et al., 2001). The N-terminal LRR domain of densin-180 mediates its plasma membrane association in fibroblasts and targeting to the basolateral membrane in epithelial cells (Quitsch et al., 2005). Overexpression of densin-180 in cultured neurons promotes dendritic branching through the N-terminal LRRs, and this effect is reversed by coexpression of Shank (Quitsch et al., 2005), suggesting that Shank antagonizes the effects of densin-180 on dendrites.

Densin-180 belongs to the LAP (LRR and PDZ) family (Bilder et al., 2000), which has three other members: Erbin (Borg et al., 2000; Huang et al., 2001), hScrib (Nakagawa and Huibregtse, 2000), and Lano (Saito et al., 2001). LAP family proteins have 16 LRRs at their N-termini and zero to four PDZ domains at their C-termini: Erbin and hScrib have one and four PDZ domains, respectively, and Lano does not have PDZ domains but has a PDZ-binding C-terminus (Fig. 1). Erbin, hScrib, and Lano mRNAs are expressed in a wide variety of tissues, including the brain (Borg et al., 2000; Nakagawa and Huibregtse, 2000; Huang et al., 2001; Saito et al., 2001).

In neurons, Erbin is concentrated in the PSD (Huang et al., 2001). A C-terminal region of Erbin excluding the PDZ domain associates with PSD-95 (Huang et al., 2001). In addition, the PDZ domain of Erbin mediates interactions with proteins, including δ-catenin (Laura et al., 2002) and ErbB2/HER2 (Huang et al., 2001; Fig. 2), a receptor tyrosine kinase for neuregulin that regulates neuronal development and synaptic plasticity (Huang et al., 2000; Holbro and Hynes, 2004; Esper et al., 2006). Erbin suppresses the Ras-Raf-MEK pathway (Huang et al., 2003), and the N-terminal LRR domain of Erbin is both required and sufficient for this inhibition (Dai et al., 2006). Interestingly, the LRR domain of Erbin interacts with Sur-8, an LRR-containing scaffold protein that associates with Ras and Raf and enhances ERK activation (Li et al., 2000), and this interaction suppresses the association of Sur-8 with active Ras and Raf and the activation of ERK (Dai et al., 2006). These findings suggest that Erbin inhibits the Ras-Raf-MEK pathway through Sur-8 binding and that the LRR domain of Erbin has a novel role in the regulation of intracellular signaling. This regulation is likely to have neuronal implications, because Sur-8 mRNAs are detected in the brain (Sieburth et al., 1998). It should be noted that the majority of the proteins that interact with densin-180 and Erbin bind to the C-terminal region. Identification of additional proteins that associate with the N-terminal LRR domain may help to clarify the functions of densin-180 and Erbin.

NGL

The NGL (netrin-G ligand) family of synaptic cell adhesion molecules has three known members; NGL-1, NGL-2 (also known as *LRRC4*), and NGL-3 (Lin et al., 2003; Zhang et al., 2005; Kim et al., 2006). Northern blot analyses with rat and human tissues indicate that NGLs are expressed mainly in the brain, although low-level expression is observed in liver (NGL-1) and heart (NGL-3; Lin et al., 2003; Zhang et al., 2005; Kim et al., 2006). NGL proteins have nine LRRs and an extracellular immunoglobulin (Ig) domain, followed by a transmembrane domain and a PDZ domain-binding motif at the C-terminus. The LRRs of NGL are flanked by cysteine-rich LRR N-terminal (LRRNT) and LRR C-terminal (LRRCT) domains (Fig. 1). NGL is modified by N-glycosylation. NGL associates with netrin-G through its extracellular region and with PSD-95 through the PDZ-binding C-terminus (Lin et al., 2003; Kim et al., 2006; Fig. 2).

Classical netrins are diffusible axon-guidance molecules related to laminin that bind to receptors such as DCC and Unc5 (Chisholm and Tessier-Lavigne, 1999). Netrin-G (also called *laminet*) is a family of netrin-like adhesion proteins that has two known members, netrin-G1 and netrin-G2 (Nakashiba et al., 2000, 2002; Yin et al., 2002). Northern blot analysis indicates that netrin-G1 and netrin-G2 mRNAs are expressed mainly in the brain (Nakashiba et al., 2000, 2002; Yin et al., 2002). Netrin-G is distinct from classical netrins in several ways (Nakashiba et al., 2000). First, netrin-G1 is linked to the plasma membrane through a glycosylphosphatidylinositol (GPI) anchor. Second, netrin-G1 does not bind to the netrin receptors (DCC or Unc5). Netrin-G1 and netrin-G2 share a similar domain structure, with the laminin N-terminal domain (LamNT; also called *domain VI*) in the N-terminal half and three laminin-type EGF-like domain (LEGF) in the C-terminal half. Interestingly, the distributions of netrin-G1 and netrin-G2 mRNAs in the brain minimally overlap (Nakashiba et al., 2000, 2002; Yin et al., 2002; Kim et al., 2006), suggesting that their

association with specific ligands may contribute to the formation of specific neural networks in the brain.

Netrin-G1 is expressed on the surface of thalamocortical axons (Nakashiba et al., 2002). The trajectory of thalamocortical axons is precisely controlled during their migration in the embryonic brain, suggesting that the migration is regulated by multiple chemorepellent and chemoattractant activities (Braisted et al., 1999). NGL-1 (netrin-G1 ligand 1) was identified as a specific receptor for netrin-G1 in a screen for extracellular molecules with the ability to influence thalamocortical axon guidance (Lin et al., 2003). The LRR region in the extracellular region of NGL-1 is sufficient for netrin-G1 binding. NGL-1-coated substrate promotes axonal outgrowth in cultured thalamic neurons. Conversely, soluble NGL-1, which competes with endogenous NGL-1, suppresses axon outgrowth in chick embryo thalamic neurons. These results suggest that the interaction between netrin-G1 and NGL-1 regulates the outgrowth and migration of thalamocortical axons. Unlike soluble NGL-1, however, soluble netrin-G1 does not suppress the growth of thalamocortical axons, suggesting that netrin-G1 is not the only NGL-1 receptor.

The expression of NGL is higher in postnatal brains than in embryonic brains (Kim et al., 2006), suggesting that NGL has additional roles in later stages of brain development. A recent study revealed that NGL can induce the formation of neuronal synapses (Kim et al., 2006). NGL-2 expressed on nonneuronal cells or linked to beads induces morphological and functional presynapses in contacting axons of cocultured neurons. Also, overexpression of NGL-2 in cultured neurons increases the number of excitatory synapses. Direct aggregation of NGL-2 on the dendritic surface induces the clustering of postsynaptic proteins, including PSD-95 and NMDA receptors. Furthermore, knockdown of NGL-2 reduces the number and function of excitatory synapses, but not inhibitory synapses, and soluble NGL-2 reduces the number of excitatory synapses in a dominant negative manner. These results suggest that NGL-2 regulates the formation of excitatory synapses via a transsynaptic interaction with netrin-G2 and a cytoplasmic interaction with PSD-95.

The netrin-G and NGL families have multiple members, indicating that there may be isoform-specific interactions. In addition to the previously identified interaction between netrin-G1 and NGL-1 (Lin et al., 2003), a recent study further revealed that netrin-G2 binds NGL-2 but not NGL-1 or NGL-3 and that netrin-G1 does not bind NGL-2 or NGL-3 (Kim et al., 2006). In addition, neither netrin-G1 nor netrin-G2 associates with NGL-3 (Kim et al., 2006). These results suggest that netrin-G and NGL associate in an isoform-specific manner and that NGL-3 may have a novel ligand.

The adhesion between presynaptic neurexins and postsynaptic neuroligins is a well-known example of heterophilic and synaptogenic adhesion (Ichtchenko et al., 1995). Their transsynaptic adhesion induces pre- and postsynaptic differentiation in a bidirectional manner (Scheiffele et al., 2000; Graf et al., 2004). The netrin-G-NGL complex shares some but not all features of the neurexin-neuroligin complex. As with neuroligin, NGL associates with PSD-95 through its C-terminus (Irie et al., 1997; Kim et al., 2006), suggesting that PSD-95 is an important postsynaptic scaffolding protein that coordinates synaptic adhesion and synaptogenesis. The ectodomain of NGL mediates heterophilic adhesion (Ichtchenko et al., 1995; Lin et al., 2003) and induces presynaptic differentiation (Scheiffele et al., 2000; Kim et al., 2006). A small difference between them is that NGL binds mainly to the first two PDZ domains of PSD-95 whereas neuroligin binds to the third PDZ domain (Irie et al., 1997; Kim et al., 2006), suggesting that NGL and neuroligin do not compete for PSD-95 binding and that they may even function synergistically.

Neuroligin-1 and neuroligin-2 differentially distribute to excitatory and inhibitory synapses, respectively (Song et al., 1999; Graf et al., 2004; Varoqueaux et al., 2004; Chih et al., 2005; Levinson et al., 2005). PSD-95 enhances synaptic localization of neuroligin-1 and translocates neuroligin-2 from inhibitory to excitatory synapses, promoting excitatory synapse formation at the expense of inhibitory synapses and thus regulating the balance of excitation and inhibition in a single neuron (Graf et al., 2004; Prange et al., 2004; Chih et al., 2005). Because NGL-2 is recruited to synapses by PSD-95 binding and regulates excitatory but not inhibitory synapse formation (Kim et al., 2006), NGL may act in concert with neuroligins and PSD-95 to regulate the excitatory/inhibitory balance.

The netrin-G-NGL interaction differs from the neurexin-neuroligin interaction in that netrin-G2 expressed in nonneuronal cells lacks the ability to induce postsynaptic differentiation in contacting dendrites, whereas NGL-2 is able to induce presynaptic differentiation in contacting axons (Kim et al., 2006). This unidirectional synaptogenic activity contrasts with the bidirectional synaptogenesis mediated by neurexins and neuroligins (Scheiffele et al., 2000; Graf et al., 2004). This difference is consistent with the notion that netrin-G might not be the only ligand of NGL (Lin et al., 2003).

Netrin-G and NGL are implicated in brain dysfunctions. Single nucleotide polymorphism analyses indicate that netrin-G1 and netrin-G2 are highly associated with schizophrenia, and netrin-G1 expression is reduced in schizophrenic brain (Aoki-Suzuki et al., 2005). Furthermore, truncation of the netrin-G1 gene by a balanced chromosomal translocation leads to Rett syndrome (Borg et al., 2005), although whether alterations in netrin-G1 are the main cause of Rett syndrome remains to be determined (Archer et al., 2006).

Several issues remain to be addressed regarding synaptogenic function of netrin-G and NGL. First, there are a large number of splice variants of netrin-G1 and netrin-G2, and they are regulated spatiotemporally (Nakashiba et al., 2000, 2002; Yin et al., 2002; Meerabux et al., 2005), similar to neurexin (Ullrich et al.,

1995). Therefore, alternative splicing of netrin-G may affect NGL binding. The function of the Ig domain of NGL is currently unknown, and, although the extracellular regions are relatively conserved between the different NGLs, their cytoplasmic regions are markedly different (Lin et al., 2003; Zhang et al., 2005; Kim et al., 2006), suggesting that the variants have different functions. Unlike netrin-G mRNAs, which have largely nonoverlapping distributions in the rat brain (Nakashiba et al., 2000, 2002; Yin et al., 2002; Kim et al., 2006), NGL mRNAs have overlapping distributions (i.e., pyramidal neurons in the CA1 region of hippocampus express mRNAs for all three NGLs; Kim et al., 2006). It is possible that different NGL isoforms segregate into different dendritic regions of a neuron to mediate synapse formation with axons of different origins. Alternatively, a single synapse may contain multiple NGLs that could act synergistically.

A recent study reported that NGL-1 binds whirlin (Delprat et al., 2005), a PDZ protein implicated in deafness (Belyantseva et al., 2003; Mburu et al., 2003). This interaction between NGL-1 and whirlin is mediated by the C-terminus of NGL-1 and the first two PDZ domains of whirlin. Whirlin is encoded by the *Whrn* gene, and mutation of this gene causes autosomal recessive deafness in mice and humans (Holme et al., 2002; Mburu et al., 2003). Whirler mice, which have a mutation in the *Whrn* gene, have shorter stereocilia, which are stiff microvilli located at the apex of cochlear inner hair cells, and they exhibit degeneration of hair cells (Holme et al., 2002). It has been suggested that NGL-1 links adjacent stereocilia through homophilic adhesion, leading to the formation of a bundle of stereocilia (Delprat et al., 2005). In support of this idea, NGL-1 molecules homophilically interact with each other in GST pull-down assays in the presence of Ca^{2+} concentrations (5–250 μM) similar to that found in endolymph, the extracellular fluid surrounding the hair cells (Delprat et al., 2005). These results suggest a novel function of NGL in hair cell regulation. However, the homophilic adhesion in NGL-1 remains to be further characterized; it is unclear whether the interaction occurs in a cis or trans conformation.

Finally, NGL-2/LRRC4 has been implicated in the suppression of glioma, a common primary malignant tumor in the central nervous system (Zhang et al., 2005; Wu et al., 2006). Northern blot analysis indicates that NGL-2/LRRC4 expression is reduced in glioblastoma cell lines and gliomas. Exogenous overexpression of NGL-2/LRRC4 suppresses the proliferation of glioblastoma cells in a manner requiring the protein's LRR region. These results suggest that NGL-2 functions as a tumor suppressor.

SALM

The SALM (synaptic adhesion-like molecule) family is a novel group of synaptic LRR proteins that includes five known members (Ko et al., 2006; Wang et al., 2006). Shortly after the initial reports, these proteins were independently described as members of the Lrfn (leucine-rich repeat and fibronectin III domain-containing) family (Morimura et al., 2006). Northern blot analysis indicates that the mRNAs for all of the SALM isoforms are expressed mainly in the brain, although lower levels of SALM3/Lrfn4 and SALM4/Lrfn3 mRNAs are found in other tissues (Ko et al., 2006; Morimura et al., 2006). SALMs contain six LRRs, an Ig domain, and a fibronectin III domain in the extracellular region, followed by a transmembrane domain and a C-terminal PDZ-binding motif (Fig. 1). The LRRs of SALMs are flanked by LRRNT and LRRCT domains. SALM is similar to NGL in its overall domain structure and its ability to bind PSD-95 (Ko et al., 2006; Wang et al., 2006; Fig. 2). Unlike NGL, SALM has a fibronectin III domain as an additional adhesion domain. Also, SALM4 and SALM5 lack the PDZ-binding motif, and the ligands for SALMs are not known. SALMs are modified by N-glycosylation (Ko et al., 2006; Morimura et al., 2006).

When overexpressed in cultured neurons, SALM1 promotes neurite outgrowth in early-stage cultured hippocampal neurons (4–6 days in vitro) but not in late-stage neurons (14–16 days in vitro; Wang et al., 2006), suggesting that SALM1 regulates an important aspect of early neuronal development. Interestingly, overexpression of SALM1 induces the surface clustering of NMDA receptors on dendrites by a mechanism that requires PDZ interaction (Wang et al., 2006), suggesting that dendritic coclustering of SALM1 and NMDA receptors requires a PDZ scaffold. In addition, SALM1 forms a complex with NMDA receptors in brain and associates with the NR1 but not the NR2 subunit of NMDA receptors in heterologous cells (Wang et al., 2006).

Previous studies have identified several NMDA receptor-associated adhesion molecules. EphB receptor tyrosine kinases directly interact with NR1, and ephrin stimulation of EphB receptors induces coclustering of EphB and NMDA receptors, tyrosine phosphorylation of NMDA receptors, and an increase in the number of synapses (Dalva et al., 2000; Takasu et al., 2002). Overexpression of neuroligin-1 induces dendritic NMDA receptor clustering through mechanisms that partially require PSD-95 binding (Chih et al., 2005), and neurexin presented to dendrites induces clustering of neuroligin and NMDA receptors (Graf et al., 2004). The neural cell adhesion molecule (NCAM) forms a complex with NMDA receptors in brain, and antibody-induced dendritic clustering of NCAM induces coclustering of NMDA receptors (Sytnyk et al., 2006). In addition, NCAM-associated polysialic acid negatively regulates NR2B-containing NMDA receptors (Hammond et al., 2006). Direct aggregation of NGL-2 on dendrites induces secondary clustering of NMDA receptors (Kim et al., 2006). Therefore, SALM1, along with EphB receptors, neuroligin, NCAM, and NGL, may participate in dendritic or synaptic clustering of NMDA receptors. The SALM1-NMDA receptor interaction may also contrib-

ute to reciprocal modulation of synaptic adhesion and NMDA receptor activity (Wang et al., 2006).

SALM2 has also been characterized (Ko et al., 2006). SALM2 expressed in nonneuronal cells does not induce presynaptic differentiation in contacting axons, suggesting that, unlike NGL, SALM2 does not have synaptogenic activity; however, overexpression of SALM2 in cultured neurons increases the number of excitatory synapses. SALM2 knockdown by RNA interference reduces the number and functions of excitatory but not inhibitory synapses, as determined by pre- and postsynaptic markers and miniature postsynaptic currents. Direct aggregation of SALM2 on the surface membrane of dendrites induces secondary clustering of excitatory postsynaptic proteins, including PSD-95, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and to a lesser extent NMDA receptors, suggesting that SALM2 clustering is sufficient to drive postsynaptic differentiation. These results suggest that SALM2 regulates the differentiation or maturation of excitatory synapses, whereas NGL contributes to excitatory synapse formation.

There are several differences between SALM2 and SALM1. SALM2 associates with both AMPA and NMDA receptors but is more strongly associated with AMPA receptors, whereas SALM1 preferentially associates with NMDA receptors (Ko et al., 2006; Wang et al., 2006). They also differ in their temporal expression patterns: SALM2 expression gradually increases during postnatal synaptic development, and SALM1 expression reaches a plateau at early stages and is maintained throughout development (Ko et al., 2006; Wang et al., 2006). Therefore, SALM2 may promote the maturation of excitatory synapses at later stages, whereas SALM1 exerts its actions in wider developmental stages. The effect of SALM2 on synaptic maturation is reminiscent of Dasm1, an Ig family adhesion-like molecule that interacts with S-SCAM and Shank PDZ proteins and regulates synaptic maturation through a selective effect on AMPA receptors (Shi et al., 2004a,b).

Several aspects of SALM function remain to be studied. Ligands of SALMs, if any, have to be identified. The ligands could be SALMs, as suggested previously (Wang et al., 2006). Although SALM2 does not mediate homophilic adhesion (Ko et al., 2006), other SALM isoforms may participate in homophilic or heterophilic adhesion. In support of this possibility, SALM1 and SALM2 are found in both axons and dendrites (Ko et al., 2006; Wang et al., 2006). Another issue that remains to be addressed is whether SALMs have lateral or *cis*-type interactions on the same plasma membrane surface, forming homo- or heteromultimers. Finally, different SALMs may have different functions. Notably, the cytoplasmic regions of SALMs are essentially unrelated except for their extreme C-termini, although their ectodomains are more conserved. In addition, SALM4 and SALM5 do not contain C-terminal PDZ-binding motifs, suggesting that they might have distinct functions.

LGI1

LGI1 (leucine-rich, glioma inactivated gene 1) is an LRR protein implicated in epilepsy (Chernova et al., 1998; Kalachikov et al., 2002; Morante-Redolat et al., 2002). LGI1 contains four LRRs in the N-terminal half and seven epitempin (EPTP) repeats in the C-terminal half (Fig. 1). Mutations in LGI1 cause a rare form of epilepsy known as *autosomal dominant partial epilepsy with auditory features* (ADPEAF; Kalachikov et al., 2002; Morante-Redolat et al., 2002). LGI1 is modified by N-glycosylation and secreted from cells in a manner requiring the EPTP repeats (Senechal et al., 2005; Sirerol-Piquer et al., 2006). LGI1 mutants found in ADPEAF patients are not secreted (Senechal et al., 2005; Sirerol-Piquer et al., 2006), suggesting that the limited secretion of LGI1 may cause epileptic conditions.

LGI1 has been implicated in tumor suppression (Chernova et al., 1998), although a recent study does not support this possibility (Piepoli et al., 2006). An important clue to the function of LGI1 has come from the tight association of LGI1 with Kv1.1 (Schulte et al., 2006), a presynaptic voltage-dependent potassium channel subunit. Kv1.1, which is a noninactivating channel, is transformed into a rapidly inactivating channel when coassembled with the Kv1.4 or Kvβ1 subunit. In the Kv1.1 protein complex, LGI1 inhibits Kvβ1-mediated Kv1.1 inactivation, and LGI1 mutants found in ADPEAF patients do not have this activity, suggesting that the rapid presynaptic Kv1.1 inactivation caused by defective LGI1 may induce epileptic activities. How does LGI1 inhibit the effect of Kvβ1 on Kv1.1? A possibility is that LGI1 mutants, which cannot be secreted, may associate with and trap Kv1.1 in the early secretory pathway. This may lead to the surface expression of Kv1.1 complexes that lack LGI1 and thus have rapid inactivation, as recently suggested (Sirerol-Piquer et al., 2006).

Another important clue to the function of LGI1 was the finding that LGI1 associates with ADAM22 (Fukata et al., 2006), a transmembrane protein associated with epilepsy in mice (Sagane et al., 2005; Fig. 2). This interaction is mediated by EPTP repeats in LGI1 and the disintegrin domain in ADAM22. An LGI1 mutant found in ADPEAF patients fails to bind ADAM22. The PDZ-binding motif at the C-terminus of ADAM22 also associates with the second half of PSD-95, which contains the third PDZ domain (Fukata et al., 2006; Fig. 2). Furthermore, LGI1, ADAM22, and PSD-95 form a tripartite complex in heterologous cells. These results suggest that LGI1 is an extracellular ligand for ADAM22 and that PSD-95 clusters LGI1 and ADAM22 at excitatory synapses.

Interestingly, addition of soluble LGI1 to hippocampal slices increases surface AMPA receptor expression, the AMPA/NMDA receptor ratio, and the frequency and amplitude of miniature excitatory postsynaptic currents (Fukata et al., 2006). These effects on synaptic transmission are blocked by preincubating LG11 with soluble ADAM22, suggesting that LGI1 acts

through ADAM22; however, hippocampal long-term potentiation is not occluded by LGI1, suggesting that LGI1 promotes glutamatergic transmission by mechanisms other than long-term potentiation.

Stargazin/TARP is a transmembrane protein that regulates AMPA receptor trafficking and gating (Nicoll et al., 2006). Stargazer mice, which are deficient in stargazin, exhibit epilepsy and ataxia (Nicoll et al., 2006). Stargazin binds to the first two PDZ domains of PSD-95 (Schnell et al., 2002), whereas ADAM22 binds to a nonoverlapping site in the second half of PSD-95 (Fukata et al., 2006). In addition, LGI1, ADAM22, and PSD-95 form a tripartite complex. Together, these results suggest that the LGI1-ADAM22 complex may stabilize the stargazin-AMPA receptor complex on PSD-95 (Fukata et al., 2006).

These results lead us toward a deeper understanding of LGI1 function, but relatively little is known about the roles of individual LGI1 domains, especially the N-terminal LRR domain. An LGI1 deletion variant that lacks the whole LRR domain is efficiently secreted, although a contrasting result was obtained from a similar LGI1 variant with a smaller LRR deletion (Senechal et al., 2005; Sirerol-Piquer et al., 2006), leaving the role of the LRR domain unclear. The domains of LGI1 involved in Kv1.1 regulation have not been identified (Schulte et al., 2006). The C-terminal EPTP repeats, but not the LRR domain, mediate ADAM22 binding (Fukata et al., 2006). Therefore, the synaptic function of the LRR domain of LGI1 remains to be determined.

PERSPECTIVES

In this Mini-Review, we have discussed an emerging group of LRR proteins with synaptic functions. These proteins are localized at different subdomains of synapses, including the PSD and the synaptic plasma membrane, and in the extracellular spaces. This suggests that synaptic LRR proteins have diverse functions, similar to other LRR proteins from neuronal and nonneuronal cells. It is now fairly clear that the LRRs in NGL and Erbin mediate binding to netrin-G and Sur-8, respectively. In contrast, the functions of the LRRs from densin-180, SALM, and LGI1 remain to be determined. Identification of additional LRR-binding proteins may elucidate the functions of the synaptic LRR proteins.

REFERENCES

Aoki-Suzuki M, Yamada K, Meerabux J, Iwayama-Shigeno Y, Ohba H, Iwamoto K, Takao H, Toyota T, Suto Y, Nakatani N, Dean B, Nishimura S, Seki K, Kato T, Itohara S, Nishikawa T, Yoshikawa T. 2005. A family-based association study and gene expression analyses of netrin-G1 and -G2 genes in schizophrenia. Biol Psychiatry 57:382–393.

Apperson ML, Moon IS, Kennedy MB. 1996. Characterization of densin-180, a new brain-specific synaptic protein of the O-sialoglycoprotein family. J Neurosci 16:6839–6852.

Archer HL, Evans JC, Millar DS, Thompson PW, Kerr AM, Leonard H, Christodoulou J, Ravine D, Lazarou L, Grove L, Verity C, Whatley SD, Pilz DT, Sampson JR, Clarke AJ. 2006. NTNG1 mutations are a rare cause of Rett syndrome. Am J Med Genet A140:691–694.

Bayer KU, De Koninck P, Leonard AS, Hell JW, Schulman H. 2001. Interaction with the NMDA receptor locks CaMKII in an active conformation. Nature 411:801–805.

Belyantseva IA, Labay V, Boger ET, Griffith AJ, Friedman TB. 2003. Stereocilia: the long and the short of it. Trends Mol Med 9:458–461.

Bilder D, Birnbaum D, Borg JP, Bryant P, Huigbretse J, Jansen E, Kennedy MB, Labouesse M, Legouis R, Mechler B, Perrimon N, Petit M, Sinha P. 2000. Collective nomenclature for LAP proteins. Nat Cell Biol 2:E114.

Borg I, Freude K, Kubart S, Hoffmann K, Menzel C, Laccone F, Firth H, Ferguson-Smith MA, Tommerup N, Ropers HH, Sargan D, Kalscheuer VM. 2005. Disruption of Netrin G1 by a balanced chromosome translocation in a girl with Rett syndrome. Eur J Hum Genet 13:921–927.

Borg JP, Marchetto S, Le Bivic A, Ollendorff V, Jaulin-Bastard F, Saito H, Fournier E, Adelaide J, Margolis B, Birnbaum D. 2000. ERBIN: a basolateral PDZ protein that interacts with the mammalian ERBB2/HER2 receptor. Nat Cell Biol 2:407–414.

Braisted JE, Tuttle R, O'Leary DD. 1999. Thalamocortical axons are influenced by chemorepellent and chemoattractant activities localized to decision points along their path. Dev Biol 208:430–440.

Chen Y, Aulia S, Li L, Tang BL. 2006. AMIGO and friends: an emerging family of brain-enriched, neuronal growth modulating, type I transmembrane proteins with leucine-rich repeats (LRR) and cell adhesion molecule motifs. Brain Res Brain Res Rev 51:265–274.

Chernova OB, Somerville RP, Cowell JK. 1998. A novel gene, LGI1, from 10q24 is rearranged and down-regulated in malignant brain tumors. Oncogene 17:2873–2881.

Chih B, Engelman H, Scheiffele P. 2005. Control of excitatory and inhibitory synapse formation by neuroligins. Science 307:1324–1328.

Chisholm A, Tessier-Lavigne M. 1999. Conservation and divergence of axon guidance mechanisms. Curr Opin Neurobiol 9:603–615.

Dai P, Xiong WC, Mei L. 2006. Erbin inhibits RAF activation by disrupting the sur-8-Ras-Raf complex. J Biol Chem 281:927–933.

Dalva MB, Takasu MA, Lin MZ, Shamah SM, Hu L, Gale NW, Greenberg ME. 2000. EphB receptors interact with NMDA receptors and regulate excitatory synapse formation. Cell 103:945–956.

Delprat B, Michel V, Goodyear R, Yamasaki Y, Michalski N, El-Amraoui A, Perfettini I, Legrain P, Richardson G, Hardelin JP, Petit C. 2005. Myosin XVa and whirlin, two deafness gene products required for hair bundle growth, are located at the stereocilia tips and interact directly. Hum Mol Genet 14:401–410.

Esper RM, Pankonin MS, Loeb JA. 2006. Neuregulins: versatile growth and differentiation factors in nervous system development and human disease. Brain Res Brain Res Rev 51:161–175.

Filbin MT. 2003. Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS. Nat Rev Neurosci 4:703–713.

Fukata Y, Adesnik H, Iwanaga T, Bredt DS, Nicoll RA, Fukata M. 2006. Epilepsy-related ligand/receptor complex LGI1 and ADAM22 regulate synaptic transmission. Science 313:1792–1795.

Funke L, Dakoji S, Bredt DS. 2004. Membrane-associated guanylate kinases regulate adhesion and plasticity at cell junctions. Annu Rev Biochem 74:219–245.

Gardoni F, Schrama LH, van Dalen JJ, Gispen WH, Cattabeni F, Di Luca M. 1999. AlphaCaMKII binding to the C-terminal tail of NMDA receptor subunit NR2A and its modulation by autophosphorylation. FEBS Lett 456:394–398.

Graf ER, Zhang X, Jin SX, Linhoff MW, Craig AM. 2004. Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. Cell 119:1013–1026.

Hammond MS, Sims C, Parameshwaran K, Suppiramaniam V, Schachner M, Dityatev A. 2006. Neural cell adhesion molecule-associated poly-

sialic acid inhibits NR2B-containing N-methyl-D-aspartate receptors and prevents glutamate-induced cell death. J Biol Chem 281:34859–34869.

Holbro T, Hynes NE. 2004. ErbB receptors: directing key signaling networks throughout life. Annu Rev Pharmacol Toxicol 44:195–217.

Holme RH, Kiernan BW, Brown SD, Steel KP. 2002. Elongation of hair cell stereocilia is defective in the mouse mutant whirler. J Comp Neurol 450:94–102.

Huang YZ, Won S, Ali DW, Wang Q, Tanowitz M, Du QS, Pelkey KA, Yang DJ, Xiong WC, Salter MW, Mei L. 2000. Regulation of neuregulin signaling by PSD-95 interacting with ErbB4 at CNS synapses. Neuron 26:443–455.

Huang YZ, Wang Q, Xiong WC, Mei L. 2001. Erbin is a protein concentrated at postsynaptic membranes that interacts with PSD-95. J Biol Chem 276:19318–19326.

Huang YZ, Zang M, Xiong WC, Luo Z, Mei L. 2003. Erbin suppresses the MAP kinase pathway. J Biol Chem 278:1108–1114.

Ichtchenko K, Hata Y, Nguyen T, Ullrich B, Missler M, Moomaw C, Sudhof TC. 1995. Neuroligin 1: a splice site-specific ligand for beta-neurexins. Cell 81:435–443.

Irie M, Hata Y, Takeuchi M, Ichtchenko K, Toyoda A, Hirao K, Takai Y, Rosahl TW, Sudhof TC. 1997. Binding of neuroligins to PSD-95. Science 277:1511–1515.

Izawa I, Nishizawa M, Ohtakara K, Inagaki M. 2002. Densin-180 interacts with delta-catenin/neural plakophilin-related armadillo repeat protein at synapses. J Biol Chem 277:5345–5350.

Kalachikov S, Evgrafov O, Ross B, Winawer M, Barker-Cummings C, Martinelli Boneschi F, Choi C, Morozov P, Das K, Teplitskaya E, Yu A, Cayanis E, Penchaszadeh G, Kottmann AH, Pedley TA, Hauser WA, Ottman R, Gilliam TC. 2002. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. Nat Genet 30: 335–341.

Kennedy MB. 2000. Signal-processing machines at the postsynaptic density. Science 290:750–754.

Kim E, Sheng M. 2004. PDZ domain proteins of synapses. Nat Rev Neurosci 5:771–781.

Kim S, Burette A, Chung HS, Kwon SK, Woo J, Lee HW, Kim K, Kim H, Weinberg RJ, Kim E. 2006. NGL family PSD-95-interacting adhesion molecules regulate excitatory synapse formation. Nat Neurosci 9:1294–1301.

Ko J, Kim S, Chung HS, Kim K, Han K, Kim H, Jun H, Kaang BK, Kim E. 2006. SALM synaptic cell adhesion-like molecules regulate the differentiation of excitatory synapses. Neuron 50:233–245.

Kobe B, Deisenhofer J. 1993. Crystal structure of porcine ribonuclease inhibitor, a protein with leucine-rich repeats. Nature 366:751–756.

Kobe B, Deisenhofer J. 1995. A structural basis of the interactions between leucine-rich repeats and protein ligands. Nature 374:183–186.

Kobe B, Kajava AV. 2001. The leucine-rich repeat as a protein recognition motif. Curr Opin Struct Biol 11:725–732.

Kolch W. 2005. Coordinating ERK/MAPK signalling through scaffolds and inhibitors. Nat Rev Mol Cell Biol 6:827–837.

Laura RP, Witt AS, Held HA, Gerstner R, Deshayes K, Koehler MF, Kosik KS, Sidhu SS, Lasky LA. 2002. The Erbin PDZ domain binds with high affinity and specificity to the carboxyl termini of delta-catenin and ARVCF. J Biol Chem 277:12906–12914.

Leonard AS, Lim IA, Hemsworth DE, Horne MC, Hell JW. 1999. Calcium/calmodulin-dependent protein kinase II is associated with the N-methyl-D-aspartate receptor. Proc Natl Acad Sci U S A 96:3239–3244.

Levinson JN, Chery N, Huang K, Wong TP, Gerrow K, Kang R, Prange O, Wang YT, El-Husseini A. 2005. Neuroligins mediate excitatory and inhibitory synapse formation: involvement of PSD-95 and neurexin-1beta in neuroligin-induced synaptic specificity. J Biol Chem 280:17312–17319.

Li W, Han M, Guan KL. 2000. The leucine-rich repeat protein SUR-8 enhances MAP kinase activation and forms a complex with Ras and Raf. Genes Dev 14:895–900.

Lin JC, Ho WH, Gurney A, Rosenthal A. 2003. The netrin-G1 ligand NGL-1 promotes the outgrowth of thalamocortical axons. Nat Neurosci 6:1270–1276.

Matsushima N, Tachi N, Kuroki Y, Enkhbayar P, Osaki M, Kamiya M, Kretsinger RH. 2005. Structural analysis of leucine-rich-repeat variants in proteins associated with human diseases. Cell Mol Life Sci 62:2771–2791.

Mburu P, Mustapha M, Varela A, Weil D, El-Amraoui A, Holme RH, Rump A, Hardisty RE, Blanchard S, Coimbra RS, Perfettini I, Parkinson N, Mallon AM, Glenister P, Rogers MJ, Paige AJ, Moir L, Clay J, Rosenthal A, Liu XZ, Blanco G, Steel KP, Petit C, Brown SD. 2003. Defects in whirlin, a PDZ domain molecule involved in stereocilia elongation, cause deafness in the whirler mouse and families with DFNB31. Nat Genet 34:421–428.

Meerabux JM, Ohba H, Fukasawa M, Suto Y, Aoki-Suzuki M, Nakashiba T, Nishimura S, Itohara S, Yoshikawa T. 2005. Human netrin-G1 isoforms show evidence of differential expression. Genomics 86:112–116.

Morante-Redolat JM, Gorostidi-Pagola A, Piquer-Sirerol S, Saenz A, Poza JJ, Galan J, Gesk S, Sarafidou T, Mautner VF, Binelli S, Staub E, Hinzmann B, French L, Prud'homme JF, Passarelli D, Scannapieco P, Tassinari CA, Avanzini G, Marti-Masso JF, Kluwe L, Deloukas P, Moschonas NK, Michelucci R, Siebert R, Nobile C, Perez-Tur J, Lopez de Munain A. 2002. Mutations in the LGI1/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. Hum Mol Genet 11:1119–1128.

Morimura N, Inoue T, Katayama K, Aruga J. 2006. Comparative analysis of structure, expression and PSD95-binding capacity of Lrfn, a novel family of neuronal transmembrane proteins. Gene 380:72–83.

Nakagawa S, Huibregtse JM. 2000. Human scribble (Vartul) is targeted for ubiquitin-mediated degradation by the high-risk papillomavirus E6 proteins and the E6AP ubiquitin-protein ligase. Mol Cell Biol 20: 8244–8253.

Nakashiba T, Ikeda T, Nishimura S, Tashiro K, Honjo T, Culotti JG, Itohara S. 2000. Netrin-G1: a novel glycosyl phosphatidylinositol-linked mammalian netrin that is functionally divergent from classical netrins. J Neurosci 20:6540–6550.

Nakashiba T, Nishimura S, Ikeda T, Itohara S. 2002. Complementary expression and neurite outgrowth activity of netrin-G subfamily members. Mech Dev 111:47–60.

Nicoll RA, Tomita S, Bredt DS. 2006. Auxiliary subunits assist AMPA-type glutamate receptors. Science 311:1253–1256.

Ohtakara K, Nishizawa M, Izawa I, Hata Y, Matsushima S, Taki W, Inada H, Takai Y, Inagaki M. 2002. Densin-180, a synaptic protein, links to PSD-95 through its direct interaction with MAGUIN-1. Genes Cells 7:1149–1160.

Papageorgiou AC, Shapiro R, Acharya KR. 1997. Molecular recognition of human angiogenin by placental ribonuclease inhibitor—an X-ray crystallographic study at 2.0 A resolution. EMBO J 16:5162–5177.

Piepoli T, Jakupoglu C, Gu W, Lualdi E, Suarez-Merino B, Poliani PL, Cattaneo MG, Ortino B, Goplen D, Wang J, Mola R, Inverardi F, Frassoni C, Bjerkvig R, Steinlein O, Vicentini LM, Brustle O, Finocchiaro G. 2006. Expression studies in gliomas and glial cells do not support a tumor suppressor role for LGI1. Neurooncol 8:96–108.

Prange O, Wong TP, Gerrow K, Wang YT, El-Husseini A. 2004. A balance between excitatory and inhibitory synapses is controlled by PSD-95 and neuroligin. Proc Natl Acad Sci U S A 101:13915–13920.

Quitsch A, Berhorster K, Liew CW, Richter D, Kreienkamp HJ. 2005. Postsynaptic shank antagonizes dendrite branching induced by the leucine-rich repeat protein Densin-180. J Neurosci 25:479–487.

Robison AJ, Bass MA, Jiao Y, MacMillan LB, Carmody LC, Bartlett RK, Colbran RJ. 2005. Multivalent interactions of calcium/calmodulin-dependent protein kinase II with the postsynaptic density proteins NR2B, densin-180, and alpha-actinin-2. J Biol Chem 280:35329–35336.

Sagane K, Hayakawa K, Kai J, Hirohashi T, Takahashi E, Miyamoto N, Ino M, Oki T, Yamazaki K, Nagasu T. 2005. Ataxia and peripheral nerve hypomyelination in ADAM22-deficient mice. BMC Neurosci 6:33.

Saito H, Santoni MJ, Arsanto JP, Jaulin-Bastard F, Le Bivic A, Marchetto S, Audebert S, Isnardon D, Adelaide J, Birnbaum D, Borg JP. 2001. Lano, a novel LAP protein directly connected to MAGUK proteins in epithelial cells. J Biol Chem 276:32051–32055.

Sala C, Piech V, Wilson NR, Passafaro M, Liu G, Sheng M. 2001. Regulation of dendritic spine morphology and synaptic function by Shank and Homer. Neuron 31:115–130.

Scheiffele P, Fan J, Choih J, Fetter R, Serafini T. 2000. Neuroligin expressed in nonneuronal cells triggers presynaptic development in contacting axons. Cell 101:657–669.

Schnell E, Sizemore M, Karimzadegan S, Chen L, Bredt DS, Nicoll RA. 2002. Direct interactions between PSD-95 and stargazin control synaptic AMPA receptor number. Proc Natl Acad Sci U S A 99:13902–13907.

Schulte U, Thumfart JO, Klocker N, Sailer CA, Bildl W, Biniossek M, Dehn D, Deller T, Eble S, Abbass K, Wangler T, Knaus HG, Fakler B. 2006. The epilepsy-linked Lgi1 protein assembles into presynaptic Kv1 channels and inhibits inactivation by Kvbeta1. Neuron 49:697–706.

Senechal KR, Thaller C, Noebels JL. 2005. ADPEAF mutations reduce levels of secreted LGI1, a putative tumor suppressor protein linked to epilepsy. Hum Mol Genet 14:1613–1620.

Shi SH, Cheng T, Jan LY, Jan YN. 2004a. The immunoglobulin family member dendrite arborization and synapse maturation 1 (Dasm1) controls excitatory synapse maturation. Proc Natl Acad Sci U S A 101:13346–13351.

Shi SH, Cox DN, Wang D, Jan LY, Jan YN. 2004b. Control of dendrite arborization by an Ig family member, dendrite arborization and synapse maturation 1 (Dasm1). Proc Natl Acad Sci U S A 101:13341–13345.

Sieburth DS, Sun Q, Han M. 1998. SUR-8, a conserved Ras-binding protein with leucine-rich repeats, positively regulates Ras-mediated signaling in C. elegans. Cell 94:119–130.

Sirerol-Piquer MS, Ayerdi-Izquierdo A, Morante-Redolat JM, Herranz-Perez V, Favell K, Barker PA, Perez-Tur J. 2006. The epilepsy gene LGI1 encodes a secreted glycoprotein that binds to the cell surface. Hum Mol Genet 15:3436–3445.

Song JY, Ichtchenko K, Sudhof TC, Brose N. 1999. Neuroligin 1 is a postsynaptic cell-adhesion molecule of excitatory synapses. Proc Natl Acad Sci U S A 96:1100–1105.

Strack S, Colbran RJ. 1998. Autophosphorylation-dependent targeting of calcium/calmodulin-dependent protein kinase II by the NR2B subunit of the N-methyl-D-aspartate receptor. J Biol Chem 273:20689–20692.

Strack S, Robison AJ, Bass MA, Colbran RJ. 2000. Association of calcium/calmodulin-dependent kinase II with developmentally regulated splice variants of the postsynaptic density protein densin-180. J Biol Chem 275:25061–25064.

Sytnyk V, Leshchyns'ka I, Nikonenko AG, Schachner M. 2006. NCAM promotes assembly and activity-dependent remodeling of the postsynaptic signaling complex. J Cell Biol 174:1071–1085.

Takasu MA, Dalva MB, Zigmond RE, Greenberg ME. 2002. Modulation of NMDA receptor-dependent calcium influx and gene expression through EphB receptors. Science 295:491–495.

Ullrich B, Ushkaryov YA, Sudhof TC. 1995. Cartography of neurexins: more than 1000 isoforms generated by alternative splicing and expressed in distinct subsets of neurons. Neuron 14:497–507.

Varoqueaux F, Jamain S, Brose N. 2004. Neuroligin 2 is exclusively localized to inhibitory synapses. Eur J Cell Biol 83:449–456.

Walikonis RS, Oguni A, Khorosheva EM, Jeng CJ, Asuncion FJ, Kennedy MB. 2001. Densin-180 forms a ternary complex with the (alpha)-subunit of Ca^{2+}/calmodulin-dependent protein kinase II and (alpha)-actinin. J Neurosci 21:423–433.

Wang CY, Chang K, Petralia RS, Wang YX, Seabold GK, Wenthold RJ. 2006. A novel family of adhesion-like molecules that interacts with the NMDA receptor. J Neurosci 26:2174–2183.

Wong K, Park HT, Wu JY, Rao Y. 2002. Slit proteins: molecular guidance cues for cells ranging from neurons to leukocytes. Curr Opin Genet Dev 12:583–591.

Wu M, Huang C, Gan K, Huang H, Chen Q, Ouyang J, Tang Y, Li X, Yang Y, Zhou H, Zhou Y, Zeng Z, Xiao L, Li D, Tang K, Shen S, Li G. 2006. LRRC4, a putative tumor suppressor gene, requires a functional leucine-rich repeat cassette domain to inhibit proliferation of glioma cells in vitro by modulating the extracellular signal-regulated kinase/protein kinase B/nuclear factor-kappaB pathway. Mol Biol Cell 17:3534–3542.

Yao I, Hata Y, Ide N, Hirao K, Deguchi M, Nishioka H, Mizoguchi A, Takai Y. 1999. MAGUIN, a novel neuronal membrane-associated guanylate kinase- interacting protein. J Biol Chem 274:11889–11896.

Yin Y, Miner JH, Sanes JR. 2002. Laminets: laminin- and netrin-related genes expressed in distinct neuronal subsets. Mol Cell Neurosci 19:344–358.

Zhang Q, Wang J, Fan S, Wang L, Cao L, Tang K, Peng C, Li Z, Li W, Gan K, Liu Z, Li X, Shen S, Li G. 2005. Expression and functional characterization of LRRC4, a novel brain-specific member of the LRR superfamily. FEBS Lett 579:3674–3682.