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Minireview

The Leucine-Rich Repeat Superfamily of Synaptic Adhesion Molecules: LRRTMs and Slitrks

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Synapses are asymmetric intercellular junctions connected by multiple synaptic cell adhesion molecules (CAMs). Synaptic CAMs function in various stages of synaptogenesis - the process of synapse creation - encompassing synapse formation, maturation, refinement, plasticity, and elimination. The list of synaptic CAMs has rapidly grown, although their precise functions of most CAMs at synapses remain incomplete. Members of an emerging class of transmembrane proteins containing leucine-rich repeat (LRR) domains have received considerable recent research attention. In this minireview, I discuss recent findings on LRR-containing synaptic CAMs that impact synapse development and circuit formation, focusing on two families of LRR synaptic CAMs: leucine-rich transmembrane proteins (LRRTMs) and Slit and Trk-like family (Slitrks). Their basic biochemical properties, proposed functions at synapses, physiological significances, and open questions are summarized.

INTRODUCTION

A functional nervous system requires precise and specific connections of neurons into neural circuits that underlie specific brain functions. Achieving this connectivity requires that axons and dendrites first contact each other, then recognize their appropriate partner cells, and form synaptic contacts with them. All of these processes that underlie this dynamic, including axon guidance, neurite outgrowth and migration, and synapse formation and validation, are largely determined by adhesion molecules. Among the factors that regulate the development of neural circuits, proteins containing extracellular leucine-rich repeat (LRR) domains have recently emerged as key organizers of connectivity (de Wit et al., 2011; Ko and Kim, 2007). Artificial synapse formation assays have shown that a host of LRR-containing proteins, which are widely and highly expressed in the brain, are capable of recruiting various synaptic scaffolds and inducing synaptic differentiation in heterologous cells in which these LRR-containing proteins are exogenously expressed (de Wit et al., 2009; Kim et al., 2006; Ko et al., 2006; 2009; Linhoff et al., 2009; Mah et al., 2010; Takahashi et al., 2011; 2012; Woo et al., 2009). Selected LRR proteins that function at synapses are shown in Fig. 1. In this minireview, I highlight recent advances in our understanding of the role of LRR proteins in the functions and dysfunctions of synapses (possibly, neural circuits). Due to space constraints, the scope of this review is limited to two classes of LRR proteins - LRRTMs (leucine-rich repeat transmembrane proteins) and Slitrks (Slit and Trk-like family) - that have emerged as important synapse organizers. For more compendious reviews on this topic and a consideration of other LRR-containing proteins, see de Wit et al. (2010), and Siddiqui and Craig (2010).

LEUCINE-RICH REPEATS (LRRS)

The LRR domain, one of the most prevalent domains in the human genome (~330 LRR-containing proteins), is a protein-protein interaction motif that was originally discovered in proteins of the immune system (Kobe and Deisenhofer, 1994; Kobe and Kajava, 2001). LRRs are 20-29 amino-acid (aa) motifs that contain the conserved 11-aa sequence, LxxLxLxxN/CxL, where x is any amino acid, and leucines and asparagine can be replaced with other hydrophobic residues (Kobe and Kajava, 2001). This domain is usually found as a tandem array of a few (or more) individual motifs (Matsushima et al., 2005). The structures of several LRR-containing proteins, including ribonuclease inhibitor and Toll-like receptors (TLRs) (Jin and Lee, 2008; Kobe and Deisenhofer, 1993), have been resolved. These studies point to a common feature of LRR proteins, namely: a characteristic curved, horseshoe-shaped structure formed by a β-strand and an α-helix connected by loops (Kobe and Deisenhofer, 1993). The concave surface of the structure is composed of a continuous β-sheet, which provides an effective ligand-binding site, whereas the convex surface consists of α-helices, which vary substantially among LRR proteins and affect the curvature of the LRR domain. Thus, the LRR domain is an efficient and versatile protein-protein interaction motif.

Because the LRR domain is such an efficient structure for protein-ligand interactions, proteins with extracellular LRR domains are well suited to regulate intercellular communication and cell-to-cell adhesion. A systematic bioinformatics study has shown that extracellular LRR domain-containing proteins have greatly expanded in mammals (135 in mouse, 139 in human) compared with worms (29 extracellular LRR proteins) and flies

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(66 extracellular LRR proteins) (Dolan et al., 2007). The ligands of these extracellular LRR proteins remain largely unknown, although the process of ligand identification has recently accelerated (de Wit et al., 2009; Ko et al., 2009; Siddiqui et al., 2010; Takahashi et al., 2011; 2012; Woo et al., 2009). Mounting evidence from invertebrate systems shows that extracellular LRR proteins control key phases of neuron development and neural circuit formation including axon guidance, target-cell recognition, and synapse formation. The importance of these proteins is further emphasized by the fact that several LRR proteins have been associated with human neurodevelopmental and neuropsychiatric disorders (Matsushima et al., 2005).

LRR SYNAPTIC ADHESION MOLECULES

Leucine-rich repeat transmembrane proteins

LRRTMs were originally identified using bioinformatics tools as part of an effort to identify genes with similarity to the LRRs of Slit proteins (Lauren et al., 2003). Four LRRTM genes are found only in vertebrates and share similar domain structures comprising 10 LRRs, a single transmembrane segment and a short cytoplasmic stretch, which ends in a type I PDZ-binding motif; this latter motif has been shown to mediate direct interactions with the postsynaptic scaffolding protein, PSD-95 (postsynaptic density 95), in heterologous cells (de Wit et al., 2009; Lauren et al., 2003; Linhoff et al., 2009). All four LRRTM mRNAs, determined by reverse transcription-polymerase chain reaction, are highly expressed in the brain and show overlapping distributions in various brain regions (Lauren et al., 2003). For example, LRRTM1 is expressed in the olfactory bulb, cerebral cortex, hippocampus, striatum and thalamus, whereas LRRTM2 is prominently expressed in deep layers, rather than superficial layers, of the cerebral cortex.

A recent unbiased expression screen revealed that LRRTM proteins are synaptogenic in artificial synapse formation assays (Linhoff et al., 2009). All four LRRTM family members display synaptogenic activities in these assays, although the induction strength of LRRTM2 is the strongest (de Wit et al., 2009; Ko et al., 2009; Linhoff et al., 2009). LRRTM2 specifically localizes in excitatory synapses, and not in inhibitory synapses (Linhoff et al., 2009). The localizations of the other LRRTMs have not yet been determined due to a lack of reliable antibodies suitable for immunohistochemical analyses. Overexpression of LRRTM1 or -2 specifically increases the number of excitatory synapses (de Wit et al., 2009; Ko et al., 2009; Linhoff et al., 2009). In addition, LRRTMs interact with neurexins, a well-known family of presynaptic adhesion molecules whose members bind to neuroligins (de Wit et al., 2009; Ko et al., 2009; Siddiqui et al., 2010). This interaction is modulated by the insertion status of alternative splice site #4 found in both α- and β-neurexins (Ko et al., 2009; Siddiqui et al., 2010). LRRTM2 specifically binds to neurexins lacking this insert, and mediates cell adhesion in the *trans*-configuration (Ko et al., 2009). This latter observation suggests the possibility that postsynaptic LRRTM2 bridges the synaptic cleft via interactions with presynaptic neurexins.

Two recent studies addressed the role of LRRTMs through systematic loss-of-function analyses, using RNA interference (RNAi) to knockdown LRRTM1, LRRTM2, and/or neuroligins (Ko et al., 2011; Soler-Llavina et al., 2011). Single knockdown of LRRTM1, LRRTM2, or neuroligin-3 did not change the number of synapses in cultured hippocampal neurons. However, triple knockdown of LRRTM1, LRRTM2, and neuroligin-3 together with neuroligin-1 knockout led to a specific and drastic reduction in excitatory synapses, but not inhibitory synapses, in cultured hippocampal neurons (Ko et al., 2011). Intriguingly, synapse loss in cultured hippocampal neurons triggered by the LRRTM/neuroligin deficiency was abrogated by chronic blockade of synaptic activity as well as by inhibition of calcium influx or calcium/calmodulin-dependent kinase activity (Ko et al., 2011). Using the same molecular tools to test the physiological significance of LRRTMs in acute brain slices, Malenka and colleagues showed that lentiviral-mediated single knockdown of neuroligin-3 in the CA1 hippocampal region of mice did not change excitatory synaptic transmission when lentiviruses were injected at either postnatal day 0 (P0), when synapses are initiated, or postnatal day 21 (P21), when synapses are mature (Soler-Llavina et al., 2011). Interestingly, in contrast to the morphological effects observed in cultured neurons (Ko et al., 2011), P0 double knockdown of LRRTM1 and LRRTM2 selectively reduced AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor-mediated synaptic currents, but not NMDA (N-methyl-D-aspartate) receptor-mediated synaptic currents (Soler-Llavina et al., 2011). P0 triple knockdown of neuroligin-3 and both LRRTMs in neuroligin-1 knockout mice yielded greater reductions in both AMPA and NMDA receptor-mediated synaptic currents, indicating functional redundancy between neuroligins and LRRTMs during early synapse development. In contrast, P21 knockdown of LRRTMs did not alter excitatory transmission, whereas neuroligin-3 knockdown in neuroligin-1 knockout mice specifically changed NMDA receptor-mediated transmission. These results suggest that two neurexin ligands, neuroligins and LRRTMs, are functionally redundant during early synapse development, but are divergent during late synapse maturation (Soler-Llavina et al., 2011).

LRRTMs have been implicated in various neurological disorders. For instance, LRRTM3 was reported to promote processing of amyloid-precursor protein (APP) by BACE1 (β-site APP-cleaving enzyme 1) (Edwards et al., 2009; Majercak et al., 2008), suggesting that LRRTM3 is a functional and positional candidate gene for Alzheimer's disease. Moreover, *in silico* analyses have shown that LRRTM3 might be involved in hereditary congenital facial paresis based on its expression in the brainstem and the results of linkage analyses (Tomas-Roca et al., 2011). LRRTM1 was reported to be associated with left-handedness and schizophrenia (Francks et al., 2007) and with susceptibility to autism spectrum disorder (Sousa et al., 2010). Consistent with this notion, *Lrrtm1*-knockout mice show impairments in various behavioral paradigms, a reduction in total hippocampus size, and deficits in synapse density (Takashima et al., 2011). Moreover, *Lrrtm1*-null mice exhibit altered distribution of the vesicular glutamate transporter, VGLUT1 (Linhoff et al., 2009).

Slit and Trk-like family

The Slitrk family consists of six members (Slitrk1-6) that are highly and widely expressed in the central nervous system (CNS) (Aruga and Mikoshiba, 2003; Aruga et al., 2003). This protein family was originally identified in a screen for genes that were differentially expressed in mice with neural tube defects (Aruga and Mikoshiba, 2003). All Slitrk proteins are type I transmembrane proteins, with extracellular domains containing two clusters of LRRs (Aruga and Mikoshiba, 2003). The extracellular LRR domains of Slitrks resemble Slit proteins, and a conserved region in their intracellular carboxyl terminus has a high degree of homology with that of the neurotrophin receptor, tropomyosin-related kinase (Trk) (Aruga et al., 2003). Genes encoding human Slitrks are present at three different loci: chromosome 3 (SLITRK3), chromosome 13 (SLITRK1, -5, and

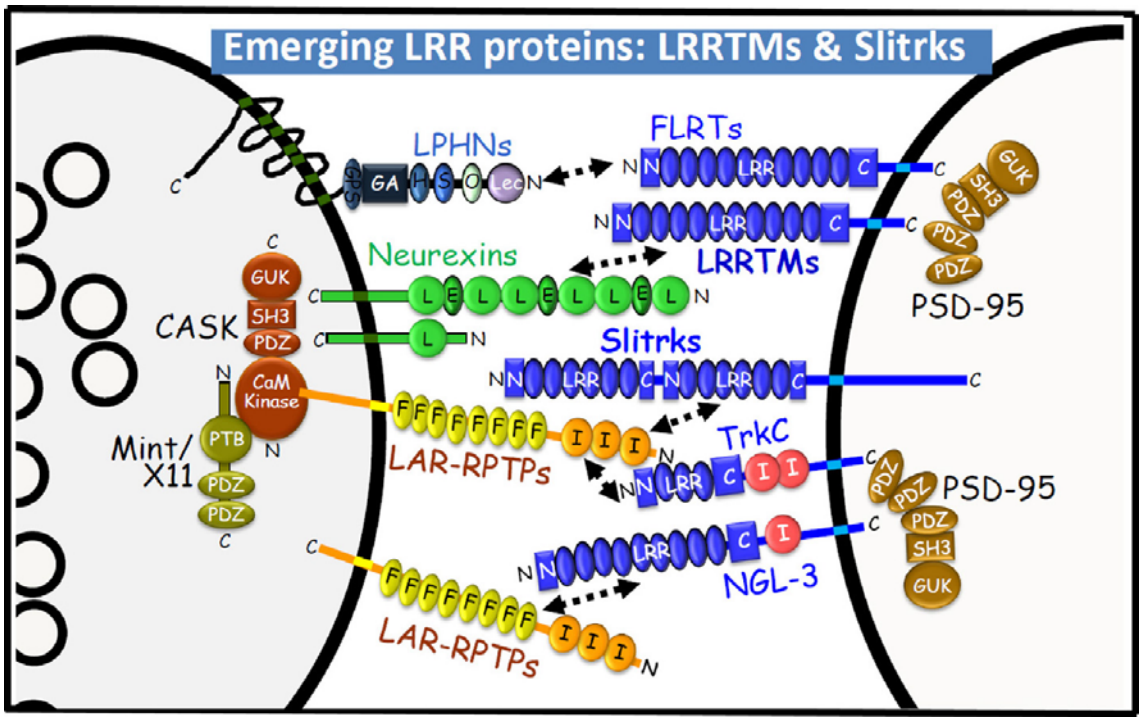

Fig. 1. Overview of leucine-rich repeat (LRR)-containing transmembrane proteins that function as synapse organizers. Six LRR proteins are diagrammed as localized in postsynapses, most of which are able to induce presynaptic differentiation in artificial synapse formation assays. Except LRRTMs (that interact with presynaptic neurexins) and FLRTs (that bind presynaptic latrophilins), other LRR proteins shown here interact with members of type IIa receptor protein tyrosine phosphatases (LAR-RPTPs; LAR, PTPδ, PTPσ). Domain abbreviations: N, Leucine-rich repeat N-terminal domain; C, Leucine-rich repeat C-terminal domain; LRR, leucine-rich repeat; I, immunoglobulin-like; L, LNS domain; E, EGF repeat; F, fibronectin type III repeat; PDZ, postsynaptic density protein (PSD-95), Drosophila disc large tumor suppressor (Dlg), and zona occludens-1 protein (ZO-1).

-6), and the X chromosome (SLITRK2 and -4) (Aruga et al., 2003). A similar chromosomal organization is conserved in the mouse, where Slitrks are located on autosomal chromosomes 3 and, 14, and the X chromosome.

In addition to their broad distribution in the mammalian CNS (Aruga and Mikoshiba, 2003; Aruga et al., 2003), Slitrks are also express in other tissues, such as hematopoietic stem cells, as well as in leukemias (Milde et al., 2007). Northern blot analyses have shown that Slitrk1, -2 and -4 transcripts are detectable as early as embryonic day 11.5/12.5 (Aruga and Mikoshiba, 2003). Mouse Slitrk6 expression is restricted to selected areas of the nervous system (namely, thalamus, lateral geniculate nucleus, and auditory and vestibular system of the ear), an expression pattern that is unique among Slitrks (Aruga and Mikoshiba, 2003; Beaubien et al., 2009; Katayama et al., 2009). Human Slitrk1-5 mRNAs are widely expressed in various brain regions, whereas Human Slitrk6 mRNA is highly expressed in the putamen, but not in the cortex (Aruga and Mikoshiba, 2003; Aruga et al., 2003).

Slitrks have been implicated in the modulation of neurite outgrowth (Aruga and Mikoshiba, 2003; Katayama et al., 2010; Martyen et al., 2011), the promotion of neuron survival (Katayama et al., 2009), and synapse formation (Proenca et al., 2011). Overexpression of each Slitrk member, except Slitrk1 or -4, was shown to decrease the number of neurites in PC12 cells upon nerve growth factor (NGF) treatment (Aruga and Mikoshiba, 2003). Similarly, electroporation of Slitrk1 cDNA into cortical neurons increased dendritic length (Kajiwara et al., 2009), suggesting that Slitrk1 plays an important role in promoting neurite outgrowth. Furthermore, phosphorylation of Slitrk1 on serine 695 by casein kinase II is important for the interaction of Slitrk1 with 14-3-3 proteins (Kajiwara et al., 2009). Mutation of this serine residue to alanine was shown to abolish the interaction of Slitrk1 with 14-3-3 proteins, and block the induction of neurite outgrowth in cultured mouse neurons (Kajiwara et al., 2009). Studies using knockout mice have implicated Slitrk5 in the dendritic complexity of medium spiny neurons of the adult striatum (Shmelkov et al., 2010), and showed that Slitrk6 exerts trophic actions (Katayama et al., 2009). *Slitrk6*-knockout mice also exhibit marked cell death in the spiral and vestibular ganglia (Katayama et al., 2009). Consistent with these latter findings, both brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) mRNA levels, as well as those of their receptors, are downregulated in the inner ear of *Slitrk6*-knockout mice.

Knockout mice have also been used recently to demonstrate the involvement of Slitrk3 and -5 in synapse formation (Shmelkov et al., 2010; Takahashi et al., 2012). In cultured neurons, Slitrk5 localizes to postsynaptic sites. Genetic ablation of Slitrk5 results in abnormalities in striatal anatomy, and altered neuronal morphology and glutamate receptor composition in the striatum, which lead to inefficient corticostriatal neurotransmission (Shmelkov et al., 2010). Recently, Slitrk3 was shown to selectively localize to inhibitory synapses and trigger inhibitory

Table 1. Leucine-rich repeat (LRR) proteins schematized in the Fig. 1

Names	Ligands	Synaptic functions
LRRTM1 LRRTM2 LRRTM3 LRRTM4	Neurexins (α- and β-neurexins) without inserts in splice site #4 (*in vitro & in vivo*)	Excitatory synapse formation and elimination via synaptic activity (de Wit et al., 2009; Ko et al., 2009; Linhoff et al., 2009)
NGL-1 NGL-2 NGL-3	Netrin-G1 (*in vitro*) Netrin-G2 (*in vitro*) LAR, PTPδ, PTPσ (*in vitro*)	Excitatory synapse formation (Kim et al., 2006; Woo et al., 2009)
SALM1 SALM2 SALM3 SALM4 SALM5	Unknown Unknown Unknown SALM4 (*in vitro*) SALM5 (*in vitro*)	Regulation of neurite outgrowth, glutamate eceptor localization (SALM1) (Wang et al., 2006). Control of excitatory synapse maturation (SALM2) (Ko et al., 2006)
Slitrk1 Slitrk2 Slitrk3 Slitrk4 Slitrk5 Slitrk6	PTPδ (*in vitro*) PTPδ (*in vitro*) PTPδ (*in vitro*) PTPδ (*in vitro*) PTPδ (*in vitro*) PTPδ (*in vitro*)	Neurite outgrowth regulation (all Six Slitrks). Inhibitory synapse formation (Slitrk3) (Takahashi et al., 2012)
TrkC	PTPσ (*in vitro*)	Excitatory synapse formation (Takahashi et al., 2011)
FLRT1 FLRT3 FLRT3	Latrophilin1 (*in vitro*) Latrophilin2 (*in vitro*) Latrophilin3 (*in vitro & in vivo*)	Excitatory synapse formation and development (O'Sullivan et al., 2012)

In vitro means the interactions were shown in heterologous cell systems, whereas *in vivo* means the interactions were shown to exist in brain samples.

presynaptic differentiation in artificial synapse formation assays (Takahashi et al., 2012). Other Slitrks induce both excitatory and inhibitory synapse differentiation. Slitrk3-deficient mice exhibit a specific decrease in inhibitory synapse number and function and an increase in seizure susceptibility (Takahashi et al., 2012). The authors of this latter study demonstrated that all six Slitrks mediate *trans*-interaction with receptor protein tyrosine phosphatase-δ (PTPδ), an action that is responsible for the inhibitory-specific synaptogenic activities of Slitrks, at least, in artificial synapse formation assays. A recent expression screen for synaptogenic proteins uncovered several LRR proteins that have synaptogenic activities (Linhoff et al., 2009). One synaptogenic protein identified in this study was Slitrk2, which was shown to induce both excitatory and inhibitory presynaptic differentiation (Linhoff et al., 2009; Takahashi et al., 2012). Taken together, these observations indicate that a subset of Slitrks function in promoting synapse formation and maturation. However, the detailed molecular mechanisms by which Slitrks function at synapses remain to be determined.

Human genetic studies have recently linked rare mutations in SLITRK genes with obsessive-compulsive spectrum disorders and other neuropsychiatric disorders (Abelson et al., 2005). A *de novo* inversion of chromosome 13 was identified in one patient who suffered from Gilles de la Tourette's syndrome (GTS) and attention deficit hyperactivity disorder (Abelson et al., 2005). The 13q33.1 breakpoint identified in this patient mapped to approximately 350 kb from SLITRK1. Sequencing of this gene in a cohort of 174 individuals with GTS revealed two mutations: one was a single-nucleotide deletion that led to a frameshift-mediated truncated protein; the other was a missense mutation in the 3'-untranslated region (3' UTR), named variant 321 (var321) (Abelson et al., 2005). The truncated SLITRK1 protein failed to promote dendritic growth when expressed in cultured neurons. The var321 of SLITRK1 altered binding to the microRNA, miR-189, further increasing the negative modulation of *SLITRK1* mRNA expression associated with miR-189. However, subsequent studies have been unable to replicate the association of SLITRK1 mutations with GTS in larger populations (Deng et al., 2006; Scharf et al., 2008; Verkerk et al., 2006; Wendland et al., 2006), arguing against co-segregation of SLITRK1 and GTS. Studies with knockout mice have revealed probable associations of Slitrks with neuropsychiatric disorders. *Slitrk1*-null mice display increase anxiety-like behavior (quantified by the elevated plus-maze test) as well as depressive-like behaviors (assessed in a forced-swim task) (Katayama et al., 2010). Neurochemical analysis revealed that *Slitrk1*-deficient mice have increased levels of norepinephrine in the prefrontal cortex, striatum, and nucleus accumbens, a finding that is consistent with the pathophysiology of GTS. These results lend support to a possible role of Slitrk1 in neuropsychiatric disorders. *Slitrk5*-null mice initially develop increased anxiety-like behaviors (evaluated by the open-field test) and display repetitive and excessive self-grooming behaviors (Shmelkov et al., 2010), that lead to the formation of severe facial skin lesions and hair loss. Chronic treatment with fluoxetine, a selective serotonin reuptake inhibitor, alleviated these characteristic phenotypes of Slitrk5-deficient mice. These mice also exhibit anatomical deficits as well as abnormal neurotransmission in the striatum. In addition, they show overactivation of the orbitofrontal cortex, determined by measuring the levels of FosB protein, a transcription factor that is commonly used to assess neuronal activity (McClung et al., 2004; Shmelkov et al., 2010). Overall, *Slitrk5*-null mice recapitulate several key aspects of obsessive-compulsive disorder (OCD), suggesting that these mice might be an animal model for OCD. Whether mutations in human Slitrk5 are associated with OCD and/or OCD spectrum disorders is not yet known, but results obtained with *Slitrk5*-null mice suggest that sequencing the SLITRK5 gene in human subjects

might be a fruitful avenue of inquiry. A point mutant (V89M) in SLITRK2 was recently found in schizophrenia patients (Piton et al., 2011), suggesting an association of SLITRK2 with this condition. However, the exact function of Slitrk2 at synapses is not yet clear. Thus, additional studies will be required to determine if Slitrk2 plays a major role in synapse formation, maturation, or refinement. In addition, generation of individual Slitrk knockout mice is necessary to validate the biological impact of Slitrk proteins on CNS function and in their relation to neuropsychiatric disorders.

CONCLUSIONS

LRR proteins regulate key aspects of neural circuit formation, from axon guidance and target recognition to synapse formation and maturation. Although the LRR motif is evolutionarily conserved across species, the two LRR proteins reviewed here (LRRTMs and Slitrks) are specifically evolved in vertebrates. We are now beginning at understanding the mechanistic details of how these proteins control synapse formation, maturation, refinement and/or elimination and how they organize pre- and postsynaptic differentiation in concert with other synaptic proteins.

Although numerous questions remain to be addressed, an increased understanding of the roles of these LRR proteins promises to provide insights into the many devastating disorders that accompany malfunctions of these proteins at synapses and may assist in the development of therapeutic strategies to cure the associated diseases.

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