Immunoglobulin-Like Receptors and Their Impact on Wiring of Brain Synapses

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Abstract

Synapse formation is mediated by a surprisingly large number and wide variety of genes encoding many different protein classes. One of the families increasingly implicated in synapse wiring is the immunoglobulin superfamily (IgSF). IgSF molecules are by definition any protein containing at least one Ig-like domain, making this family one of the most common protein classes encoded by the genome. Here, we review the emerging roles for IgSF molecules in synapse formation specifically in the vertebrate brain, focusing on examples from three classes of IgSF members: (*a*) cell adhesion molecules, (*b*) signaling molecules, and (*c*) immune molecules expressed in the brain. The critical roles for IgSF members in regulating synapse formation may explain their extensive involvement in neuropsychiatric and neurodevelopmental disorders. Solving the IgSF code for synapse formation may reveal multiple new targets for rescuing IgSF-mediated deficits in synapse formation and, eventually, new treatments for psychiatric disorders caused by altered IgSF-induced synapse wiring.

INTRODUCTION

Since synapses were first described by Sherrington (47) as the sites of communication between neurons, the question of how these connections form and change over time has been of central interest. Synapses are the substrate of learning and cognition, and disruption of synaptic function is the basis for many, if not all, neurodevelopmental and psychiatric disorders (122, 123, 170a). The process of wiring synaptic connections during development consists of several steps—the formation of contacts between two neurons, recruitment of synaptic proteins to those contacts, stabilization of the contacts, strengthening and/or weakening of the synapse, and, finally, elimination of a subset of synapses. Synapse formation is mediated by a surprisingly large number and wide variety of genes encoding

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many different protein classes (186). These synaptogenic proteins include neurexins (NRXs) and neuroligins (NLGs) (76, 158), cadherins (142), ephs/ephrins (69), leucine rich repeat (LRR) proteins (29, 135), and integrins (117), among many others (186).

One of the families that is increasingly implicated in synapse wiring but less well understood is the immunoglobulin superfamily (IgSF), which is the focus of this review. Immunoglobulin (Ig)-like receptors perform many functions in all cells of the body, including recognition, adhesion, growth factor binding, and signal transduction. They bind a diverse set of ligands, often via their defining feature: the Ig-like domain. The Ig-like domain was first identified as the antigen recognition domain of human antibodies and is composed of two beta sheets that form a fold stabilized by an intradomain disulfide bond (129). This bond distinguishes these domains from other similar fold-forming domains such as the fibronectin type III (FNIII) domain (10). Ig-like domains exist in four different subtypes named for their resemblance to Ig domains of immunoglobulins: constant 1, constant 2, variable, and intermediate (C1, C2, V, and I). An IgSF molecule is by definition any protein containing at least one Ig-like domain, making this family one of the most common protein classes encoded by the genome. More than 10,000 annotated IgSF proteins are found in humans, 3,400 in mice, and 590 in *Drosophila*, encoded by 1,500, 888, and 317 loci, respectively (43). Some of most well-known IgSF members are the Down syndrome cell adhesion molecules (DSCAMs) and Sidekicks, which have been proposed to form an IgSF code that guides the formation of layer-specific connections in the retina (184). IgSF molecules also regulate the formation of the neuromuscular junction and play roles in synapse formation in *Drosophila* and *Caenorhabditis elegans* (193). Here, we review the emerging roles for IgSF molecules in synapse formation specifically in the vertebrate brain, focusing on examples from three classes of IgSF members: (*a*) cell adhesion molecules, (*b*) signaling molecules, and (*c*) immune molecules expressed in the brain.

CELL ADHESION MOLECULES

Homophilic and heterophilic sticky molecules such as the IgCAMs are of importance to synapse wiring for multiple reasons. They act early in the initiation of synapse formation to specify where and with which partners neurons should form synapses through their role in self-recognition. Further, adding or removing homophilic molecules can act to stabilize or destabilize synapses by modulating adhesive forces at the synaptic contact. The functions of these molecules are diverse, with some impacting many different types of synapses, whereas other playing roles specifically at either excitatory or inhibitory synapses.

Neural Cell Adhesion Molecule (NCAM)

NCAM was one of the earliest identified IgSF molecules. NCAM is a homophilic cell adhesion molecule that plays a wide range of important roles in nervous system development and function (161), including synapse formation and stabilization. NCAM is transported in dynamic *trans*–Golgi network (TGN) packets in axons and dendrites before and during synapse formation in cultured mouse hippocampal neurons (160). Fewer of these TGN organelles accumulate at new axodendritic contacts between cultured neurons from $Ncam^{-/-}$ mice than from wild-type mice, and the packets that are recruited are less stable at

those contacts (160), suggesting that NCAM is necessary for recruiting proteins to, and stabilizing them at, nascent synapses. Removal of NCAM in all neurons does not decrease synaptophysin (a major synaptic vesicle protein) staining or spine density, but NCAM does appear to regulate synapse wiring when it is present at different levels on neighboring neurons. Neurons cultured from $Ncam^{-/-}$ mice have a lower overall intensity of synaptophysin contacting their dendrites only when mixed with wild-type neurons in the same culture (31).

The polysialic acid (PSA) sugar modification on NCAM appears to be responsible for recruiting presynaptic proteins to synapses since PSA removal using the enzyme Endo-Neuraminidase-N (Endo-N) causes the same deficit in synaptophysin intensity in cultured wild-type neurons as in the $Ncam^{-/-}$ neurons (32). PSA removal in vivo by intracranial Endo-N injections in mice also regulates spine density on hippocampal CA1 interneurons, but in a more complicated way, initially increasing spine density and then decreasing it, suggesting that PSA–NCAM is likely required for the formation or stability of synapses on hippocampal neurons (61). NCAM also regulates the formation of a subset of inhibitory synapses through EphrinA signaling, as shown by a reduction in perisomatic GAD65, an inhibitory presynaptic marker, in layer 2/3 of cingulate cortex of $Ncam^{-/-}$ mice (14).

The L1 Family

The L1 family of genes includes *L1 cell adhesion molecule* (*L1cam*), *Neurofascin* (*Nfasc*), *neuronal cell adhesion molecule* (*Nrcam*), and *close homolog of L1* (*Chl1*). The proteins encoded by this gene family have large extracellular domains with six Ig-like domains and four to five FNII domains. These molecules play important roles in multiple stages of development and synaptic plasticity, and we are starting to see evidence that most family members also regulate synapse formation or elimination in the vertebrate brain. L1CAM has been implicated in the formation of perisomatic inhibitory synapses. When the interaction between L1CAM and ankyrin is disrupted in knockin mice, the density of perisomatic GAD67 puncta and symmetric synapses visualized by electron microscopy is reduced (60). Similarly, in ankyrin-g ($Ankg^{-/-}$) knockout mice, the graded distribution of the L1 family member NFASC is disrupted in the cerebellum, with a concurrent decrease in GAD65 positive puncta and positioning of the puncta onto Purkinje neurons (7). Thus, the proper localization of L1 family proteins is necessary for perisomatic inhibitory synapse formation, and this is likely mediated by ANKG.

CHL1 also regulates synapse formation. Perisomatic VGAT puncta are increased on hippocampal pyramidal neurons in $Chl1^{-/-}$ mice, indicating that CHL1 limits GABAergic synapse formation in the hippocampus (108). However, it plays the opposite role in the cerebellum, where CHL1 expressed on Bergmann glia is necessary for the formation of inhibitory synapses from stellate neurons onto Purkinje neurons, as shown by a reduction in both GAD65 puncta and asymmetric inhibitory synapses in $Chl1^{-/-}$ mice (8). Finally, another family member, NrCAM, is also a potent regulator of synapse formation. $Nrcam^{-/-}$ mice display increased excitatory synapse and spine densities, as well as increased miniature excitatory postsynaptic current (mEPSC) frequency, in layer 4 star pyramidal neurons of the visual cortex (30). NrCAM may limit synapse density through its role as a coreceptor

for SEMA3F signaling; it binds to neuropilins 1 and 2 and associates with plexin A3. *Sema3f* genetically interacts with *Nrcam*, and *Nrcam*$^{-/-}$ neurons do not display reductions in dendritic spine density when treated with SEMA3F, as seen in wild-type cultured cortical neurons (30).

Nectins and Synaptic Cell Adhesion Molecules (SynCAMs)

NECTINS and SynCAMs are structurally related proteins that play important roles in synapse wiring. The NECTINs and the SynCAMs are transmembrane proteins that have three extracellular Ig-like domains and cytoplasmic tails bearing motifs that allow interaction with intracellular proteins (11, 92). There are four NECTINs and four SynCAMs (the SynCAMs are also referred to as the nectin-like *necl* genes, although there is one *necl* gene that is not part of the SynCAM group and is more closely related to the NECTINs). NECTINs are both homophilic and heterophilic cell adhesion molecules. NECTIN1 and NECTIN3, expressed on axons and dendrites, respectively, accumulate at the sites of contact between cultured hippocampal neurons. When their interaction is blocked by the application of glycoprotein D, a known NECTIN1 inhibitor, to cultured neurons, synaptophysin clusters on the dendrites of the treated neurons are reduced, possibly indicating a reduction in synapses (101, 170). Similarly, hippocampal neurons cultured from *Nectin1*$^{-/-}$ mice display immature-looking dendritic spines with increased length and decreased head width (170). Consistent with these results, knockdown of NECTIN3 on newly integrated dentate gyrus granule neurons in the mouse hippocampus reduces their dendritic spines (176).

SynCAMs were one of the first IgSF members identified as synapse-organizing molecules that are sufficient to induce accumulation of synaptic proteins to new sites of contact. SynCAM1 expressed in HEK293 cells induces the formation of active presynaptic sites capable of neurotransmitter release on the axons of cocultured hippocampal neurons (11). SynCAMs are rapidly recruited to sites of contact between axons and dendrites in hippocampal cultures (44, 155). SynCAM1 accumulation is concurrent with the recruitment of pre- and postsynaptic proteins and is stable over time, suggesting that SynCAMs are among the first molecules to accumulate at synapses to mediate synapse formation (155). SynCAMs exhibit homophilic and heterophilic binding across the synaptic cleft (11, 44). Surprisingly, SynCAM1 overexpression is not sufficient to induce the formation of new synapses or dendritic spines in cultured hippocampal neurons, but it does increase mEPSC frequency selectively during the early period of synapse formation in young neurons (139). This increase in excitability of the neurons may be mediated through erythrocyte membrane protein band 4.1 like 3 (EPB41L3; also referred to as 4.1B), which interacts with SynCAM1 and aids in the recruitment of *N*-methyl-D-aspartate receptors (NMDARs) to these sites (68).

In vivo, *Syncam1* clearly promotes synapse formation. A mouse line overexpressing SynCAM1 exhibits elevated excitatory synapse and spine density in hippocampal CA1 neurons, as well as increased mEPSC frequency (133). SynCAM1 must be continually overexpressed to maintain these increases in synapse number, suggesting that it is likely essential for maintaining the stability and strength of synapses (133). Excitatory synapse number in vivo in stratum radiatum of mouse hippocampal CA1 measured by electron microscopy and spine density on distal dendrites of CA3 pyramidal neurons and medium

spiny neurons in the nucleus accumbens are decreased in *Syncam1*$^{-/-}$ mice (56, 116, 133), suggesting that SynCAM1 alone is necessary for synapse formation. In contrast, other reports suggest that lowering levels of any individual SynCAM1 does not alter synapse density (16, 49). The latter report showed that synapse density is reduced only when SynCAM1–3 are knocked down together, suggesting that SynCAM1–3 may be functionally redundant for synapse formation in neurons (49). Whether this discrepancy is due to a difference in technical approach or cell type examined has yet to be determined (49).

Consistent with some of the transient effects on overexpression, SynCAM1 is localized to the periphery of the synapse and not the center, as with many transsynaptic organizers that play a role in forming the synapse (124). Positioning of synaptic proteins in discrete functional nanodomains may be critical to their roles at synapses (104, 167). The strength of SynCAM1 adhesion at synapses is also important to its function, as a reduction in transsynaptic binding strength of SynCAM1 resulting from a reduction in its *cis*-oligomerization decreases SynCAM1's ability to induce presynaptic structures on hippocampal neurons in coculture and its ability to constrain synapse size on more mature cultured neurons (46). *N*-glycosylation of SynCAM1 varies across brain regions and across ages. Loss of *N*-glycosylation reduces the ability of SynCAM1 to bind both itself and SynCAM2 and to induce presynaptic differentiation in hippocampal neurons in coculture assays (45). Thus, the strength of SynCAM adhesion plays a significant role in its ability to induce and stabilize synaptic circuitry.

Mam Domain–Containing Glycosylphosphatidylinositol Anchors (MDGAs)

Members of the IgSF not only are transmembrane proteins, as described above, but also can be glycosylphosphatidylinositol (GPI)-linked to the membrane and synapses. Two of the GPI-linked IgSF proteins implicated in synapse formation are MDGA-1 and MDGA-2, which are composed of six Ig domains, an FNIII domain, and a MAM domain. These two MDGAs are expressed specifically in the nervous system during pre- and postnatal development (86). Knockdown of MDGA-1 and MDGA-2 increases the density of clusters of the inhibitory synapse protein VGAT along dendrites of cultured hippocampal neurons, and these levels can be rescued with MDGA-1 (80). Double knockdown does not seem to be necessary to increase inhibitory synapse density, as knockdown of MDGA-1 alone in cultured rat hippocampal neurons is sufficient to increase inhibitory synapse density (125). Conversely, overexpression of MDGA-1 in cultured neurons reduces inhibitory synapse density (80, 125). In contrast, when MDGA-2 is overexpressed in cultured hippocampal neurons, both excitatory and inhibitory synapse density are reduced, accompanied by decreases in both miniature inhibitory postsynaptic current (mIPSC) and mEPSC frequency, but not amplitude, relative to controls (27).

Consistent with a role for MDGA-2 in limiting excitatory synapses, heterozygous knockout mice display increases in excitatory, but not inhibitory, synapse density as well as increases in mEPSC frequency and amplitude in hippocampal CA1 slices compared with wild-type animals. Knockdown of MDGA-1 in cultured *Mdga2*$^{+/-}$ hippocampal neurons leads to an increase in mIPSC frequency (27), suggesting that MDGA-1 and MDGA-2 have similar but nonidentical roles in synapse wiring. Both molecules act to limit synapse density,

but MDGA-1 acts solely to limit inhibitory synapses, while MDGA-2 may act to limit both excitatory and inhibitory synapses. The role of the MDGAs in synapse formation recently became murkier and controversial as the result of a study showing that MDGA-2 overexpression in cultured rat cortical neurons increases the density of inhibitory synapse markers contacting dendrites, while MDGA-2 knockdown alone has no effect on synapse density and only knockdown of both MDGA-1 and MDGA-2 increases excitatory and inhibitory vesicle density (87). Further research is required to assess the findings from this report and determine why they led to different conclusions compared with other reports (27, 80, 125).

Both MDGA-1 and MDGA-2 regulate synapse formation through binding to NLGs. MDGA-1 and MDGA-2 were initially found to bind to Neuroligin-2 (NLGN2), thereby inhibiting the ability of NLGN2 to induce inhibitory presynaptic terminals on cocultured neurons in human embryonic kidney (HEK) cell coculture assays (80, 125). The interaction of MDGA-1 with NLGN2 requires Ig domains 1–3 of MDGA-1 (80, 125) and blocks the ability of NLGN2 to bind to its transsynaptic partner NRX1, providing a mechanism by which MDGA-1 limits inhibitory synapse formation (54). Another recent report showed that MDGAs bind both NLGN1 and NLGN2 in vitro, but MDGA-1 interacts only with NL2 and not NL1 in vivo by an unidentified mechanism (74). The crystal structure of the extracellular domain of MDGA-1 and the NL1–MDGA-1 complex has since revealed that the relative expression levels of MDGAs and NLGNs determine whether MDGAs will regulate synapse density on their own or function through suppressing NLGN function (36). Understanding this mechanism and how MDGAs interact with all of the NLGN isoforms in vivo may help to resolve some of the disputed roles of these IgSF members in synapse formation.

IGSF9 Family

IGSF9 and IGSF9b, two highly related evolutionarily conserved members of the IgSF, are mediators of inhibitory synapse formation in mice. Both contain five Ig-like domains in their extracellular region and two FNIII domains. IGSF9 is also known as dendrite arborization and synapse maturation 1 (Dasm1) in mice. IGSF9 was originally identified in a search for molecules homologous to the *Drosophila* protein Turtle (144). In *Drosophila*, Turtle and its close relative Borderless have been implicated in dendrite branching and self-avoidance, photoreceptor axon tiling, and synaptic layer targeting (18, 42, 89). Initially, IGSF9 was found to regulate dendrite arborization and glutamatergic synapse formation in cultured hippocampal neurons and organotypic slice culture, respectively, by knockdown with RNAi or overexpression of a putative dominant negative form of the protein (143, 144). More recent experiments contradict the initial reports and show normal dendrite and excitatory synapse development in the hippocampus of *Igsf9*$^{-/-}$ mice. An off-target RNAi effect likely explains the original phenotype since the previously utilized RNAi constructs cause the same effects in both *Igsf9*$^{-/-}$ and wild-type mice (99). Interestingly, more recent work indicates that knockout of *Igsf9* likely does alter synapse density—but of inhibitory rather than excitatory synapses. *Igsf9*$^{-/-}$ mice show reduced levels of postsynaptic proteins found at GABAergic synapses, including an enzyme, GAD67, necessary for production of GABA in the hippocampus and of gephyrin in cultured hippocampal neurons. Inhibitory synapse density and mIPSC frequency is also reduced in interneurons in which IGSF9 levels

are reduced using shRNA, while glutamatergic synapse density onto these interneurons is unchanged (100). Although IGSF9 clearly regulates inhibitory synapse formation, it is not sufficient to induce inhibitory synapse formation when expressed on HEK293 cells that are cocultured with hippocampal neurons (100). IGSF9 performs its functions on inhibitory synapses independently of its intracellular domain, as knockin mice lacking the IGSF9 cytoplasmic tail have normal inhibitory synapse development, suggesting that its extracellular domain mediates these effects possibly through homophilic adhesion (100). Thus, IGSF9 is necessary, but not sufficient, for formation of a subset of inhibitory synapses in the hippocampus.

IGSF9b is highly related to IGSF9. When IGSF9b is knocked down by shRNA in cultured hippocampal neurons, it reduces inhibitory postsynaptic markers (181). IGSF9b was unable to induce inhibitory synapse formation by expression in heterologous cells in coculture, much like IGSF9 (100, 181). The cytoplasmic domain of IGSF9b binds to a synaptic protein called membrane-associated guanylate kinase-2 (MAGI2), which when knocked down reduces colocalization of NLGN2 and IGSF9b at synapses as well as GABAergic synapse density. Thus, IGSF9 has been proposed to induce the formation of inhibitory synapses through its interactions with NLGN2 mediated by MAGI2, although direct evidence for this has yet to be seen (181). Whether IGSF9 and IGSF9b function through their characterized homophilic interactions, heterophilic transsynaptic interactions, or some other mechanism has yet to be addressed (100, 181). Fully describing their mechanisms of function will be important to elucidating their precise function in synapse development.

IGSF21

IGSF21 is a two Ig domain–containing GPI-linked protein identified in a cDNA screen for synaptogenic proteins in neuron coculture assays (85). IGSF21 is a bona fide synaptogenic molecule for inhibitory synapses since it induces inhibitory presynapse formation in hippocampal neurons in a HEK293 cell coculture synapse induction assay (166). Strikingly, when coated on beads and cocultured with neurons, IGSF21 is also sufficient to induce inhibitory presynaptic specializations, indicating that this molecule is among the select group of molecules that is minimally sufficient for inducing presynapse formation (166). This process is mediated by the binding of IGSF21 to NRX2α. Addition of exogenous, soluble NRX2α to these cocultures inhibits the ability of IGSF21 to induce presynaptic specializations. Endogenous IGSF21 is necessary for inhibitory synapse formation since the inhibitory synaptic proteins VGAT and gephyrin are reduced in cortical synaptosomes, VGAT levels are lower in hippocampal synaptosomes and in hippocampal tissue, and presynaptic vesicles at inhibitory presynaptic terminals are also specifically reduced in $Igsf21^{-/-}$ mice. Consistent with decreases in inhibitory synapse density, the frequency of mIPSCs from hippocampal CA1 pyramidal neurons is also decreased, indicating a decrease in overall inhibitory synaptic transmission (166). These data strongly suggest that IGSF21 promotes functional inhibitory synapse assembly in mice.

IgLONs

The immunoglobulin limbic system–associated membrane protein (LAMP), opioid binding cell adhesion molecule (OBCAM), kindred of IgLON (KILON), and neurotrimin (NTM)

are members of a family known as the IgLON family, a subfamily of homologous IgSF glycoproteins, all consisting of three extracellular Ig-like domains and a GPI anchor (126, 157). The IgLONs are a group of five human and four rodent proteins that can bind to themselves homophilically or to one another heterophilically. Many of the IgLON family members regulate synapse formation. Overexpression of LAMP in cultured hippocampal neurons increases synapse density (63). Disrupting OBCAM with an antibody in cultured mouse hippocampal neurons reduces synapsin density along dendrites, suggesting that OBCAM normally promotes synapse formation (183). Consistent with this, reducing OBCAM levels in cultured rat hippocampal neurons using an interfering oligonucleotide decreased staining for presynaptic proteins along dendrites, suggestive of a decrease in synapse density (183). Conversely, overexpression of OBCAM increases synapsin cluster density on dendrites (63, 183), suggesting that OBCAM typically acts to promote synapse formation. Conversely, overexpression of KILON, also referred to as neuronal growth related 1 (NEGR1), in cultured hippocampal neurons reduces the density of the presynaptic protein synapsin, suggesting that KILON may inhibit synapse formation or stability (63, 64). Further experiments examining knockout animals to assess dendritic spine formation and whether the effects on changes in presynaptic puncta represent a change in excitatory or inhibitory synapse density will be required to begin to assess the mechanisms by which these proteins mediate changes in presynaptic markers.

Contactins

The contactins (CNTNs) are a family of six GPI-linked IgSF proteins, each having six Ig-like domains and four FNIII-like domains. CNTNs play roles in many neurodevelopmental processes, especially axon guidance, but the impact of most family members on synapse formation remains unclear (146). CNTN1 does regulate synaptic plasticity but appears not to alter synapse number or structure (103). Likewise, CNTN4 and CNTN5 regulate neuritogenesis (98). To date, only one CNTN family member clearly regulates synapse wiring. CNTN6, also called NB-3, is expressed presynaptically in the cerebellum, where it colocalizes with VGLUT1 and is enriched in synaptosomes. Loss of CNTN6 in $Cntn6^{-/-}$ mice reduces the number of VGLUT1 puncta along the dendrites of Purkinje cells, suggesting that CNTN6 promotes excitatory synapse formation (137). Consistent with a role in selectively regulating glutamatergic synapses, CNTN6 colocalizes with glutamatergic presynaptic markers VGLUT1 and VGLUT2 and not the inhibitory presynaptic marker VGAT in the hippocampus. Like the synaptic effects seen in the cerebellum, the density of glutamatergic, but not GABAergic, presynaptic proteins are reduced in the hippocampi of $Cntn6^{-/-}$ mice (136). Although CNTN6 clearly promotes glutamatergic synapse formation, the mechanism underlying these effects is unknown. Further work is required to identify CNTN6 binding partners; the cellular and molecular pathways that are involved; and whether other CNTN family members, apart from CNTN6, regulate synapse formation.

THE SIGNALING MOLECULES

The proteins described in this section are important for synapse formation and are also known to activate intracellular signaling cascades or contain domains implicated in signaling pathways. Some of these proteins use these signaling cascades to regulate synapse formation

while others appear to regulate synapse formation independently of their intracellular signaling roles.

DCC Protein

Deleted in colorectal cancer (DCC) is a transmembrane IgSF protein that is highly conserved across species and primarily known in the nervous system for its critical roles in axon guidance, where it acts as the receptor for the netrin ligands (22, 73). Recently, evidence that this prototypic axon guidance molecule is also involved in synapse wiring has emerged. Treatment of cultured cortical neurons with netrin increases synapse density, while application of an antibody that blocks netrin function reduces it (59). Netrin plays an instructive role in synapse formation since netrin-coated beads can induce accumulation of pre- and postsynaptic protein clusters at sites of contact with dendrites from cocultured neurons. Netrin increases glutamatergic synapse density and mEPSC frequency and amplitude, while a netrin function–blocking antibody has the opposite effect (59). The synapse-inducing effects of netrin are mediated by DCC since they are blocked using a DCC function-blocking antibody (59). Surprisingly, knockout of *Dcc* in hippocampal CA1 pyramidal neurons in mice does not reduce dendritic spine density, but spines shift toward smaller sizes (67). It remains to be seen whether DCC knockout influences cortical synapse density in vivo, as would be suggested from the experiments in cultured cells, but it is possible that netrin may have effects on synapse formation independent of DCC. Further experiments are needed to address these possibilities.

Receptor Protein Tyrosine Phosphatases and Their Binding Partners

The receptor protein tyrosine phosphatases (RPTPs) are cell surface proteins with variable extracellular regions that act as receptors to bind ligand and more conserved intracellular regions containing protein tyrosine phosphatase domains, which signal by removing phosphate groups from tyrosine residues on neighboring target proteins. In vertebrates, the Type IIα RPTPs, also called the leukocyte antigen–related (LAR)-RPTPs, are a family composed of LAR, PTPδ, and PTPσ. All members of the Type IIα RPTPs are characterized by three N-terminal Ig-like domains, a variable number of FNIII domains, a transmembrane domain, a membrane proximal D1 tyrosine phosphatase domain, and a membrane distal D2 inactive phosphatase domain (111). Recently, the importance of these molecules in synapse formation has been highlighted, and the RPTPs have even been proposed to be hubs as important for synapse assembly as are the NLGs and NRXs (62, 163).

Type IIα RPTPs are present throughout the brain, with LAR and PTPσ localized to glutamatergic synapses (162) and PTPδ mainly found at GABAergic synapses (164). These molecules were first shown to play a role in mammalian synapse wiring when LAR, PTPσ, and PTPδ were individually knocked down, leading to a reduction in PSD-95 puncta and dendritic spine density in cultured rat hippocampal neurons. This reduction could be further enhanced if any two or all three of the Type IIα RPTPs were to be knocked down. Conversely, overexpression of LAR increases mEPSC frequency in cultured neurons, suggesting an increase in functional synapses (34). LAR appears to be sufficient to induce postsynaptic densities since LAR expression in HEK293 cells increases the intensity of clusters of the excitatory postsynaptic proteins, while levels of the inhibitory postsynaptic

protein gephyrin were unchanged in cocultured hippocampal neurons (180). The Type IIα RPTPs regulate synapse formation through interaction with several other classes of synaptogenic molecules, each described below.

Liprin-α.

The promotion of synapse formation by LAR is mediated by both liprin-α and the tyrosine phosphatase activity of LAR. Overexpression of mutant forms of LAR that disrupt either liprin-α binding or its phosphatase activity in cultured neurons decreases pre- and postsynaptic puncta, dendritic spine density, and mEPSC frequency and amplitude. These results suggest that postsynaptic LAR regulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) trafficking—a hypothesis consistent with the reported physical interaction of LAR with liprin-α and glutamate receptors, and the reduction of surface glutamate receptors following liprin-α disruption (182). LAR also alters clustering of postsynaptic β-catenin, suggesting that it can affect synaptic adhesion as well as recruitment of proteins to new contacts (34).

Netrin-G-like 3 (NGL3).

Type IIα RPTPs also regulate synapse formation through binding to a protein called netrin-G-like 3 (NGL3). Overexpression of NGL3 in cultured hippocampal neurons increases the intensity of excitatory presynaptic terminals onto transfected neurons, and knockdown of NGL3 reduces glutamatergic synapse density. LAR mediates this effect of NGL3 on synapse formation since soluble LAR reduces NGL3-induced excitatory presynaptic differentiation in cultured hippocampal neurons (180). All three RPTPs can bind NGL3 through their first two FNIII domains; however, only the FNIII domains of LAR and PTPσ are capable of inducing postsynaptic PSD-95 clusters on cultured neurons, suggesting that PTPδ may only mediate unidirectional presynapse formation with NGL3 (78).

Netrin-G1 (NG1).

LAR also interacts with netrin-G1 (NG1) to enhance glutamatergic presynaptic terminal differentiation. This interaction is a novel *trans*-induced *cis*-interaction in which presynaptic NG1 initially binds to postsynaptic netrin-G1 ligand-1 (NGL1), which induces a *cis* interaction between NG1 and LAR. Decreasing LAR levels in dissociated rat hippocampal neurons prevents soluble NGL1 from inducing presynaptic differentiation. Additionally, NGL1-Fc is able to precipitate LAR only when NG1 is coexpressed (151). This is a fascinating mechanism for transsynaptic signaling that may be generalizable to other synaptic wiring processes.

Synaptic adhesion-like molecules (SALMs).

All three Type IIα RPTPs interact with SALMs 3 and 5 to induce presynaptic differentiation in culture. In coculture, decreasing levels of neuronal RPTPs reduces the ability of SALM5 expressed on HEK cells to induce presynaptic terminals; knockdown of all three RPTPs has the strongest reduction in SALM5-induced presynaptic puncta (25, 82). Further complicating this mechanism, when SALM4 is coexpressed with SALM3 or 5 it blocks their ability to interact with LAR to induce synapse formation (83). A structural study has shown

that SALM5 induces dimerization of PTPδ to induce presynaptic differentiation (84). This dimerization of Type IIα RPTPs may provide a generalizable mechanism for the action of RPTP ligands on RPTPs in synaptic differentiation, but further experiments will be needed to test this hypothesis.

Tropomyosin-related kinase C (TrkC).

Like LAR and PTPδ, PTPσ also binds to multiple distinct classes of synapse-organizing molecules. PTPσ regulates synapse wiring through binding to another IgSF protein, tropomyosin-related kinase C (TrkC), through the Ig-like domains of PTPσ (162). TrkC induces glutamatergic presynaptic differentiation, measured by clustering of synapsin and VGLUT1, in HEK cell coculture assays with dissociated hippocampal neurons. Similarly, beads coated with the ectodomains of either TrkC or PTPσ induce excitatory pre- and postsynaptic differentiation in cultured neurons (162). Abolishing the interaction of TrkC and PTPσ using an antibody against TrkC reduces glutamatergic synapse density in cultured neurons, mimicking the effects of decreasing TrkC levels on synapse density in those cells (162). TrkC induction of presynapse differentiation is enhanced by addition of neurotrophin-3 (NT-3) in HEK cell coculture assays with dissociated rat hippocampal neurons (5). This effect appears to be due to an increase in the ability of PTPσ to bind to TrkC after NT-3 binding, as surface binding of PTPσ to TrkC expressing COS7 cells is increased after NT-3 treatment (5).

SLIT and TRK-like proteins (SLITRKs).

The LAR-RPTP family members PTPδ and PTPσ, but not LAR, also mediate the synaptogenic activities of another family of synapse organizers, the SLITRKs. PTPδ regulates GABAergic synapse formation through interacting with multiple SLITRKs. Clustering of the inhibitory synapse protein VGAT, but not the glutamatergic protein VGLUT1, is increased in rat hippocampal neurons at sites of contact with SLITRK-expressing HEK293 cells (164, 188). This increase in VGAT clustering is reduced when PTPδ is knocked down on the cocultured neurons, suggesting that SLITRK-induced formation of inhibitory presynaptic terminals requires PTPδ (164, 188). In contrast, reducing levels of PTPσ in cocultured neurons in the same HEK cell synapse induction assay prevents SLITRK1- and SLITRK2-induced clustering of VGLUT1 but not GAD67 (188). Thus, PTPδ and PTPσ mediate the effects of specific SLITRKs to induce glutamatergic and GABAergic synapse selectively.

THE IMMUNE MOLECULES

These molecules were originally described for their roles in the immune system, however recent results have revealed critical roles for these molecules in the brain, and in synapse formation in particular. In many instances, the synaptogenic functions of these proteins are mediated by mechanisms similar to how they signal in the immune system.

Intercellular Cell Adhesion Molecules (ICAMs)

The intercellular cell adhesion molecule (ICAM) family is composed of five genes encoding transmembrane proteins ICAM1–5 with a variable number of Ig-like domains in their

extracellular regions. These molecules have been studied extensively in the immune system, where they regulate the formation of immunological synapses between antigen-presenting cells and leukocytes through binding in *trans* to integrins (177). While little is known about the function of most ICAM family members in the brain, one particular ICAM, ICAM5, clearly plays an important role in synapse wiring. ICAM5, also known as telencephalin because of its discovery as a forebrain-specific molecule, is expressed in the mammalian central nervous system (CNS) and has nine Ig-like domains in its extracellular segment (52). Hippocampal neurons cultured from $Icam5^{-/-}$ mice display an increase in synapse density, suggesting that ICAM5 inhibits synapse formation (109). Because spine density at older ages is similar to that found in wild-type cultures, the effect of $Icam5^{-/-}$ likely represents a delay in dendritic spine maturation. Consistent with this idea, blocking β1 integrin (the binding partner of ICAM5 in the immune system) or ICAM5 using function-blocking antibodies in cultured hippocampal neurons shifts dendritic spines toward a more mature phenotype soon after their formation, while activating β1 integrin causes them to revert to a more immature filopodial phenotype. Similarly, filopodial dendritic protrusions are decreased in $Icam5^{-/-}$ mice and increased when ICAM5 is overexpressed in both hippocampal slice and dissociated culture (95, 109).

The ability of ICAM5 to regulate synapse wiring is highly responsive to neuronal activity and cytokine levels, both of which dynamically regulate ICAM5 expression levels and proteolytic shedding (26, 90, 177). Activation of NMDARs and matrix metalloproteinases (MMPs) increases cleavage of the ectodomain of ICAM5, which enhances dendritic spine maturation (169). ICAM5 binding to β1 integrin protects against cleavage and therefore limits spine maturation (109). The cleaved ICAM5 appears to promote spine maturation through preventing microglial engulfment of active synapses, a process that mediates synapse elimination in the brain. ICAM5 also changes the cytokines secreted by microglia, which may also regulate synapse density and function (114). Thus, ICAM5 binding to β1 integrin reduces the strength and stability of synapses between neurons in the mammalian brain using mechanisms similar to those in the immune system.

Major Histocompatibility Complex Class I (MHCI) Molecules and Their Receptors

MHCI molecules are expressed by all nucleated cells in the body and are encoded by genes that are the most polymorphic genes known, with a distinct set of alleles found in each individual called their haplotype (106, 145). HLA-A, -B, and -C encode classical MHCI molecules in humans, while H2-K, -D, and -L encode classical MHCI molecules in mice. There are also many nonclassical genes (MHCIb) that are less well studied (145). The classical MHCI molecules are heterotrimeric complexes composed of a heavy chain containing two alpha helices that form a peptide-binding groove, a highly conserved invariant Ig-like domain, and a light-chain single-Ig-domain molecule called β2-microglobulin (β2m). The invariant Ig-like domain partially mediates binding to β2m and to MHCI's immune receptors (40, 65). After the heavy chain is formed, peptides produced by the cellular proteasome are loaded onto MHCI molecules in the endoplasmic reticulum, followed by association with β2m (91, 120). Peptide loading and β2m are required for classical MHCI molecules to be expressed on the surfaces of cells (153, 178), where they can be recognized by receptors on effector immune cells to trigger cell death or survival. In

addition to their roles as ligands for peptide presentation, MHCI molecules may act directly to transduce extracellular signals in nonneuronal, nonimmune cell types (121). Indeed, the cytoplasmic domain of MHCI molecules contains several PSD-95, disc large, zonula occludens 1 (PDZ) protein–protein interaction domains that could mediate signaling through phosphorylation and binding other effector molecules at the synapse (51). Originally, MHCI molecules were believed to be expressed in the CNS only under pathological conditions (107, 179), but this assumption was reversed with work showing that MHCI mRNAs are expressed in the healthy CNSs of many species, including rodents, cats, marmosets, and humans (17, 28, 94, 96, 97, 131, 132, 168). Subsequent studies showed that MHCI proteins are present in both neurons (pre- and postsynaptically) and glial cells in several regions of the CNS throughout development and into adulthood (21, 57, 58, 105, 131, 132, 156).

MHCI proteins play important roles in synapse wiring, where they act to limit synapse density. Acute overexpression of H2-K^b MHCI proteins in cultured cortical neurons reduces both glutamatergic and GABAergic synapse densities exclusively during early stages of synapse formation (57). Conversely, acute knockdown of β2m, which reduces the surface levels of most classical MHCI molecules, increases synapse density in cultured visual and frontal cortical neurons (38, 57). Synapse density on visual cortical neurons is also elevated in vitro during early stages of synapse formation and in vivo throughout development and into adulthood in mice lacking β2m (and therefore surface MHCI molecules) (57). Similarly, spine density and intracortical connectivity is also elevated in mice lacking both classical MHCI genes, *H2-K1* and *H2-D1* [*H2-K(b)*, *H2-D(b)*$^{-/-}$ mice] (2). A similar elevation in synapse density is observed in the CA3 region of the hippocampus from mice lacking β2m (*β2m*$^{-/-}$) and *H2-K(b)*,*H2-D(b)*$^{-/-}$ mice (33), although synapse density was not altered in hippocampal cultures from mice lacking both β2m and the transporter associated with antigen processing (TAP1) (*β2m*$^{-/-}$/*Tap1*$^{-/-}$ mice) (58).

In addition to limiting synapse density, MHCI molecules also negatively regulate synaptic transmission and plasticity. Cortical and hippocampal neurons cultured from *β2m*$^{-/-}$ and *β2m*$^{-/-}$/*Tap1*$^{-/-}$ mice show increased mEPSC frequency consistent with an increase in functional excitatory synapses (57, 58). Cortical neurons from several mouse lines lacking β2m and/or MHCI molecules also show increased mEPSC amplitude, suggesting that MHCI molecules may negatively regulate AMPAR content at newly formed glutamatergic synapses in visual cortex (2, 57, 79). MHCI molecules also appear to tonically repress NMDAR function in hippocampal neurons, thereby regulating NMDAR-mediated AMPAR trafficking (48).

Although the mechanisms underlying the effect of MHCI molecules on limiting synapse density are mostly unknown, recent reports indicate that MHCI molecules require neuronal and synaptic activity, downstream activation of calcineurin, and activation of myocyte enhancer factor 2 (MEF2) transcription factors to negatively regulate synapse density between cultured cortical neurons (38). In hippocampal neurons, MHCI molecules limit synapse density by inhibiting the prosynaptogenic effect of insulin receptor signaling in the hippocampus (33). The effects of MHCI molecules in negatively regulating synapse wiring may also be mediated by their classical immune receptors, some of which are also IgSF members. Although there is no evidence that classic T cell receptors are present in

the CNS (159), natural killer (NK) cell receptors that bind MHCI molecules are present in the brain. Some of these NK receptors are IgSF members and include the leukocyte immunoglobulin like receptors (LILRs) in humans (66) and their orthologs, the paired immunoglobulin receptors (PIRs), in mice (165). The PIRs were identified as a pair of gene families (*Pira* and *Pirb*) encoding Ig-like receptors with six Ig-like domains and different transmembrane regions homologous to the human Fc receptor (77). PIRA proteins are encoded by multiple genes, while there is a single locus for PirB (77, 185). Like MHCI molecules, PIRB negatively regulates synapse formation in the developing brain. Blocking endogenous PIRB signaling using either a soluble PIRB protein (12) or a germline *Pirb*$^{-/-}$ mouse line (173) increases dendritic spine density and mEPSC frequency on neurons in mouse visual cortex. This effect on spine density is absent at early ages (P23) but was observable at P30, suggesting that PIRB promotes synapse pruning from P23 to P30 (173). A molecule related to PIRB, leukocyte immunoglobulin-like receptor A3 (LILRA3), which is a secreted protein with four Ig-like domains, increases synapse density in mouse cortical cultures (6), suggesting that LILRA3 functions in a manner very similar to the way that PIRB functions in mouse.

The IL-1 Receptor Family

The immunoglobulin like interleukin-1 (IL-1) receptors—IL-1 receptor 1 (IL1R1), IL-1 receptor accessory protein (IL1RAcP), IL-1 receptor accessory protein like 1 (IL1RAPL1)—are Ig-like proteins with three Ig-like domains in their extracellular regions and a Toll IL-1 receptor like domain in their intracellular regions (112). Although a direct role for IL1R1 in synapse formation has not yet been reported, IL1R1 is present at excitatory synapses and IL-1β treatment for just 30 min increases its localization with PSD-95 in cultured hippocampal neurons, suggesting that IL-1 signaling is rapidly modulated at synapses (55). In contrast, the IL1R accessory proteins clearly play a role in synapse wiring at basal levels, although whether IL-1β modulates the effects of IL1RAPL1 or IL1RAcP on synapse formation remains to be determined.

IL1RAPL1 positively regulates glutamatergic synapse formation. Overexpression of IL1RAPL1 in cultured hippocampal neurons increases PSD-95 clustering, likely through a physical interaction of PSD-95 with a PDZ binding motif in the terminal eight amino acids of IL1RAPL1. Removal of these residues in IL1RAPL1 results in loss of binding to PSD-95, and overexpression of mutant constructs lacking these residues prevents IL1RAPL1-induced PSD-95 clustering (119). This effect of IL1RAPL1 on PSD-95 clustering probably represents an increase in synapse formation since overexpression of IL1RAPL1 in cultured hippocampal neurons increases mEPSC frequency, and loss of protein in *Il1rapl1*$^{-/-}$ mice decreases mEPSC frequency, clusters of both pre- and postsynaptic markers in cultured hippocampal neurons, and asymmetric synapse density and spine density on CA1 pyramidal neurons (119). This loss of spine density was also seen on the basal dendrites of CA1 hippocampal neurons and cortical layer 2/3 pyramidal neurons from germline *Il1rapl1*$^{-/-}$ mice (187).

IL1RAcP regulates glutamatergic and GABAergic synapse formation. It induces the formation of excitatory and inhibitory presynaptic terminals when expressed on HEK293

cells in coculture with cortical neurons (189). IL1RAcP-coated beads are also sufficient to induce excitatory presynapse formation measured by aggregation of bassoon and VGLUT1 on cocultured neurons (189). In cortical neuronal cultures, knockdown of IL1RAcP reduces the density of presynaptic proteins, while overexpression increases it (189). Consistently, dendritic spine density is decreased on the basal dendrites of both cortical layer 2/3 neurons and hippocampal CA1 pyramidal neurons in *Il1rap*$^{-/-}$ mice (189). IL1RAcP mediates its effects at least partially through binding to PTPδ through PTPδ's Ig domains. The ability of IL1RAcP to induce the formation of presynaptic terminals when expressed on HEK293 cells in coculture is reduced in *Ptprd* knockout mouse neurons. Conversely, PTPδ-coated beads induce fewer postsynaptic Shank2 accumulations when cultured with *Il1rap* knockout neurons (189). Together, these data indicate that IL1RAcP and PTPδ bind heterophilically to induce formation of at least a subset of synapses.

Coxsackievirus and Adenovirus Receptor (CAR)

CAR is an Ig-like transmembrane protein containing two Ig-like domains. This protein was first identified for its role in mediating coxsackievirus and adenovirus entry into cells, notably in the brain (134, 152). CAR binds to itself homophilically through both of its Ig domains and to extracellular matrix ligands heterophilically through its second Ig domain (118). CAR colocalizes with both excitatory and inhibitory presynaptic markers as well as PSD-95 in cultured hippocampal neurons (195). In vivo, CAR is expressed in the presynaptic compartment. It is found in presynaptic fractions from synaptosomes and excluded from the postsynaptic density fraction in lysates from both mouse and human brain (195). CNS-specific knockout of CAR, generated by crossing a floxed *Car* mouse with a Nestin-Cre driver line, leads to reductions in the levels of several synaptic proteins in hippocampal homogenates, with more broad and pronounced reductions in the levels of these markers in female mice (195).

CONCLUSIONS

Because the IgSF constitutes one of the most common protein classes encoded by the genome, it is not surprising that many IgSF members are critical mediators of synapse wiring in the brain. Classic IgSF cell adhesion molecules, including NCAM, the L1 family, Nectins, and SynCAMs, play a wide range of roles in synapse formation, from permissive roles in stabilizing contacts to instructive roles in inducing the recruitment of synaptic proteins to nascent contacts. Proteins within each of these families bind homophilically or heterophilically to induce or enhance excitatory and inhibitory synapse formation. Although it was originally thought that IgSF members bind only to proteins within their own family, recent results are revealing multiple mechanisms, including within-family binding as well as crosstalk between these molecules and non-IgSF members or other IgSF synapse organizers. Such crosstalk can enhance the function of the synapse organizer—for example, NCAM promoting inhibitory synapse formation through EphA molecules, NrCAM limiting synapse density through binding to neuropilin1/2 complexes, or IGSF21 binding to NRX2α to induce inhibitory synapse formation. Alternatively, this crosstalk can inhibit the function of the synapse organizer, as when MDGA proteins bind to NLGNs to suppress NLGN function and limit inhibitory synapse formation.

This crosstalk between IgSF members and synapse organizers is even more complex for the Type IIα RPTPs. To regulate synapse wiring, LAR, PTPσ, and PTPδ each bind to several synaptogenic molecules, including NG1, TrkC, IL1RAcP, and to several SLITRKs and SALMs (62, 186). Evidence that these interactions may occur at specific types of synapses is emerging, but a full mechanistic understanding of the dynamic interactions that must occur between these multiple binding partners as synapses form, are stabilized, and are eliminated has yet to be achieved. As the complexity of the interactions of the IgSF members is revealed, the field will need to move toward understanding how the binding of each IgSF protein to multiple possible partners is regulated over time, at distinct synapse types, and by activity. Moreover, the hypothesis that alternative splicing of IgSF members could further enhance this complexity raises the question of whether these molecules have roles in guiding synaptic specificity in development in addition to regulating synapse formation, similar to the proposed roles for IgSF proteins in *Drosophila* (193) and in the retina (184).

One of the most striking features of some of the IgSF subfamilies is that they play roles in both the brain and the immune system. Although the function of these molecules in the brain is just beginning to be revealed, it is possible that their ability to regulate synapse formation in the CNS will mimic their function in regulating the formation of the immune synapse (23). The similarities between ICAMs in the immune and nervous system, such as being responsive both to neuronal activity and to cytokines and potentially functioning by the same mechanisms, make these molecules of interest for future study. In the immune system, MHCI molecules on antigen-presenting cells bind to inhibitory receptors on NK cells, including PirB, to inhibit immune synapse formation (88). Similarly, MHCI molecules may act to limit synapse formation and dendritic spine density through binding to inhibitory NK receptors, including PirB. Future work is needed to determine the full complement of the immune IgSF proteins found in the CNS, their function in regulating synapse wiring, and whether their mechanism in the CNS mimics their function in the immune system. Given the complex interactions between other nonimmune members of the IgSF, it will also be important to determine whether these immune IgSF molecules alter synapse formation through similar diverse and complex interactions with other IgSFs and non-IgSF synaptogenic molecules.

Finally, the role for IgSF members in regulating synapse formation may explain the ever-growing body of literature that implicates these proteins in neuropsychiatric and neurodevelopmental disorders. *Ncam* expression is altered in the brains of patients with bipolar disorder or schizophrenia (171, 172), and mutations in genes encoding members of the L1 family are linked to autism, schizophrenia, and intellectual disability (93, 138, 147, 191). Similarly, the human orthologs of *Syncam1* and *Syncam2* and those of *CADM1* and *CADM2* have been identified in genomic studies as being associated with autism spectrum disorder (ASD) (20, 192), while *CADM2* also has been genetically associated with attention deficit hyperactivity disorder (ADHD) (3). *IGSF9b* is genetically associated with both schizophrenia and major depressive disorder (132a, 148), *IGSF21* transcript levels are lower in the brains of schizophrenic individuals (53), and genome-wide association studies have found schizophrenia to be associated with several IgLONs: *opioid binding cell adhesion molecule like* (*Opcml*), the human ortholog of *Obcam* (110, 115); *Lsamp* (24, 75); and *Ntm* (175). Several studies have genetically linked MDGAs to neuropsychiatric

disorders, including autism, schizophrenia, and bipolar disorder (15, 71, 81). The CNTNs in general and *CNTN6* specifically have been linked to multiple neuropsychiatric and neurodevelopmental disorders (70). Variants of *CNTN4*, *CNTN5*, and *CNTN6* have been associated with ASD, as reviewed by Zuko et al. (194). Additionally, copy number variants in *CNTN6* are linked to intellectual disability (72) and anorexia (174).

There are several lines of evidence linking Type II RPTPs to neuropsychiatric disease, primarily though disease-related genetic associations of their binding partners. Variants and deletions in *PTPRD* in humans are linked to restless legs syndrome and ADHD, respectively (37, 141). Genetic studies have linked mutations in *SLITRK1* to Tourette's syndrome, and single-nucleotide polymorphisms associated with *SLITRK2* are linked to bipolar disorder and schizophrenia (1, 127, 150). *NTRK3*, the human ortholog of *Trkc*, is linked to panic disorder, obsessive compulsive disorder, and childhood-onset mood disorders (4, 9, 41), and *NG1* is associated with Rett syndrome, bipolar disorder, ASD, and schizophrenia (13, 35, 113). The fact that the RPTPs can be linked to many neurodevelopmental and neuropsychiatric diseases highlights their importance as a molecular hub for synapse wiring.

The immune IgSF members are also linked to a wide range of diseases. Changes in expression of MHCI genes have been linked to neuropsychiatric conditions such as ASD (102) and schizophrenia (149). In mouse models, changes in MHCI molecule expression in neurons mediate synapse density changes following maternal immune activation (MIA) (38), which mimics a key risk factor for neuropsychiatric disease (39) and firmly places these Ig-like molecules at the intersection of genetic and environmental factors that may contribute to these conditions. Several studies have also linked mutations in *IL1RAPL1* to X-linked intellectual disability and ASD (19, 50, 128, 130, 190). Finally, CAR expression decreases in the brain following lipopolysaccharide treatment and treatment with inflammatory cytokines, while hippocampal homogenates from Alzheimer's disease patients also display a reduction in CAR expression (195).

Whether modulated by genetic mutation or downstream from environmental factors, IgSF proteins potently regulate synapse wiring. These molecules may provide a critical bridge between genetically hardwired mediators of synapse formation and the environmental factors driving neuropsychiatric disease. While the growing complexity of IgSF function in regulating synapse formation is daunting, solving the IgSF code may reveal multiple new targets for rescuing IgSF-mediated deficits in synapse formation and, eventually, new treatments for psychiatric disorders caused by altered IgSF-induced synapse wiring.

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