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ECM receptors in neuronal structure, synaptic plasticity, and behavior

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Abstract

During central nervous system development, extracellular matrix (ECM) receptors and their ligands play key roles as guidance molecules, informing neurons where and when to send axonal and dendritic projections, establish connections, and form synapses between pre- and postsynaptic cells. Once stable synapses are formed, many ECM receptors transition in function to control the maintenance of stable connections between neurons and regulate synaptic plasticity. These receptors bind to and are activated by ECM ligands. In turn, ECM receptor activation modulates downstream signaling cascades that control cytoskeletal dynamics and synaptic activity to regulate neuronal structure and function and thereby impact animal behavior. The activities of cell adhesion receptors that mediate interactions between pre- and post-synaptic partners are also strongly influenced by ECM composition. This chapter highlights a number of ECM receptors, their roles in the control of synapse structure and function, and the impact of these receptors on synaptic plasticity and animal behavior.

Keywords

integrin receptor; cell adhesion receptor; heparan sulfate proteoglycan; lipoprotein receptor; tetraspanin; L-type voltage-dependent calcium channel

1 INTRODUCTION

During early postnatal development, the nervous system is highly plastic, continuously forming, eliminating, and remodeling dendrites and dendritic spines. This plasticity allows for proper synaptic connectivity to develop in an experience-dependent fashion. At early developmental ages, the extracellular matrix (ECM) provides a dynamic and permissive environment to allow for heightened neuronal plasticity (Dansie and Ethell, 2011;

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Kochlamazashvili et al., 2010). As the brain matures, the ECM is remodeled and replaced by an adult form that is localized to the intercellular space between neurons and glia. Additionally, the adult ECM is found in specialized structures, including perineuronal nets (PNNs) that surround interneurons. This adult ECM provides an external physical barrier to restrict dendrite and dendritic spine plasticity (Dityatev and Schachner, 2003). In addition to acting as a scaffold, ECM proteins can bind specifically to cell surface receptors, activating signaling cascades to regulate neuronal function (Dansie and Ethell, 2011). This chapter will review the functions of important ECM receptors in the brain, including integrins, syndecans, agrin, lipoprotein receptors (LPRs), and tetraspanins.

2 INTEGRINS

2.1 INTRODUCTION

Integrins are a class of adhesion receptors that serve as physical and functional links between the ECM and the cytoskeletal control pathways. They are expressed in nearly every cell type in the body and regulate diverse functions including cell survival, migration, attachment, focal adhesion assembly, and cell differentiation (Anton et al., 1999; Campbell and Humphries, 2011). There are 24 known integrin heterodimers of $\alpha\beta$ subunits, and a subset of these are expressed in the brain, including in the hippocampus, cortex, thalamus, and cerebellum (Chan et al., 2003; Dansie and Ethell, 2011; McGeachie et al., 2011). In neurons, some integrins are enriched at synaptic membranes and localized to the postsynaptic density of dendritic spines (Bernard-Trifilo et al., 2005; Bourgin et al., 2007; Chavis and Westbrook, 2001; Kerrisk et al., 2013; Mortillo et al., 2012; Pinkstaff et al., 1999; Warren et al., 2012). In particular, integrin subunits $\alpha3$, $\alpha5$, $\alpha8$, $\alpha(V)$, $\beta1$, and $\beta3$ function in a variety of roles in the brain, including neuronal migration, synapse and dendrite development, morphogenesis and stability, and synaptic plasticity (Gupton and Gertler, 2010; McCarty et al., 2005; Rehberg et al., 2014; Wu and Reddy, 2012). Perturbation of integrin function impacts learning and memory, likely by affecting underlying neuronal structure, function, and synaptic plasticity.

2.2 INTEGRIN STRUCTURE

Integrins are composed of noncovalently bonded heterodimers of α and β subunits. Integrin β subunits contain intracellular tails that bind to cytoplasmic signaling proteins and activate signaling cascades, while integrin α subunit extracellular head domains bind to and confer ligand specificity. Additionally, there are a number of integrin-binding proteins that can act as coreceptors, providing additional ligand specificity or altering integrin function, including N-cadherin (Mortillo et al., 2012) and tetraspanin (Bassani and Cingolani, 2012; Berditchevski et al., 2001). When inactive, integrins are thought to adopt a compact conformation that occludes both extracellular ligand-binding and intracellular effector binding sites (Shattil et al., 2010). Integrin receptors can be activated bidirectionally and activation causes major conformational changes in the heterodimer structure (Hynes, 2002; Kim et al., 2003). Inside-out signaling is initiated by talin or the kindlin family of proteins binding to intracellular β tails (Kim et al., 2003; Moser et al., 2008). Intracellular binding of these molecules to integrin β tails translates force across the plasma membrane into a conformational change in the integrin head domains, promoting binding to extracellular

ligands (Calderwood et al., 2013; Kong et al., 2013). Once bound to β integrins, talin interacts with F-actin, thus establishing a mechanical link between the ECM and the intracellular cytoskeleton (Calderwood et al., 2013). While talin and kindlin favor integrin activation, other proteins stabilize integrins in an inactive state by competing with talin or kindlin for binding to β integrin tails. For example, the actin-binding protein filamin binds β integrin C-termini at a site overlapping that for talin, thus inhibiting talin-dependent activation and establishing an alternative linkage between integrins and actin (Kiema et al., 2006).

From the extracellular side, ECM proteins and other soluble ligands can bind to integrin head domains and activate the receptor via an outside-in mechanism. This separates the intracellular tails, allowing them to bind to and initiate signaling cascades typically to regulate cytoskeletal control pathways (Hynes, 2002). The two alternative conformations of integrin structure have been elucidated using X-ray crystallography (Xiong et al., 2001), nuclear magnetic resonance (Lau et al., 2009), and electron microscopy (Choi et al., 2013) of active and inactive forms. Integrins have been finely tuned by evolution to respond quickly to changes in both intracellular and extracellular environments, making them ideal receptors to respond to activity-dependent signaling events and mediate synaptic plasticity.

2.3 INTEGRIN ECM LIGANDS

While numerous integrin ligands have been identified *in vitro* and in nonneuronal cells, identifying and characterizing ECM receptor interactions in neurons of the central nervous system (CNS) have proven more difficult. This difficulty stems in large part from the lack of extensive basement membranes in the CNS, making the purification of large amounts of ECM receptor complexes difficult. Recent progress has been made in developing methods to extract chondroitin sulfate proteoglycans (CSPGs) from the dense ECM-containing PNNs that surround parvalbumin-expressing fast-spiking interneurons (Deepa et al., 2006; Hartig et al., 1999). PNNs, which are composed mainly of CSPGs, tenascin-R, and hyaluronic acid (Yamaguchi, 2000), will be discussed in more detail in the subsequent chapters.

Each distinct integrin receptor has different ligand-binding specificities, with some receptors binding to only one ligand and others binding to several. Receptors with $\alpha 5$, $\alpha 8$, and $\alpha(V)$ subunits are considered “RGD” receptors because they recognize an Arg-Gly-Asp binding motif found in many extracellular ligands. This includes fibronectin, vitronectin, tenascins, and thrombospondins. Integrins with $\alpha 1$, $\alpha 2$, $\alpha 10$, and $\alpha 11$ are collagen receptors that recognize the peptide sequence “GFOGER.” Finally, integrins with $\alpha 3$, $\alpha 6$, and $\alpha 7$ subunits bind to the laminin family proteins (Belkin and Stepp, 2000; Campbell and Humphries, 2011; Humphries et al., 2006; Hynes, 2002).

Within “RGD” receptors, integrin $\alpha V\beta 3$ has been shown to interact with several different ECM ligands and counterreceptors on adjacent cells. For example, in dorsal root ganglion neurons, integrin $\alpha V\beta 3$ binds to the L1 cell adhesion molecule of the immunoglobulin superfamily. This RGD-dependent interaction involves the sixth immunoglobulin-like domain of L1 (Blaess et al., 1998), and it is important for promoting neurite outgrowth in culture (Yip et al., 1998). L1 is expressed in many neurons of the CNS at the onset of differentiation, where it interacts with multiple extracellular partners to regulate several

aspects of neuronal migration, axon growth, and synaptic transmission (Dityatev et al., 2008). Thus, it is tempting to speculate that a specific interaction between integrin $\alpha V\beta 3$ and L1 might contribute to neurite outgrowth also *in vivo*.

More recently, the astrocyte-secreted protein SPARC (secreted protein, acidic and rich in cysteine) has been shown to inhibit integrin $\alpha V\beta 3$ at excitatory hippocampal synapses to control the levels of AMPA-type glutamate receptor (AMPA) expression (Jones et al., 2011). Astrocytes release SPARC in response to changes in neuronal network activity and, in turn, SPARC acts on neurons to downregulate surface expression of $\beta 3$ integrin subunit and of GluA1- and GluA2-containing AMPARs (Jones et al., 2011). Notably, in retinal ganglion cells, SPARC antagonizes the synaptogenic function of another member of the SPARC family, hevin. Similar to SPARC, hevin is released by astrocytes (Kucukdereli et al., 2011); however, it affects synapses by interacting with the cell adhesion molecules neuroligins and neuroligins (Clarke and Barres, 2013). Thus, integrin $\alpha V\beta 3$ appears to cooperate with other synaptic cell adhesion molecules to regulate synaptic function in response to astrocyte-released factors.

Many of the integrins present at developing and mature synapses are heterodimers containing the $\beta 1$ subunit (Mortillo et al., 2012; Ning et al., 2013). In olfactory bulb axons, $\beta 1$ subunit-containing integrins have been shown to interact with Semaphorin 7A (Sema7A), which is a secreted and glycosylphosphatidylinositol-anchored semaphorin expressed during neural development (Pasterkamp et al., 2003). Whereas many semaphorins are repellent to growing axons, Sema7A boosts axon growth and is required for proper lateral olfactory tract formation during embryonic development. These effects on axon outgrowth require Sema7A to interact with $\beta 1$ integrins in an RGD-dependent manner and to activate downstream MAP kinase signaling pathways (Pasterkamp et al., 2003). It appears therefore that integrins expressed on the growth cone can regulate axon guidance in part by interacting directly with the cues that stimulate axonal outgrowth (Myers et al., 2011).

Recently, $\beta 1$ integrins, most likely $\alpha 5\beta 1$, have been shown to interact directly also with telencephalin (TLCN; *aka* intercellular adhesion molecule-5, ICAM-5), which is a member of the immunoglobulin superfamily of cell adhesion molecules selectively expressed in the mammalian forebrain (Conant et al., 2011; Ning et al., 2013). TLCN is enriched in the soma, dendritic shafts, dendritic filopodia, and immature dendritic spines of excitatory neurons. Symmetrically, $\beta 1$ integrins is expressed predominantly at presynaptic sites in nascent synapses (Hellwig et al., 2011; Matsuno et al., 2006; Ning et al., 2013). At early stages of synapse formation, TLCN and $\beta 1$ integrins likely start forming loose and dynamic contacts between filopodia tips and axonal terminals (Conant et al., 2011; Ning et al., 2013). Notably, either deletion of cell adhesion molecules or inhibition of their interactions with function-blocking antibodies promotes structural and functional maturation of dendritic spines (Matsuno et al., 2006; Ning et al., 2013). Thus, a key function of the TLCN- $\beta 1$ integrin interaction is likely to maintain filopodia and immature spines in a highly dynamic state and to oppose their development into larger and more stable mushroom spines.

Another $\beta 1$ integrin, $\alpha 3\beta 1$, binds with high affinity to laminins *in vitro* (Nishiuchi et al., 2006). Laminins are complexed with integrin $\alpha 3$ at the neuromuscular junction (NMJ) and

in hippocampal synapses (Carlson et al., 2010; Yang et al., 2011). Additionally, integrin $\alpha 3\beta 1$ can bind to the ECM protein reelin and regulate neuron–glia interactions necessary for proper cortical lamination. The effects of reelin on cortical migration require its interaction with integrin $\alpha 3$, and loss of integrin $\alpha 3\beta 1$ reduces phosphorylation of DAB1, a well-characterized effector downstream of reelin signaling (Dulabon et al., 2000).

CSPGs, the major components of PNNs, have also recently been implicated in integrin $\beta 1$ signaling. Digestion of CSPGs with chondroitinase ABC (ChABC) in live hippocampal slices increases the motility of dendritic spines and causes the appearance of abnormal spine head protrusions. Interestingly, these changes to dendritic spines correlate with activation of integrin $\beta 1$ receptors and focal adhesion kinase (FAK) at synaptic sites (Orlando et al., 2012). These data suggest that CSPGs may be ligands for integrin $\beta 1$ -containing receptors or may regulate access of other ligands to the receptor to control dendritic spine dynamics. Future studies will determine which of these mechanisms mediate the effects of CSPGs on integrin activation and spine morphology.

2.4 INTEGRINS IN SYNAPTIC PLASTICITY

2.4.1 Early Research—The role of integrin receptors in synaptic function and plasticity first became evident in the early 1990s. Studies from several laboratories used integrin-blocking peptides containing the RGD-motif or function-blocking anti-integrin antibodies to demonstrate that integrin inhibition caused significant impairment in long-term potentiation (LTP) in hippocampal slices (Peng et al., 1991; Staubli et al., 1990). A seminal study by Chavis and Westbrook in 2001 provided important clues regarding the molecular mechanisms by which integrins may influence LTP. The authors first found that a high probability of glutamate release from immature synaptic boutons correlated with high expression of the NMDA receptor GluN2B subunit at postsynaptic sites. As synapses matured, glutamate release probability decreased, while NMDA receptor subunit composition transitioned to those containing predominantly GluN2A subunits, which have faster kinetics (Cull-Candy et al., 2001). Importantly, chronic inhibition of the integrin $\beta 3$ receptor blocked the coordinated maturation of hippocampal synapses, preventing both the decrease in release probability and the switch in NMDA receptor subunit composition, resulting in hypersensitivity to glutamate, a phenotype representative of more immature hippocampal synapses (Chavis and Westbrook, 2001). These observations implicated integrin receptors in the control of glutamate release, NMDA receptor function, and synapse maturation.

2.4.2 Integrin α Subunits in Synaptic Plasticity—Several studies have demonstrated important roles for integrins in both structural synaptic plasticity and functional synaptic plasticity. Application of the disintegrins echistatin, which inhibits $\beta 1$ - and $\beta 3$ -containing receptors, and triflavin, which targets preferentially integrin $\alpha 5\beta 1$ receptors, to hippocampal slices rapidly suppresses LTP (Chun et al., 2001). Additionally, blocking integrin receptors with RGD peptides yields a twofold increase in the amplitude and duration of NMDA receptor synaptic currents (Lin et al., 2003, but see Cingolani et al., 2008), and genetic disruption of integrin $\beta 1$ in mature excitatory neurons impairs selectively LTP (Chan et al., 2006; Huang et al., 2006). When integrin $\beta 1$ is instead deleted in excitatory neurons from

early stages of embryonic development, deficits in both LTP and presynaptic release probability are observed in the hippocampus (Huang et al., 2006). Thus, β 1-class integrins appear to be important for presynaptic function at early stages of development and for LTP in mature synapses (Huang et al., 2006; Ning et al., 2013).

Activating β 1-containing integrins in synaptosome preparations or acute hippocampal slices results in rapid activation of Src family kinases (SFKs) and phosphorylation of NMDA receptor subunits GluN2A and GluN2B (Bernard-Trifilo et al., 2005). Furthermore, application of the SFK inhibitor PP2 can prevent the NMDA receptor current increase in RGD-inhibited slices (Lin et al., 2003). Taken together, these results suggest that integrin β 1 receptors may signal via SFKs to control LTP and synaptic function.

Integrins also regulate dynamic changes in dendrite and dendritic spine morphology. In cultured neurons, activation of integrin β 1 induces dendritic spine elongation, an effect that can be blocked using integrin function-blocking antibodies or NMDA receptor antagonists (Shi and Ethell, 2006). Inhibiting integrin β 1 in retinal ganglion neurons causes rapid dendrite retraction and overall reduction of dendrite arborization (Marrs et al., 2006). Integrin β 1 knockout mice exhibit an age-dependent loss of hippocampal dendrite arborization and synapse density (Warren et al., 2012). Together, these results suggest that synaptic integrins regulate kinase signaling cascades to modulate NMDA receptor function, dendritic spine morphology, dendrite arborization, and synaptic plasticity.

A recent study reported that integrin β 1 receptors have a more specific temporal control on synaptic plasticity than previously appreciated. Babayan et al. (2012) used a specific antibody that recognizes the active integrin β 1 conformation to quantitate integrin activation at various time points following theta burst stimulation (TBS) in CA1 hippocampal slices. Interestingly, integrin β 1 became activated immediately, in less than 2 min, following TBS, but activation levels returned to baseline after 7 min. Following a second TBS, integrin β 1 was resistant to further activation for at least 30 min but could once again be activated by 60 min poststimulation. Interestingly, the pattern of integrin activation in response to TBS was unaffected by protein synthesis inhibitors, but could be disrupted by inhibitors of endosomal trafficking. These observations suggest that TBS promotes increased integrin trafficking to the plasma membrane and support a hypothesis that integrin β 1 participates in both the rapid response to TBS and the slower consolidation of LTP over time (Babayan et al., 2012).

Integrin β 3 has been shown to be a central regulator of homeostatic synaptic plasticity (HSP) (Thalhammer and Cingolani, 2014). Blockade of neuronal network activity to induce HSP increases surface levels of integrin β 3 subunits, and HSP itself, but not LTP or LTD, is blocked in β 3 integrin knockout mice (Cingolani and Goda, 2008; Cingolani et al., 2008; McGeachie et al., 2012). At the synapse, β 3 integrin subunits interact directly with the GluA2 subunit of AMPA receptors to regulate AMPA receptor trafficking and synaptic strength (Pozo et al., 2012). Moreover, the inhibition of integrin β 3 with echistatin results in AMPA receptor endocytosis via a pathway requiring the Rap1 small GTPase, which yields overall decreased synaptic transmission (Cingolani et al., 2008). Interestingly, surface levels of integrin β 3 subunits in neurons are also sensitive to astrocyte-secreted factors, such as tumor necrosis factor- α (Cingolani et al., 2008) and SPARC (Jones et al., 2011), suggesting

that integrin $\beta 3$ might regulate HSP in response to astrocytic signals. These multifaceted studies indicate that integrin $\beta 1$ - and $\beta 3$ -containing receptors have both distinct and overlapping roles in regulating spine morphology, synaptic efficacy, and multiple forms of synaptic plasticity.

2.4.3 Integrin α Subunits in Synaptic Plasticity—Work over the last 15 years has begun to reveal roles for specific integrin α subunits in synaptic plasticity and LTP (Dityatev et al., 2010). For example, function-blocking antibodies to the integrin $\alpha 5$ subunit cause a 30% reduction in LTP after 45 min, but do not affect initial basal transmission. Furthermore, inhibiting integrin $\beta 1$ with antagonist peptides produces the same effect as inhibiting integrin $\alpha 5$, suggesting that integrin $\alpha 5\beta 1$ regulates LTP in the hippocampus (Chun et al., 2001). Conversely, blocking $\alpha(V)$ or $\alpha 2$ subunits does not alter either baseline transmission or synaptic plasticity (Chun et al., 2001).

Local infusion of integrin $\alpha 3$ function-blocking antibodies into CA1 of rat hippocampal slices reduces LTP 40 min after induction (Kramar et al., 2002). Genetic disruption of integrin $\alpha 3$ from mice compromises hippocampal LTP, synapse and dendrite stability, and animal behavior (Chan et al., 2003, 2007; Kerrisk et al., 2013), but does not impact paired-pulse facilitation (PPF), a parameter sensitive to changes in presynaptic neurotransmitter release probability (Chan et al., 2003). Reducing the gene dosage of integrins $\alpha 3$ and $\alpha 5$ together is sufficient to cause defects in PPF, while simultaneous reduction of integrin $\alpha 3$, $\alpha 5$, and $\alpha 8$ gene dosage in a triple heterozygous animal yields defects in spatial memory and hippocampal LTP (Chan et al., 2003). Furthermore, genetic disruption of only integrin $\alpha 8$ from excitatory neurons causes impairments in LTP, but not working memory, PPF, LTD, or basal synaptic transmission (Chan et al., 2010). Collectively, these results suggest both independent and redundant roles for integrin α subunits in the brain. For example, multiple α subunits contribute to LTP induction, but loss of specific individual subunits differentially impacts animal behavior and PPF.

2.5 INTEGRINS IN LEARNING AND MEMORY

Due to their important roles in dendrite structure, synapse stability, and synaptic plasticity, genetic disruption of specific integrin subunits causes impairments in animal behavior, particularly in tasks related to learning and memory. Selective knockout of integrin $\alpha 3$ in forebrain excitatory neurons yields defects in hippocampal LTP maintenance. These defects correlate with impairments in hippocampus-dependent working memory tasks (Chan et al., 2007) and novel object recognition behavior (Kerrisk et al., 2013). Mice triply heterozygous for integrins $\alpha 3$, $\alpha 5$, and $\alpha 8$ have additional impairments in a water maze-based spatial memory task (Chan et al., 2003, 2010; Kramar et al., 2002). Furthermore, loss of integrin $\beta 1$ causes defects in novel object recognition behavior as well as heightened sensitivity to cocaine (Warren et al., 2012; Wiggins et al., 2009). In contrast, mice with loss of integrin $\beta 3$ have normal conditioned fear behavior (McGeachie et al., 2012). Thus far, most integrin mutants examined have impairments in a battery of behavioral tasks, consistent with their fundamental roles in neuronal and synapse morphogenesis, stability, and function.

2.6 SIGNALING DOWNSTREAM OF INTEGRINS

Integrin β subunit cytoplasmic tails can bind to and activate kinase signaling cascades. For example, integrin $\beta 1$, but not integrin $\beta 3$, binds directly to the kinase domain of the Abl2/Arg nonreceptor tyrosine kinase, and these two genes interact to control long-term dendrite and synapse stability (Warren et al., 2012). Integrin binding activates Arg kinase activity to modulate multiple signaling pathways (Lin et al., 2013; Warren et al., 2012). For example, Arg phosphorylates p190RhoGAP (p190), a Rho GTPase inhibitor, which promotes p190 binding to p120RasGAP (p120) and attenuates RhoA GTPase activity (Bradley et al., 2006). Elevated RhoA activity in neurons destabilizes dendrites via downstream effectors including ROCKII (Sfakianos et al., 2007; Threadgill et al., 1997). Thus, Arg signaling through the p190–p120 complex in neurons acts as a clamp on RhoA activation to preserve long-term dendrite stability.

Additionally, dendritic spine destabilization resulting from Arg knockdown in cultured neurons can be rescued by blocking NMDA receptors (Lin et al., 2013). Furthermore, the actin regulatory protein cortactin was identified as a substrate of Arg in an unbiased proteomic screen (Boyle and Koleske, 2007), and subsequently, these two proteins were shown to interact through a series of binding and phosphorylation events to regulate the formation and stability of actin-rich cellular structures (Lapetina et al., 2009; MacGrath and Koleske, 2012; Weaver et al., 2001). In neurons, cortactin is enriched in dendritic spines (Hering and Sheng, 2003), but the knockdown of Arg reduces the amount of cortactin and F-actin in spine heads by 40% (Lin et al., 2013). Fusion of the Arg C-terminal domain to cortactin lacking its SH3 domain mimics an “activated” Arg-bound cortactin. This cortactin–Arg fusion protein localizes to dendritic spine heads and prevents both the loss of F-actin and the reduction of dendritic spine density in Arg knockdown cultures (Lin et al., 2013). These results support a model in which Arg regulates dendrites and dendritic spines downstream of integrin receptors via signaling to cytoskeletal regulatory pathways, including RhoA GTPase and cortactin. Finally, recent work has identified integrin $\alpha 3$ as the major partner for $\beta 1$ that regulates this Arg-mediated dendrite and dendritic spine maintenance (Kerrisk et al., 2013).

Modulation of integrin $\beta 1$ activity also regulates other biochemical cascades in neurons. For example, inhibition of integrin $\beta 1$ in cultured neurons using ligand-blocking peptides destabilizes dendritic spines via inhibition of intracellular signaling cascades to CAMKII, SFKs, FAK, and the closely related proline-rich tyrosine kinase 2 (Pyk2) (Bernard-Trifilo et al., 2005; Shi and Ethell, 2006). Conversely, activation of these kinases downstream of integrin signaling induces rapid tyrosine phosphorylation of GluN2A and GluN2B intracellular tails (Bernard-Trifilo et al., 2005; Lin et al., 2003). Another consequence of blocking integrin $\beta 1$ function using an RGD peptide is the dephosphorylation of Crk-associated substrate (Cas), leading to decreased dendritic spine density and length (Bourgin et al., 2007). Clearly, integrin $\beta 1$ is a critical regulator of multiple signaling cascades that control the actin cytoskeleton to regulate synaptic function and morphology.

Additional specific signaling mechanisms have also been determined for one of integrin $\beta 1$'s heterodimeric partners, integrin $\alpha 5$. Integrin $\alpha 5$ activates SFK signaling to Rac1 GTPase and its adaptor protein GIT1 to regulate spine development and morphogenesis in developing

neurons. Knockdown of integrin $\alpha 5$ results in a dramatic loss of dendritic spines (Webb et al., 2007). Interestingly, treatment of hippocampal slices with AMPA increased levels of functional integrin $\alpha 5 \beta 1$ receptors via protein kinase C signaling (Lin et al., 2005). These results suggest that glutamate receptors and integrin receptors regulate each other reciprocally and that this positive feedback loop reinforces synaptic potentiation.

2.7 INTEGRINS AND MATRIX METALLOPROTEASES

Matrix metalloproteases (MMPs) are a large family of extracellular proteases that cleave multiple ECM proteins and have important roles in synaptic plasticity, which will be discussed further in Chapter 8. In particular, MMP9 has prominent roles in both integrin signaling and regulation of synaptic plasticity. Direct application of purified MMP9 to hippocampal slices induces a potentiation of excitatory postsynaptic currents (Bozdagi et al., 2007; Nagy et al., 2006; Szklarczyk et al., 2002) and leads to dendritic spine head enlargement (Wang et al., 2008), both of which are blocked by application of integrin inhibitors. MMPs cleave a large number of ECM proteins and integrin ligands, including laminin, N-cadherin, dystroglycans, ICAMs, and proteoglycans (Ethell and Ethell, 2007). Therefore, MMPs likely influence integrin signaling and synaptic plasticity by targeting one or more of these substrates.

2.8 CONCLUSION

In summary, integrin-mediated signaling events in neurons regulate glutamate receptor activity and downstream control of the neuronal cytoskeleton. These actions are critical for the proper development, function, and plasticity of dendrites and dendritic spines, and complex animal behaviors. It is important to note that many of the current studies use exogenous, nonnatural activators or inhibitors of integrins. Thus, a future priority must be to identify and characterize endogenous extracellular ligands that regulate the activities of integrins in the brain.

3 ADDITIONAL ECM RECEPTORS

3.1 MEMBRANE-BOUND HEPARAN SULFATE PROTEOGLYCANS

Heparan sulfate proteoglycans are composed of a protein core to which multiple linear polysaccharide heparan sulfate (HS) molecules are covalently linked (Ethell and Yamaguchi, 1999; Winzen et al., 2003). In the brain, the heparan sulfate proteoglycan (HSPG) family includes both syndecans and agrin receptors, which regulate diverse processes, discussed in detail here.

3.1.1 Syndecans—The syndecan receptor family is a class of transmembrane HSPGs with four family members, syndecans-1–4. Syndecan-2–3 are prominently expressed in the brain (Carey et al., 1997), where they play important roles in neuronal development and dendritic spine formation and structure (Ethell et al., 2001). Syndecans often act as coreceptors with integrins for many ECM proteins including heparin-binding growth-associated molecule (HB-GAM) (Kaksonen et al., 2002; Raulo et al., 1994), laminin, fibronectin (Woods and Couchman, 2001), tenascin, collagen, and thrombospondins (Carey et al., 1997; Dansie and Ethell, 2011). Like integrins, the syndecan family proteins have

short cytoplasmic tails that interact with intracellular regulators of cytoskeletal structure (Dansie and Ethell, 2011).

Syndecan-3 (*aka* N-syndecan) is a receptor for HB-GAM, which promotes neurite outgrowth, guidance, and synaptic plasticity during development (Pavlov et al., 2004). Inhibiting syndecan-3 with function-blocking antibodies inhibits neurite growth and synaptogenesis in embryonic neurons cultured on HB-GAM-coated plates (Raulo et al., 1994). Addition of syndecan-3 to hippocampal slices prevents LTP induction (Lauri et al., 1999) and genetic loss of the protein in mice results in heightened LTP and impaired performance in hippocampal-based memory tasks (Kaksonen et al., 2002). Activation of syndecan-3 by HB-GAM induces Src and Fyn kinase activation and subsequent cortactin phosphorylation. This signaling trio provides critical regulatory control of the actin cytoskeleton and LTP, which ultimately impacts animal behavior (Kinnunen et al., 1998a,b).

Syndecan-2 is enriched at synapses, where it regulates dendritic spine development, excitatory synaptic function, and synaptic plasticity (Ethell and Yamaguchi, 1999; Hsueh et al., 1998). Overexpression of syndecan-2 induces the precocious transition of dendritic filopodia into mature mushroom spines, and this requires its interaction with EphB2 receptors (Ethell and Yamaguchi, 1999; Ethell et al., 2001). In contrast, syndecan-2 knockdown reduces the number of dendritic spines in cultured hippocampal neurons (Lin et al., 2007). Despite the effects of syndecan-2 on neuronal structure and stability, relatively little is known about the specific downstream signaling cascades regulated by this receptor. However, many PDZ domain-containing proteins, which anchor AMPA and NMDA receptors at the synapse, have been shown to interact with syndecan-2–3 (Gao et al., 2000; Grootjans et al., 2000; Hsueh et al., 1998). This observation suggests that the syndecans may help organize neurotransmitter receptor surface localization, trafficking, or stability via scaffolding to the postsynaptic density.

3.1.2 Agrin—The HSPG agrin regulates clustering of acetylcholine receptors at the NMJ (Singhal and Martin, 2011). The agrin extracellular domain has nine follistatin-like domains, a serine-/threonine-rich region, and EGF- and laminin-like repeats. Importantly, agrin contains both chondroitin sulfate and heparin glycosaminoglycan sugar side chains (Winzen et al., 2003). Agrin also binds to a number of ECM proteins, including laminin (Mascarenhas et al., 2003), as well as other cell surface receptors, including α dystroglycan (Deyst et al., 1995).

Several agrin splice isoforms are produced in the nervous system, including both soluble and membrane-bound forms (Bezakova and Ruegg, 2003). In addition to its prominent role at the NMJ, transmembrane agrin also localizes to the dendrites and axons of pyramidal neurons in the hippocampus and cortex. Agrin knockdown in hippocampal cultures reduces dendritic spine density (McCroskery et al., 2009), while brain-specific agrin conditional knockout mice exhibit a 30% reduction in cortical excitatory synapses relative to controls. Consistent with the reduction in synapse number, these agrin conditional knockout mice have significant decreases in miniature excitatory postsynaptic current (mEPSC) frequency (Ksiazek et al., 2007). Furthermore, the clustering of agrin with specific antibodies in

cultured neurons can induce the formation of filopodia along developing neurites, supporting a role for agrin in early synapse formation (Annie et al., 2006).

The observation that agrin knockout mice have reduced mEPSC frequency (Ksiazek et al., 2007) raises the question of whether synaptic activity may, in turn, affect agrin function. The extracellular protease neurotrypsin, which is secreted in response to activity (Frischknecht et al., 2008), has been implicated in the cleavage of the C-terminal extracellular domain of agrin (Reif et al., 2007). Specifically, levels of the agrin C-terminal fragment are reduced in neurotrypsin knockout mice, and exogenous application of this fragment to knockout slices is sufficient to rescue LTP-dependent dendritic spine density increases in the hippocampus (Matsumoto-Miyai et al., 2009). Furthermore, the agrin N-terminus contains the HS chains and is necessary for dendritic filopodia formation in cultured neurons, a process that requires activation of the Rac1 and Cdc42 GTPases (Lin et al., 2010; McCroskery et al., 2009). In summary, the multidomain protein agrin is activated downstream of extracellular signaling, which promotes GTPase activity and regulates dendritic spine morphology and synaptic function.

3.2 LIPOPROTEIN RECEPTORS

LPRs are a class of single-pass transmembrane proteins that function in endocytosis, cholesterol transport, signal transduction, and synaptic plasticity. There are seven known LPR family members in mammals: low-density lipoprotein receptor (LDLR), very low-density lipoprotein receptor (VLDLR), apolipoprotein E receptor 2 (ApoER2), multiple epidermal growth factor repeat-containing protein 7 (MEGF7), low-density lipoprotein-related protein (LRP), LDL-related protein-1B (LRP-1B), and megalin (Rogers and Weeber, 2008). The LPR extracellular domain consists of a cysteine-rich ligand-binding domain, an EGF precursor homology domain, and an oligosaccharide-rich domain, followed by a transmembrane domain. The intracellular tail contains a conserved NPxY motif that signals through tyrosine kinases to activate downstream signaling modules (Beffert et al., 2002) including MAP kinases and ligand-gated ion channels (Rogers and Weeber, 2008). Finally, LPRs have a domain required for receptor internalization, which is employed by these receptors to endocytose their ligands (Zhuo et al., 2000).

The best characterized LPR ligand is reelin, a 400-kDa ECM protein that plays an essential regulatory role in the laminar organization of neurons in the cortex and hippocampus. During early development, cortical neurons migrate in an inside-out manner, with early-born neurons positioned in the inner layers of the cortex and later-born neurons migrating to the outer layers. In contrast, neurons in reelin-deficient mice have an inverted cortical laminar pattern and defects in neuronal polarization, contributing to synaptic and behavioral defects (Herz and Chen, 2006; Matsuki et al., 2010; Ramos-Moreno et al., 2006). Reelin binds to multiple cell surface receptors including VLDLR, ApoER2 (Herz and Chen, 2006), and integrin $\alpha3\beta1$ (Dulabon et al., 2000), which activate SFKs to phosphorylate the reelin cytoplasmic adaptor protein Disabled-1 (DAB1) and other substrates (Franco et al., 2011).

In addition to targeting DAB1, reelin activates SFKs, which phosphorylate the GluN2B subunit of NMDA receptors, implicating reelin in NMDA-mediated LTP. Exogenous application of reelin to wild-type hippocampal slices induces increased field excitatory

postsynaptic potentials and heightens the level of LTP following high-frequency stimulation (Niu et al., 2004; Weeber et al., 2002). Cultured reelin knockout neurons have shorter and less branched dendrites. These defects are rescued by adding exogenous reelin to cultures but are blocked by inhibiting reelin's interactions with LPR receptors (Niu et al., 2004). Together, these experiments implicate reelin activation of LPR signaling in controlling LTP and dendrite structure.

3.2.1 ApoER2—ApoER2 is enriched in the postsynaptic densities of hippocampal excitatory synapses, where it forms a complex with NMDA receptors and PSD95 (Herz and Chen, 2006). Application of reelin to hippocampal slices activates the ApoER2 receptor and leads to tyrosine phosphorylation of NMDA receptor subunits, mostly likely via SFKs. Reelin application to slices also induces alternative splicing of the intracellular domain ApoER2 and enhances LTP (Bock and Herz, 2003). Interestingly, genetic deletion of this alternatively spliced ApoER2 prevents phosphorylation of the NMDA receptor and results in mice that have poor performance in learning and memory tasks (Beffert et al., 2005), suggesting that this specific ApoER2 splice isoform is responsible for enhancing LTP and regulating animal behavior. Additionally, reelin application heightens the insertion of AMPA receptors into the postsynaptic membrane, leading to the maturation of silent synapses, and heightens glutamatergic transmission, a process that can be blocked by phosphoinositide 3-kinase (PI3K) inhibitors (Qiu et al., 2006). ApoER2 overexpression in primary neuronal cultures causes an increase in dendritic spine density, while ApoER2 knockout mice have a decrease in spine density (Dumanis et al., 2011; Trotter et al., 2011). Taken together, these results suggest that ApoER2 functions to regulate dendritic spine structural stability and that loss of this control leads to aberrant neuronal function and animal behavior.

3.2.2 VLDLR—Loss of both VLDLR and ApoER2 is required to yield the inverted cortical lamination phenotype found in reelin knockout mice (Trommsdorff et al., 1999), suggesting that these receptors play overlapping roles in regulating neuronal migration in response to reelin. However, to test if VLDLR and ApoER2 may have subtler, more specific roles in the cortex, Hack et al. (2007) used a variety of labeling techniques to precisely track receptor localization within the cortex at various points during development in single and double receptor mutants. They found that VLDLR acts as a stop signal for early migrating neurons in the cortex, while ApoER2 is essential for the migration of late-generated neurons (Hack et al., 2007). Furthermore, recent research has found that VLDLR and ApoER2 can form complexes with ephrin-B1–3 receptors, which are essential for receptor clustering, recruitment of DAB1, and proper neuronal migration (Senturk et al., 2011), suggesting that multiple receptors coordinately control intracellular signaling and neuronal migration downstream of reelin (Figs. 1 and 2).

3.2.3 Low-Density LRP—LRP is one of the largest receptors in the LPR family at 600 kDa, and it recognizes over 40 distinct ligands, including TGF- β , the protease tissue plasminogen activator (tPA), and apolipoprotein E (ApoE). In the brain, LRP is expressed in pyramidal neurons and plays an important role in synaptic transmission (Harris-White and Frautschy, 2005). LRP is believed to act as a scavenger in the brain, binding to and

removing cholesterol and lipid products and in some cases even scavenging extracellular proteases (Harris-White and Frautschy, 2005). LRP knockout mice have heightened locomotor activity (Elder et al., 2008) and impaired learning and memory behavior (Mulder et al., 2004), suggesting an underlying defect with neuronal structure, function, or plasticity. Furthermore, overexpression of LRP heightens the activity of tPA, while inhibition of LRP via infusion of the receptor antagonist receptor-associated protein (RAP) blocks the ability of tPA to induce acute LTP in hippocampal slices (Zhuo et al., 2000). LRP binds directly to the NMDA receptor-associated scaffolding protein PSD95 (Gotthardt et al., 2000), suggesting it may directly impact NMDA receptor function to modulate synaptic signaling.

3.3 TETRASPANINS

Tetraspanins are a family of conserved membrane proteins that regulate cell motility, morphology, signaling, plasma membrane dynamics, and protein trafficking (Boucheix and Rubinstein, 2001; Hemler, 2008). Tetraspanins get their name from their four transmembrane domains, which are interspersed with short intra- and extracellular loops that form binding sites for other proteins (Berditchevski et al., 2001). Interestingly, tetraspanins can interact with integrin receptors, opening the possibility of coordination between multiple different ECM receptors (Bassani and Cingolani, 2012). Specifically, tetraspanin 7 (TSPAN7) interacts with the extracellular head domain on integrin $\alpha 3$ and regulates intracellular signaling pathways to phosphoinositide 4-kinase (Yauch and Hemler, 2000; Yauch et al., 2000). TSPAN7 is highly enriched in cortical and hippocampal neurons, and TSPAN7 mRNA is dramatically upregulated following treatment with kainic acid (Boda et al., 2002), implicating TSPAN7 in the neuronal responses to activity. TSPAN7 is also essential for dendritic spine stability and synaptic transmission. For example, overexpression of TSPAN7 in cultured hippocampal neurons is sufficient to promote dendritic spine formation and increase dendritic spine head size (Bassani et al., 2012). Additionally, TSPAN7 interacts with PICK1, which controls the trafficking and recycling of AMPA receptors (Bassani et al., 2012), suggesting a mechanism by which TSPAN7 might influence synaptic activity.

3.4 L-TYPE VOLTAGE-DEPENDENT CALCIUM CHANNELS

L-type voltage-dependent calcium channels (LVDCCs) promote the induction of LTP by contributing to the increase in intracellular calcium levels following high-frequency stimulation (Huber et al., 1995). Mice lacking the ECM protein tenascin C (TNC) have impairments in LVDCC-dependent hippocampal synaptic plasticity (Evers et al., 2002), suggesting that TNC may signal through LVDCCs. Furthermore, direct injection of TNC into the hippocampus also impairs LTP (Strekalova et al., 2002), suggesting that TNC may interact with LVDCCs to control receptor properties. Enzymatic removal of hyaluronic acid from the hippocampus impairs LTP, alters ERK1 and CREB signaling, and reduces hippocampus-dependent contextual fear conditioning. These phenotypes can be rescued by pharmacological potentiation of LVDCCs (Kochlamazashvili et al., 2010), suggesting that hyaluronic acid might act through these channels to mediate synaptic plasticity and animal behavior. In support of this hypothesis, recordings from Chinese hamster ovary cells found that hyaluronic acid potentiates the activity of $Ca_v1.2$ channels (Kochlamazashvili et al., 2010), which are the predominant type of LVDCCs in the hippocampus (Moosmang et al.,

2005). There is currently no direct evidence that LVDCC directly interacts with TNC or hyaluronic acid; however, all three components are present in the synaptic cleft, and based on their roles in synaptic plasticity, it has been suggested they may make up a larger complex needed to regulate calcium signaling in the hippocampus (Dityatev et al., 2010).

4 LINK TO HUMAN BRAIN DISEASE

Studies of knockout mice or knockdown of ECM receptors in cultured neurons reveal that they play critical roles in the development of synaptic connectivity, long-term synapse and dendrite maintenance, synaptic plasticity, and overall learning and memory. These observations strongly suggest that dysfunction of ECM receptors plays central roles in brain diseases that are associated with defects in dendrite, dendritic spine, and synapse development, function, stability, and plasticity. These defects are hallmarks of schizophrenia (Glantz and Lewis, 2000; Kalus et al., 2000; Law et al., 2004), depression (Cotter et al., 2001; Duman and Aghajanian, 2012), intellectual disability (Kaufmann and Moser, 2000; Kaufmann et al., 2000; Ramakers, 2000), autism spectrum disorders (ASDs) (Won et al., 2013), and Alzheimer's disease (AD) (Thies and Bleiler, 2012; Uylings and de Brabander, 2002). Indeed, ECM ligands have been implicated in diverse disorders from AD to epilepsy (Bonneh-Barkay and Wiley, 2009). Surprisingly, there are few examples of well-characterized genetic links between ECM receptors and human brain diseases. In some cases, genetic disruption of ECM receptors likely leads to early lethality before defects in brain development or function become evident. In addition, it is likely that ECM receptors play important roles in diseases with complex etiologies (e.g., ASDs and many psychiatric diseases) likely caused by contributions from collections of genes acting in combination with environmental factors.

4.1 INTEGRIN LINKS TO HUMAN BRAIN DISEASE

Chromosomal microdeletions involving the integrin $\alpha 3$ gene and duplications of integrin $\alpha 3$ coding regions have been found in patients with intellectual disability (Preiksaitiene et al., 2012; Zahir et al., 2009). Likewise, microdeletions involving the gene for integrin $\beta 1$ (Megarbane et al., 2001; Talkowski et al., 2012) and its downstream signaling partner Arg kinase (Chaabouni et al., 2006; Scarbrough et al., 1988; Takano et al., 1997) have been identified in cases of intellectual disability that are associated with developmental disorders in human patients. Mice with mutations in key components of this pathway exhibit defects in dendrite stability and dendritic spine density and morphology that resemble those observed in neurodevelopmental disorders and also exhibit widespread problems with learning, memory, and behavioral flexibility (Gourley et al., 2009, 2012; Kerrisk et al., 2013; Moresco and Koleske, 2003; Moresco et al., 2005; Sfakianos et al., 2007; Warren et al., 2012).

Integrins have also been implicated in the field of addiction, specifically in structural changes produced in response to cocaine administration. Integrin $\beta 1$ receptor shows increased levels following cocaine exposure (Wiggins et al., 2009), while integrin $\beta 3$ has decreased levels (Wiggins et al., 2011). Genetic loss of integrin $\beta 1$ in mice results in exaggerated psychomotor sensitivity to cocaine (Warren et al., 2012), likely due to the underlying impairments in neuronal structure and plasticity observed in these mice.

Interestingly, inhibiting integrin activation by injecting an RGD peptide into the nucleus accumbens core can prevent the relapse of cocaine-seeking behavior in mice (Wiggins et al., 2011), suggesting that integrin-mediated signaling may serve as a therapeutic target in the treatment of addiction.

Several studies have found a genetic association between *ITGB3*, the gene encoding for integrin $\beta 3$, and ASDs in a number of population cohorts (Abrahams and Geschwind, 2008; Aldinger et al., 2011; Cantor et al., 2005; Weiss et al., 2006), and a rare missense mutation in *ITGB3* has recently been identified in an individual with ASD (O’Roak et al., 2012). Notably, constitutive knockout mice for integrin $\beta 3$ display lack of preference for social novelty in the three-chamber social test and increased grooming behavior in novel environments (Carter et al., 2011). These abnormalities have strong analogies with the two criteria used to diagnose ASDs in humans (abnormal social interactions and repetitive behaviors (American Psychiatric Association, 2013)), making integrin $\beta 3$ knockout mice a good animal model for investigating the neurobiology of ASDs. Future studies should determine whether integrin $\beta 3$ knockout mice display autism-related abnormalities because of impairments in HSP (Ramocki and Zoghbi, 2008; Toro et al., 2010) or because of alterations in synaptic connectivity, as it occurs for mutations in other cell adhesion molecules (Betancur et al., 2009).

4.2 LDLRs AND ALZHEIMER’S DISEASE

While not itself an ECM receptor, the glycoprotein ApoE has a critical role in AD. ApoE is a ligand for many LDLRs, including the reelin receptors ApoER2 and LRP, and plays an important role in phospholipid and cholesterol homeostasis in the brain (Harris-White and Frautschy, 2005). The *apolipoprotein E (APOE)* gene has been genetically linked to sporadic AD, which accounts for over 95% of AD cases. The E4 allele of the *APOE* gene has been identified as the most important risk factor for developing late-onset AD (Saunders et al., 1993). One copy of the *APOE4* allele increases the risk of developing AD, while two copies further heighten that risk (Farrer et al., 1997). Conversely, the E2 allele of *APOE* serves a protective role in the development of AD (Corder et al., 1994).

AD is characterized by aberrant production of amyloid- β ($A\beta$) peptide and accumulation of $A\beta$ -containing plaques in the brains of affected individuals eventually leading to cognitive decline. ApoE physically binds to toxic $A\beta$ species and plays an essential role in the clearance of this peptide from the brain. Binding of ApoE- $A\beta$ complex to LRP promotes endocytosis of the complex and subsequent lysosomal degradation of $A\beta$ -peptide (Rebeck et al., 1993). Loss of all ApoE alleles or overexpression of its LRP receptor dramatically reduces amyloid-peptide aggregation and alters disease pathology in AD model mice (Bales et al., 1997, 2009; Kim et al., 2009). Exactly how different isoforms of *APOE* influence AD risk is still unclear, although the leading hypothesis is that ApoE controls $A\beta$ aggregation in the brain by promoting $A\beta$ -peptide clearance through LPRs (Castellano et al., 2011).

5 QUESTIONS AND DIRECTIONS FOR FUTURE RESEARCH

ECM molecules and their receptors play important roles in the formation, maintenance, and plasticity of the nervous system. As ECM receptors are cell surface receptors, they make

ideal drug targets for small molecules that could either prevent or mimic ligand binding to impact intracellular signaling cascades and treat human brain diseases. Also, the downstream signaling cascades by which they function will also be key potential targets for therapeutic intervention. Some ECM receptor signaling cascades have been well characterized, such as integrin $\alpha 3\beta 1$ activation of Arg kinase (Kerrisk and Koleske, 2013) or extracellular reelin signaling to ApoER2/ VLDLR and DAB1 (Niu et al., 2004). However, surprisingly little is known about the molecular mechanisms by which other receptors signal. Additionally, many ECM receptors interact with each other, and determining which receptor is responsible for a particular neuronal phenotype is often difficult. Improved technologies, including improvements in mass spectrometry, superresolution microscopy, optogenetics, and optical reporters of biochemical activities and protein–protein interactions, will be instrumental in elucidating the molecules and signaling events that act downstream of ECM receptors to coordinate changes in synaptic function. A major goal will be to determine whether these receptor-mediated mechanisms in the brain can be therapeutically targeted, as they have been in other tissues, to stabilize neuronal structure, restore synaptic function, and ameliorate disease (Desgrosellier and Cheresch, 2010; Wu and Reddy, 2012).

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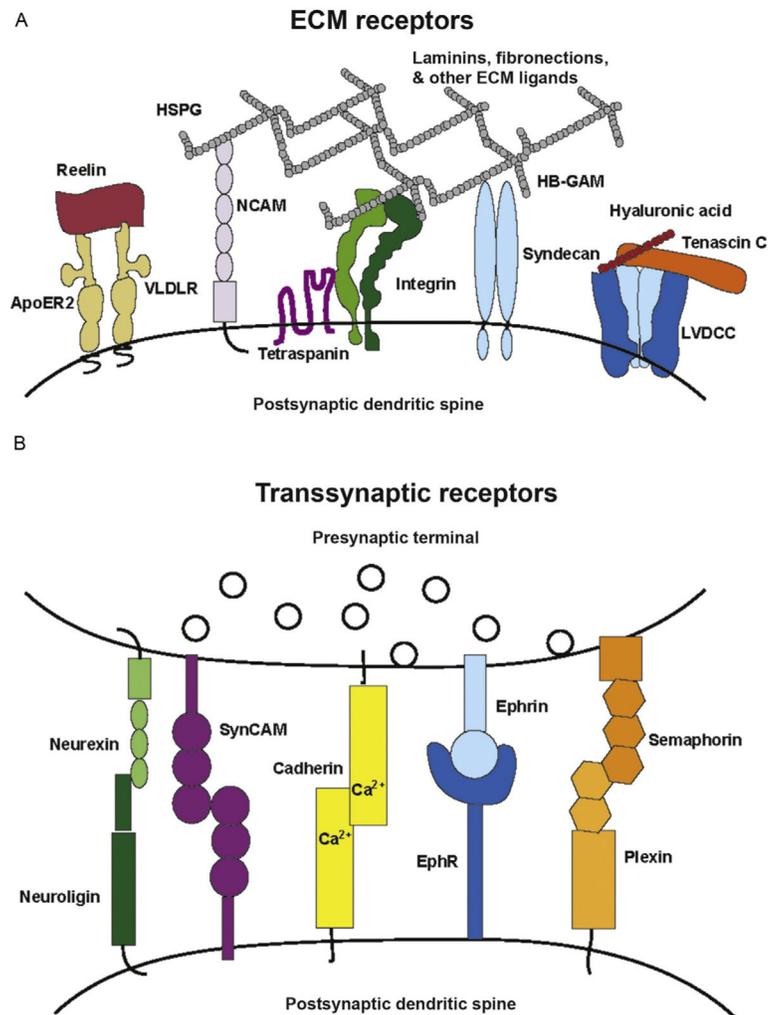


FIGURE 1. Overview of ECM and transsynaptic receptors in the brain

(A) Many of the ECM receptors that are localized to the postsynaptic membrane and their ECM ligands are depicted: Reelin signals to very low-density lipoprotein (VLDLR) and apolipoprotein E (ApoER2); HSPGs signal via NCAM; integrin receptors are activated by a number of ECM ligands including laminin and fibronectin and can be modulated by transmembrane tetraspanin proteins; HB-GAM can activate syndecan receptors; tenascin C and hyaluronic acid act upstream of L-type voltage-dependent calcium channels (LVDCC). (B) Transsynaptic adhesion molecules engage their partners across the synaptic cleft and can be influenced by the ECM and ECM receptors: Presynaptic neurexins bind to postsynaptic neuroligins; synaptic cell adhesion molecules (SynCAMs) can bind in *trans* (shown here) or in *cis*; cadherins bind transsynaptically in a calcium-dependent manner; presynaptic ephrins bind to postsynaptic ephrin receptors (EphR); presynaptic or secreted semaphorins can bind to postsynaptic plexins.

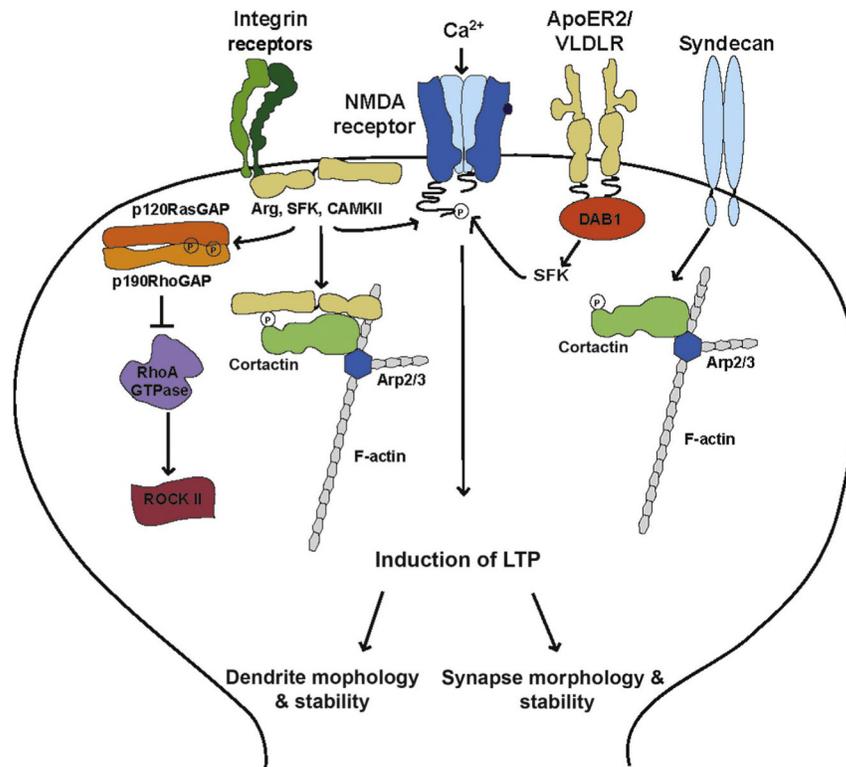


FIGURE 2. Biochemical signaling cascades downstream of ECM receptors

ECM receptors control a key set of biochemical signaling modules, shown here within a dendritic spine. Integrins can activate a number of kinase signaling cascades that regulate downstream proteins to modulate the actin cytoskeleton and control dendrite and synapse stability. Additionally, some of these cascades activate NMDA receptors via phosphorylation of different NMDA subunit intracellular tails, which leads to calcium (Ca^{2+}) influx and the induction of LTP. Very low-density lipoprotein (VLDLR) and apolipoprotein E (ApoER2) signal through a well-characterized pathway to Disabled-1 (DAB1). Finally, syndecans can activate the actin regulatory molecule cortactin to control F-actin stability and impact synaptic function. Together, these pathways impact cytoskeletal regulation, LTP induction, neuronal morphology, and stability.