Extracellular Matrix: Functions in the Nervous System

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An astonishing number of extracellular matrix glycoproteins are expressed in dynamic patterns in the developing and adult nervous system. Neural stem cells, neurons, and glia express receptors that mediate interactions with specific extracellular matrix molecules. Functional studies in vitro and genetic studies in mice have provided evidence that the extracellular matrix affects virtually all aspects of nervous system development and function. Here we will summarize recent findings that have shed light on the specific functions of defined extracellular matrix molecules on such diverse processes as neural stem cell differentiation, neuronal migration, the formation of axonal tracts, and the maturation and function of synapses in the peripheral and central nervous system.

Extracellular matrix (ECM) glycoproteins are widely expressed in the developing and adult nervous system. Tremendous progress has been made in defining the roles of specific ECM components in controlling the behavior of neurons and glia (Sanes 1989; Reichardt and Tomaselli 1991; Venstrom and Reichardt 1993; Milner and Campbell 2002; Nakamoto et al. 2004). Here, we will provide an overview of ECM functions in the nervous system, emphasizing recent findings that have shed light on the mechanisms by which ECM glycoproteins regulate such diverse processes as neural stem cell (NSC) behavior, neuronal migration, formation of axonal processes and their myelin sheets, and synapse formation and function.

NEURAL STEM CELL BEHAVIOR AND NEURONAL MIGRATION

NSCs give rise to neurons and glia, and the ECM provides a microenvironment that modulates NSC behavior (Perris and Perissinotto 2000; Sobeih and Corfas 2002; Zimmermann and Dours-Zimmermann 2008). Radial glial cells (RGCs) of the developing central nervous system (CNS) are a well-studied class of NSCs (Fig. 1) (Temple 2001; Fishell and Kriegstein 2003; Kriegstein and Noctor 2004; Noctor et al. 2007; Malatesta et al. 2008; Miller and Gauthier-Fisher 2009). RGCs are also precursors of neural progenitors maintained in the adult brain (Kokovay et al. 2008; Miller and

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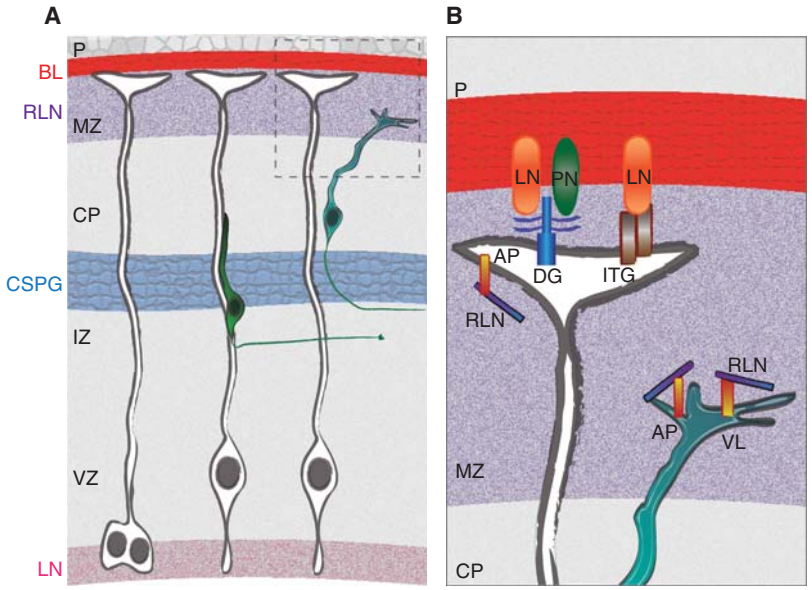

Figure 1. ECM molecules in the developing neocortex. (*A*) Overview of some ECM molecules found in the embryonic neocortex. Laminin (LN) is a major component of the basal lamina (BL) under the pia mater (P) and is also found in the ventricular zone (VZ). Reelin (RLN) is secreted in the marginal zone (MZ) by Cajal-Retzius cells. Chondroitin sulfate proteoglycans (CSPGs) are concentrated in the subplate region above the intermediate zone (IZ). (*B*) Higher magnification schematic of the boxed region in (A). RGC endfeet interact with ECM molecules in the BL, such as LN and perlecan (PN), through the integrin (ITG) and dystroglycan (DG) receptors. Radial glia and neurons engage in reelin signaling via the ApoER2 (AP) and VLDLR (VL) receptors.

Gauthier-Fisher 2009). RGCs have a radial morphology, with apical processes contacting the ventricle and basal processes extending across the respective CNS structures (Fig. 1). Many neurons use basal RGC processes as a scaffold for migration. The ECM shapes the niche where NSCs reside, modulates their maintenance and differentiation, and influences migration of their progeny (Sobeih and Corfas 2002; Porcionatto 2006; von Holst 2008).

Laminins

The ECM forms a basal lamina (BL) surrounding the brain and blood vessels throughout the CNS (Timpl and Brown 1996; Erickson and Couchman 2000). In the neocortex, the BL at the pial surface is contacted by RGCs' endfeet (Fig. 1). A number of studies have shown that the pial BL is crucial for neocortical development. Removal of the BL leads to detachment of RGC fibers, affecting RGC survival and cortical lamination (Sievers et al. 1986; von Knebel Doeberitz et al. 1986; Sievers et al. 1994; Radakovits et al. 2009). Laminins are major components of the BL (Timpl et al. 1979) and are also present in the VZ of the developing neocortex (Campos et al. 2004; Lathia et al. 2007). Laminins promote the expansion, migration, and differentiation of NSCs in vitro (Drago et al. 1991; Liesi 1992; Liesi et al. 1992; Kearns et al. 2003; Campos et al. 2004; Flanagan et al. 2006; Hall et al. 2008; Ma et al. 2008; Silva et al. 2009; Pierret et al. 2010). Expression of several laminin subunits in cultured NSCs is dependent on the transcription factor RE1 Silencing Factor (REST) (Otto et al. 2007; Sun et al. 2008). REST regulates neurogenesis by repressing neurogenic genes in nonneuronal tissues (Schoenherr et al. 1996; Chen et al. 1998). REST-null embryonic stem cells have defects in cell adhesion, NSC generation and neuronal

differentiation, phenotypes that can be rescued by exogenously added laminin (Sun et al. 2008). However, the effects of laminins on NSCs and the importance of the REST/Laminin interaction still await examination in vivo. Mice lacking laminin γ1 die during embryogenesis (Smyth et al. 1999); those bearing a mutation affecting solely the laminin γ1 nidogen-binding domain survive until birth and display disruptions of the pial BL and neuronal ectopias (Halfter et al. 2002). Inactivation of laminin γ1 in a subset of cortical neurons causes cortical lamination defects (Chen et al. 2009). However, defects of NSC maintenance or differentiation have not been reported in these mutants.

In vivo evidence for a role of laminins in controlling NSC behavior comes from studies of their dystroglycan and integrin receptors. Human patients with mutations in enzymes that glycosylate dystroglycan show cortical neuronal ectopias (Yoshida et al. 2001; Beltran-Valero de Bernabe et al. 2002). Mice without dystroglycan in the CNS or bearing mutations in dystroglycan glycosyltransfserases display BL disruptions and neuronal migration defects (Grewal et al. 2001; Michele et al. 2002; Moore et al. 2002). Inactivation of β1 integrins in RGCs results in abnormal neocortical lamination and fusion of cerebellar folia (Graus-Porta et al. 2001; Blaess et al. 2004). These abnormalities are caused by detachment of RGCs from the pia and disorganization of the pial BL and cortical marginal zone (MZ) (Fig. 1) (Graus-Porta et al. 2001; Blaess et al. 2004; Radakovits et al. 2009). In the neocortex of β1-deficient animals, neurons associate with intact RGCs and migrate, but form ectopias in the MZ (Graus-Porta et al. 2001). Similar phenotypes are observed in mice lacking the α6 integrin subunit or both α6 and α3, which heterodimerize with β1 to form laminin receptors (Georges-Labouesse et al. 1998; De Arcangelis et al. 1999; Colognato et al. 2005). Deletion of β1 integrin solely in migrating neurons results in normal neocortical lamination, indicating that abnormalities in neuronal migration are secondary to defects in RGCs (Graus-Porta et al. 2001; Belvindrah et al. 2007a).

Disruption of β1 integrin function in the VZ by antibody injections leads to detachment of RGC apical processes (Loulier et al. 2009). Apical detachment of RGCs is also observed in mice lacking laminin α2 (Loulier et al. 2009). Thus, β1 integrins and laminins appear to maintain both apical and basal RGC processes. In addition, loss of laminin γ1 prevents neurons from migrating towards the MZ (Chen et al. 2009), a phenotype that differs from those resulting from loss of β1 integrins, indicating that other surface receptors are involved. For example, β4, β8, α3, α4, and α5 integrins have been implicated in NSC development, neocortical lamination, and/or neuronal migration (Murgia et al. 1998; Mobley et al. 2009; Stanco et al. 2009; Marchetti et al. 2010). Furthermore, ECM molecules and integrins likely play context-dependent roles. For example, in the adult brain, β1 integrins and laminins α2/α4 are required for the formation of cell chains in the rostral migratory stream (RMS) (Belvindrah et al. 2007b).

Proteoglycans

Proteoglycans are prominently expressed in the nervous system (Gu et al. 2007; Gu et al. 2009; Abaskharoun et al. 2010), and enzymatic digestion of chondroitin sulfate proteoglycans disrupts the development of NCSs in culture (von Holst et al. 2006; Gu et al. 2009). Yet, no major abnormalities have been described in the CNS of mice lacking proteoglycans, likely because of either functional redundancy or early embryonic lethality (Hartmann and Maurer 2001; Zimmermann and Dours-Zimmermann 2008). One exception is the BL component perlecan. Genetic ablation of perlecan results in exencephaly following massive BL disruptions, or in neuronal ectopias in mutant brains with less severe BL defects (Haubst et al. 2006; Giros et al. 2007). In the latter cases, cell cycle progression in NSCs is affected, likely because of decreased levels of sonic hedgehog (Giros et al. 2007). Interestingly, proliferation of granule cell precursors in the cerebellum is also affected in mice lacking β1 integrins, a phenotype that is caused at least

in part by defective sonic hedgehog signaling (Blaess et al. 2004).

Tenascins

Tenascin-C (TN-C) is expressed in the CNS in regions of active neurogenesis (Bartsch et al. 1992; Jankovski and Sotelo 1996). Tenascin-R (TN-R) expression is prominent in myelinating glia, in subsets of interneurons and in the deepest layers of the olfactory bulbs (Saghatelyan et al. 2004; Huang et al. 2009). In NSCs in culture, TN-C facilitates the switch from production of neuronal to glial progenitors (Lillien and Raphael 2000; Garcion et al. 2004; Liao et al. 2008), whereas TN-R inhibits migration of NSC-derived neurons (Huang et al. 2009). In vivo, TN-C regulates myelinating glial lineage development and glomerulogenesis in the olfactory bulbs (OBs) (Garcion et al. 2001; Treloar et al. 2009). TN-R promotes detachment of chain-migrating neuroblasts in the RMS and their migration within the OBs. Interestingly, OB expression of TN-R is activity-dependent and reduced on odor deprivation (Saghatelyan et al. 2004).

Reelin

Reelin is one of the best-studied ECM glycoproteins in the CNS. During development, reelin is secreted by specific cell types in laminated brain structures, including the neocortex (Fig. 1). Reelin binds to the lipoprotein receptors ApoER2 and VLDLR (D'Arcangelo et al. 1999), which are expressed by migrating neurons and RGCs (Luque et al. 2003). ApoER2 and VLDLR bind to the adaptor protein Dab1, which is phosphorylated by Src-family kinases on reelin binding to its receptors (Howell et al. 1999; Arnaud et al. 2003). Phosphorylated Dab1 recruits signaling molecules including PI3K (Bock et al. 2003), Crk/CrkL (Ballif et al. 2004; Chen et al. 2004; Huang et al. 2004), and Lis1 (Assadi et al. 2003). Mutations in reelin signaling in humans cause lissencephaly and cerebellar hypoplasia (Hong et al. 2000), and in mice severe CNS abnormalities characterized most notably by severe lamination defects in the cerebellum, hippocampus and neocortex (Mariani et al. 1977; Caviness and Korde 1981; Caviness 1982; Goffinet 1983; Goffinet et al. 1984; Hoffarth et al. 1995). Defective neocortical lamination is caused by failure of newborn neurons to move past their predecessors, creating a disorganized cytoarchitecture lacking the typical inside-out layering pattern of the normal neocortex. Because the number and types of neocortical neurons generated appears unaffected in *reeler* mutants (Caviness 1973), reelin is thought to primarily control migration. However, the cellular mechanism by which reelin regulates cell positioning is not known. Reelin has variably been proposed to be a chemoattractant (Gilmore and Herrup 2000), repellent (Ogawa et al. 1995; Schiffmann et al. 1997), stop (Sheppard and Pearlman 1997), or detachment (Sheppard and Pearlman 1997; Dulabon et al. 2000; Sanada et al. 2004) signal for migrating neurons.

A role for reelin as a detachment signal is supported by the observation that postmigratory neurons remain associated with RGC fibers in *reeler* mice, creating a "traffic jam" (Pinto-Lord et al. 1982), and by studies suggesting that reelin down-regulates integrin-mediated adhesion, allowing migrating neurons to detach from the RGC scaffold (Dulabon et al. 2000; Sanada et al. 2004). However, when reelin-responsive and nonresponsive neurons coexist, wild-type cells migrate normally (Sanada et al. 2004; Olson et al. 2006; Hammond et al. 2010). Genetic studies also do not support a role for integrins on migrating neurons in reelin signaling (Belvindrah et al. 2007a). In addition, the detachment hypothesis does not account for migration defects in early-born neurons, which do not migrate along RGCs (Nadarajah et al. 2001). Finally, cell-autonomous perturbations of reelin signaling in radially migrating neurons block their movement and addition of recombinant reelin to slice cultures from *reeler* mice restores migration (Jossin et al. 2004; Olson et al. 2006; Young-Pearse et al. 2007; Hashimoto-Torii et al. 2008), indicating that reelin promotes motility. Because recent observations show that neocortical neurons migrate by glia-dependent and glia-independent modes

(Nadarajah et al. 2001), it has been proposed that reelin stimulates detachment of neurons from RGCs as well as glia-independent migration (Luque et al. 2003; Cooper 2008).

Studies demonstrating cross talk between reelin and other signaling pathways, such as integrins (Dulabon et al. 2000; Calderwood et al. 2003; Sanada et al. 2004), Notch (Hashimoto-Torii et al. 2008), amyloid precursor protein (Young-Pearse et al. 2007) and thrombospondins (Blake et al. 2008) indicate that reelin is part of a complex developmental paradigm with distinct mechanisms of action in different brain regions (Trommsdorff et al. 1999; Benhayon et al. 2003; Beffert et al. 2006; Hack et al. 2007; Forster et al. 2010).

AXONAL GROWTH AND MYELINATION

Wiring of the nervous system depends on a coordinated sequence of events, including axon growth to precise targets and their subsequent myelination. CNS myelination is performed by oligodendrocytes, whereas Schwann cells myelinate peripheral nerves (Sherman and Brophy 2005; Simons and Trajkovic 2006). The ECM is crucial for axon formation and myelination (Colognato et al. 2005; Chernousov et al. 2008) (Fig. 2), and is a component of glial scar tissue at sites of CNS injury (Rolls et al. 2009).

Laminins

Some of the first results implicating ECM molecules in nervous system development showed that laminins promote neurite outgrowth in an integrin-dependent manner (Calof and Reichardt 1985; Lander et al. 1985a; Lander et al. 1985b; Hall et al. 1987; Tomaselli and Reichardt 1988). These findings have been extended by others (e.g., Gomez and Letourneau 1994; Luckenbill-Edds 1997; Esch et al. 1999; Menager et al. 2004). Laminins have also been implicated in axonal guidance in vivo. For example, ablation of *Drosophila* laminin A results in pathfinding defects in sensory nerves (Garcia-Alonso et al. 1996). In *Xenopus*, laminin-1 modulates growth cone behavior of retinal neurons, converting the attraction cue provided by netrin-1 into repulsion (Hopker et al. 1999). In mice, laminin γ1 deficiency results in abnormal branching of myelinated axons from the corpus callosum (Chen et al. 2009). The mutants also show abnormal neuronal migration (see below), impaired activation of integrin downstream effectors like focal adhesion kinase and paxillin, and disrupted AKT/GSK-3β signaling, which has been implicated in neurite growth (Yoshimura et al. 2005). The exact mechanisms underlying these abnormalities await investigation.

In the peripheral nervous system (PNS), Schwann cells are surrounded by a basal lamina (BL) that contains laminin 2 (α2β1γ1), laminin 8 (α4β1γ1), and laminin 10 (α5β1γ1) (Feltri and Wrabetz 2005). Schwann cells migrate into peripheral nerve and use a mechanism known as radial sorting to establish a 1:1 association with each larger diameter axon (Shy 2009) (Fig. 2). Human patients suffering from congenital muscle dystrophy (MDC) lack laminin α2 and develop demyelinating peripheral neuropathy (Shorer et al. 1995; Di Muzio et al. 2003). In laminin α2-deficient mice, sorting and axon myelination are impaired following reduced Schwann cell proliferation and inability to extend myelin sheets (Bray et al. 1977; Helbling-Leclerc et al. 1995; Feltri et al. 2002). These defects are most prominent in nerve roots. Conversely, loss of laminin α4 leads to axonal sorting defects that are pronounced in distal nerve; when both laminin α2 and α4 are missing, all axon segments are affected (Wallquist et al. 2005; Yang et al. 2005). Similarly, mice lacking laminin γ1 in Schwann cells show decreased Schwann cell proliferation, differentiation, and survival, radial sorting impairment, hypomyelination and reduced nerve conduction velocity (Yu et al. 2005; Yu et al. 2007). Mice lacking β1 integrin in Schwann cells show radial axonal sorting defects and hypomyelination, but normal Schwann cell proliferation and survival (Feltri et al. 2002), suggesting that β1 integrins only mediate some laminin functions. Dystroglycan is mainly expressed postnatally in Schwann cells but is another crucial laminin receptor. Dystroglycan-null mice have abnormally folded

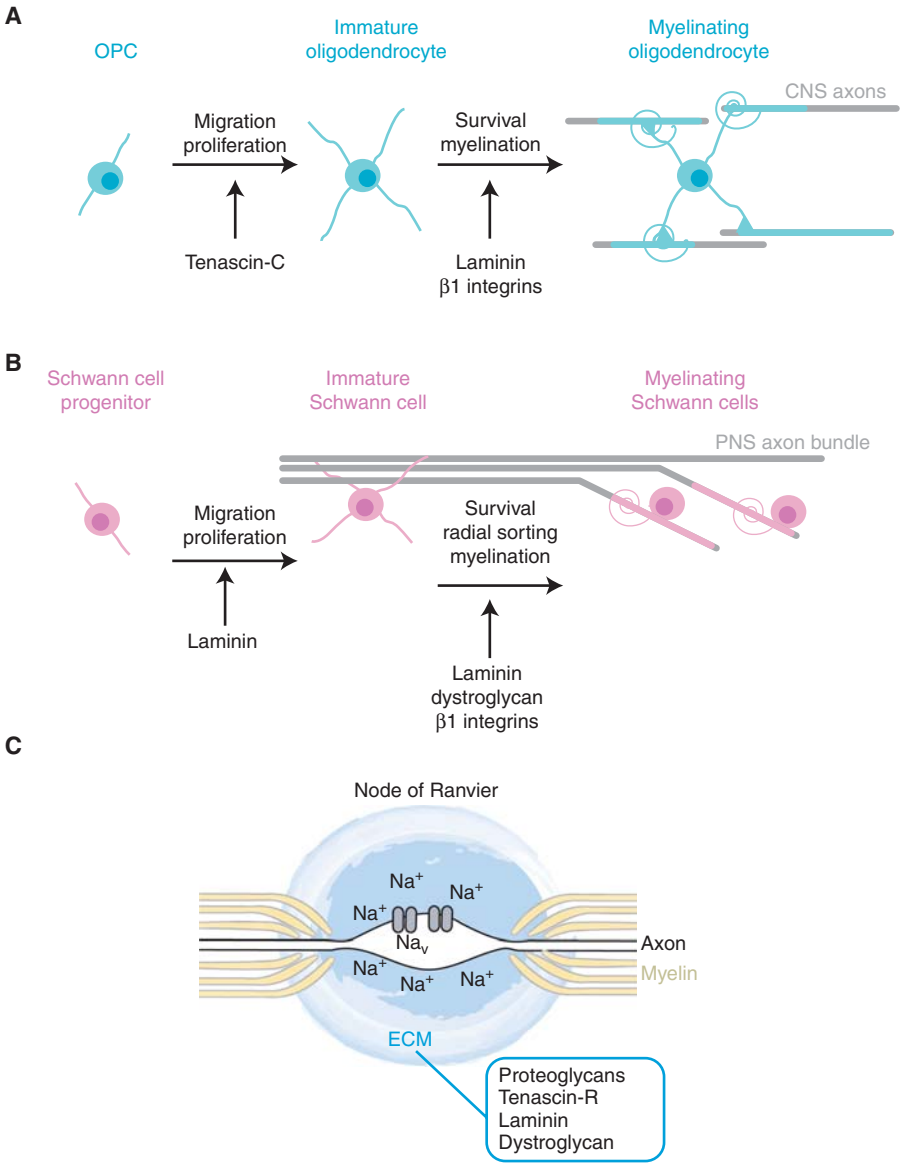

Figure 2. ECM and myelination. (*A*) Oligodendroglia differentiate in sequential stages to generate mature oligodendrocytes. Each oligodendrocyte myelinates several CNS axons. Tenascin-C, laminin, and their β1 integrin receptors play roles at different developmental stages, as indicated. (*B*) Schwann cells myelinate peripheral nerves. Immature Schwann cells sort out axonal bundles to individually myelinate each axon. Laminin regulates all stages of Schwann cell development, whereas dystroglycan and β1 integrin receptors control axonal sorting and myelination. (*C*) The ECM surrounding nodes of Ranvier may regulate the local concentration of cations and clusters voltage-gated sodium channels, which allow for saltatory electrical conductivity. Several proteoglycans, tenascin-R, laminin and dystroglycan contribute to the formation of nodal matrices. Na_v, voltage-gated channel; Na^+, sodium cations.

myelin and reduced clustering of sodium channels at the nodes of Ranvier (Saito et al. 2003).

In the CNS, oligodendrocytes derive mainly from precursors residing in the ventral VZ and ganglionic eminences. They proliferate and migrate before becoming mature myelinating cells (Bradl and Lassmann 2010). Oligodendrocytes are not associated with a BL and each cell extends multiple sheets able to myelinate several axons (Colognato et al. 2005; Simons and Trotter 2007) (Fig. 2). Expression of laminins correlates with the onset of CNS myelination (Colognato et al. 2002; Colognato et al. 2005), and varied degrees of defects have been found in white matter tracts of patients suffering from MDC (Caro et al. 1999; Leite et al. 2005). Mice lacking laminin α2 have a developmental delay in oligodendrocyte maturation, resulting in hypomyelination (Chun et al. 2003; Relucio et al. 2009). The degree of developmental delay is region-specific, which may reflect different laminin α2 requirements (Relucio et al. 2009). Abnormalities in Fyn signaling, which is modulated by laminins in cultured oligodendrocytes, were observed in the mutant brains, suggesting one explanation for the temporary stall in oligodendrocyte differentiation (Colognato et al. 2004; Relucio et al. 2009). Interestingly, β1 integrins not only affect PNS but also CNS myelination (Relvas et al. 2001; Barros et al. 2009). Deletion of β1 integrins in the CNS results in thinner myelin sheaths in several regions, and cultured oligodendrocytes require β1integrin signaling via Akt to extend myelin sheets (Barros et al. 2009).

Proteoglycans

A major obstacle for regeneration after CNS injury is the axon growth-inhibitory activity of the glial scar (Rolls et al. 2009). Chondroitin sulfate proteoglycans (CSPGs) are main scar components and found up-regulated in injured rat brains and spinal cords (Silver and Miller 2004; Galtrey and Fawcett 2007). In vitro, phosphacan and all soluble hyaluronan-binding CSPGs (aggrecan, versican, neurocan, and brevican) inhibit axonal growth (Bandtlow and Zimmermann 2000; Yamaguchi 2000). Enzymatic digestion of CSPGs reduces their inhibitory activity (McKeon et al. 1995; Smith-Thomas et al. 1995) and promotes axon regrowth and functional recovery after spinal cord injury (Moon et al. 2001; Bradbury et al. 2002; Yick et al. 2003; Caggiano et al. 2005; Bai et al. 2010).

Proteoglycans have been proposed to participate in the assembly of the extracellular meshwork surrounding nodes of Ranvier (Fig. 2). Differential proteoglycan expression is observed in central versus peripheral nodes of Ranvier and between large and small diameter CNS axons (Peles and Salzer 2000; Melendez-Vasquez et al. 2005). In brevican-deficient mice, the CNS nodal matrix composition is reorganized; components typically associated with large diameter nodes, such as phosphacan and TN-R, no longer show a diameter-dependent association (Bekku et al. 2009). Molecular alterations of the nodal ECM are also observed in a mouse model lacking the versican splice variant V2 (Dours-Zimmermann et al. 2009). However, no conduction velocity defects were obvious in either of these mutants (Bekku et al. 2009; Dours-Zimmermann et al. 2009). In contrast, loss of brain-specific hyaluronan-binding link protein 1 (Bral1), which also localizes over nodes of Ranvier and forms complexes with brevican and versican V2, inhibits the stabilization of nodal matrices and is thought to impair accumulation of cations at nodes, resulting in slow conduction velocities (Bekku et al. 2010).

Tenascins

TN-R and TN-C have been implicated in neurite growth. In vitro, both TNs promote or retard neuritogenesis, depending on the neuronal cell types (Faissner and Kruse 1990; Pesheva et al. 1993; Taylor et al. 1993; Lochter et al. 1994; Rigato et al. 2002; Mercado et al. 2004). Although no axonal pathfinding defects have been reported in TN-R mutant mice, TN-R acts as a repellent for optic axons in zebrafish (Becker et al. 2003; Becker et al. 2004). In the OB, TN-C is an inhibitory boundary molecule, preventing axonal growth of sensory neurons before glomerulogenesis (Treloar et al. 2009).

TN-R and TN-C also regulate myelinating glia and axonal function (Fig. 2). TN-R is expressed in immature and mature oligodendrocytes, and TN-C in oligodendrocyte precursor cells (OPCs) (Fuss et al. 1993; Czopka et al. 2009). TN-R facilitates OPC differentiation in vitro, whereas oligodendrocyte maturation is reduced on TN-C substrates. Conversely, loss of TN-C accelerates oligodendrocyte differentiation (Pesheva et al. 1997; Garwood et al. 2004; Czopka et al. 2009). Despite these opposing effects, TN-C and TN-R inhibit extension of myelin sheets by oligodendrocytes in vitro (Garcion et al. 2004; Czopka et al. 2009). However, neither TN-R nor TN-C knockout mice show myelination abnormalities (Kiernan et al. 1999; Weber et al. 1999). TN-C mutants have increased migration and reduced rate of OPC proliferation, but decreased cell death in myelination areas likely corrects for any reduction in oligodendrocyte density (Garcion et al. 2001). Interestingly, in TN-R knockout mice, expression of phosphacan along white matter tracts is perturbed and axonal conduction velocity is decreased (Weber et al. 1999), suggesting that TN-R may have an essential function in ECM assembly at nodes of Ranvier.

Thrombospondin Type-1 Repeat Proteins

ECM proteins sharing thrombospondin type-1 repeats regulate axon outgrowth and guidance. These include members of the thrombospondin (TSP) family, F-spondin, SCO-spondin, and others (Adams and Tucker 2000; Tucker 2004; Meiniel et al. 2008). TSP isoform-1 is the best-characterized member of the TSP family and is secreted by astroglia. TSP1 promotes neurite outgrowth in many types of cultured neurons (Neugebauer et al. 1991; O'Shea et al. 1991; Osterhout et al. 1992). This effect is mediated by β1 integrins in retinal and sympathetic neurons (Tomaselli et al. 1990; DeFreitas et al. 1995). TSP1 is also detected along white matter tracts and promotes migration of OPCs (Scott-Drew and ffrench-Constant 1997). Additionally, TSP1 levels are up-regulated at sites of injury, and correlate with the capacity of axons to regenerate (Moller et al. 1996; Hoffman and O'Shea 1999a; Hoffman and O'Shea 1999b).

F-spondin is expressed in the floor plate and in developing peripheral nerves. It inhibits adhesion and influences migration of neural crest cells, promotes commissural axon outgrowth, and acts as a contact-repellent molecule for embryonic motor neurons (Klar et al. 1992; Burstyn-Cohen et al. 1998; Burstyn-Cohen et al. 1999; Debby-Brafman et al. 1999; Tzarfati-Majar et al. 2001). F-spondin is also thought to influence repair in injured peripheral sensory neurons (Burstyn-Cohen et al. 1998). SCO-spondin is secreted by ependymal cells of the subcommissural organ (SCO) in the developing vertebrate brain (Gobron et al. 1996; Goncalves-Mendes et al. 2003; Meiniel et al. 2008). TSR motifs of SCO-spondin induce neurite extension in neuronal cell lines in a β1-integrin-dependent fashion; immunohistochemical evidence suggests it may control axonal development in vivo (Bamdad et al. 2004; Caprile et al. 2009; Hoyo-Becerra et al. 2010).

Netrins and Slits

The secreted molecules netrins and slits are part of two of the major protein families with crucial roles in axonal outgrowth and guidance. They provide instructive cues repelling or attracting axons depending on the repertoire of receptors presented at the surface of the neuronal growth cones and the activated intracellular signaling pathways. Netrins and slits also function in a variety of other processes within and outside the CNS, controlling cell adhesion, migration and polarity (Killeen and Sybingco 2008; Bradford et al. 2009; Ypsilanti et al. 2010).

Netrins are evolutionary related to the ECM molecule laminin and contain binding sites for heparan sulfate proteoglycans (HSPG), glycolipids and the integrins α3β1 and a6β4 (Bradford et al. 2009). The first identified netrin ortholog, Unc6, was found in *Caenorhabditis elegans. Unc6* mutants showed axon guidance defects and an uncoordinated (Unc) crawling phenotype (Hedgecock et al. 1990). Netrins were then found in many other organisms including *Drosophila*, zebrafish and mammals.

In vertebrates, the netrin family comprises the secreted netrin-1, netrin-3, and netrin-4 proteins and the glycosylphosphatidylinostol (GPI)-membrane anchored netrins G1 and G2 (reviewed in Cirulli and Yebra 2007; Bradford et al. 2009). Netrins are dynamically expressed in the developing CNS and in all species described so far netrin-1 is secreted by midline cells. The chemoattractant effects of netrin-1 are mediated through axonal receptors of the deleted in colorectal cancer (Dcc) family, which include the vertebrate Dcc and neogenin, the *C. elegans* UNC40 and the *Drosophila* Frazzled (Fra) proteins (Chan et al. 1996; Keino-Masu et al. 1996; Kolodziej et al. 1996). More recently, the Down syndrome cell adhesion molecule (Dscam) has also been shown to act as a netrin receptor promoting axonal attraction (Ly et al. 2008). Repulsive netrin-1 effects are mediated solely through Unc5 receptors or in combination with Dcc (Hong et al. 1999; Keleman and Dickson 2001). Netrin-1 acts both as a short-range and a long-range guidance cue and is particularly significant for the steering of comissural axons. For example, mouse mutants for netrin-1 or Dcc completely lack the corpus callosum and hippocampal comissure, among defects in numerous other axonal tracts (reviewed in Barallobre et al. 2005).

The first member of the slit family was identified in *Drosophila* as a midline glia secreted protein (Kidd et al. 1999), but slits have since been discovered in several species (Ypsilanti et al. 2010). In mammals there are three slit genes (*Slit1-3*), all of which are expressed in the CNS (Itoh et al. 1998). Slits are glycoproteins that function as ligands for Roundabout (Robo) receptors. They act as major axonal repulsion cue and also inhibit axonal attraction (Stein and Tessier-Lavigne 2001; Killeen and Sybingco 2008; Ypsilanti et al. 2010). There are three Robo proteins in the CNS of *Drosophila* and of most vertebrates (Robo/Robo1, Leak/Robo2, and Robo3). Yet, Robos are not the only receptors for slits and vice-versa. For example, the EVA-1 transmembrane protein functions as a SLT-1/slit co-receptor in *C. elegans* and the interaction of HSPGs with slit proteins is required or potentiates their activity in some axonal tracts (Hu 2001; Piper et al. 2006; Fujisawa et al. 2007; Seiradake et al. 2009). As for netrin/Dcc, slit/Robo signaling is also essential for the establishment of many axonal tracts. For instance, mouse mutants for both *Slit1* and *Slit2* show axon guidance errors in a variety of pathways, including the corticofugal, callosal, and thalamocortical tracts (Bagri et al. 2002).

During development, the netrin and slit pathways are best known for their function in dorsal-ventral axonal guidance but they also play a role in anterior-posterior and longitudinal guidance (Killeen and Sybingco 2008). The two guidance cues are often tightly coordinated as exemplified in many studies of midline crossing by commissural axons in vertebrates and invertebrates. In brief, commissural axons are at first attracted towards the midline by netrin and are insensitive to the slit repulsive cue because its reception by the growth cone is transiently repressed. In flies, this negative regulation of the slit-Robo pathway is performed by commissureless, which is only transiently expressed in precrossing commissural neurons, ensuring that at that stage newly synthesized robo proteins are not trafficked to the growth cones but instead are targeted for degradation (Keleman et al. 2002; Keleman et al. 2005). In mice, this function is provided by the Robo3.1 isoform, which is also transiently expressed in precrossing neurons, although the precise mechanism involved is not yet clear (Chen et al. 2008). Once across the midline, axons increase their robo expression (but specifically down-regulate Robo3.1 in mice) and thus acquire slit sensitivity. In this way, the slit/Robo chemorepellent activity forces axons away from the midline and prevents their re-entrance. In addition, Robo seems also able to inhibit the attraction mediated by the netrin attractant receptor Dcc, possibly explaining how post-crossing axons lose their sensitivity to netrin (Stein and Tessier-Lavigne 2001; reviewed in Dickson and Gilestro 2006; Evans and Bashaw 2010; Ypsilanti et al. 2010).

Although considerable progress has been made in determining the function of netrins and slits during axonal guidance, many questions

await further investigation, such as how the different ligands and receptor subtypes precisely mediate varying effect in different contexts and in a temporal manner. In this respect, it will be crucial to further investigate the interactions of netrins and slits with additional coreceptors including other ECM molecules.

SYNAPTOGENESIS AND NEURAL CIRCUIT FORMATION

Synapses are surrounded by a protein meshwork secreted by neurons and astrocytes (Dityatev and Schachner 2006). The vertebrate neuromuscular junction (NMJ), where motoneurons contact muscle fibers (Fig. 3), has served as a model to study ECM functions at peripheral synapses. In the CNS, the ECM forms perineuronal nets (PNNs) enwrapping neuronal cell bodies and processes (Fig. 4), which affect their development and function (Celio et al. 1998).

The Neuromuscular Junction

At the NMJ, motoneuron terminals release acetylcholine (ACh), which binds ACh receptors (AChr) at postsynaptic membranes, leading to muscle contraction (Wu et al. 2010). NMJs are embedded in a specialized BL containing collagen IV, laminins, heparan sulfate proteoglycans (HSPs) and various other glycoproteins (Fig. 3) (Patton 2003).

Agrin and Laminins

Agrin is a HSP released by motoneurons into the BL. In addition, muscle fibers and Schwann cells produce distinct agrin isoforms (Werle 2008). *Agrin*-deficient mice lack NMJs (Gautam et al. 1996), and agrin can induce postsynaptic-like membranes in denervated muscles (Gesemann et al. 1995; Jones et al. 1997). Agrin binds to low-density lipoprotein receptor-related protein 4 (Lrp4), which interacts with MuSK, a receptor tyrosine kinase that acts as a signalosome for postsynaptic NMJ development (Fig. 3) (Glass et al. 1996; Strochlic et al. 2005; Kim et al. 2008; Zhang et al. 2008; Wu et al. 2010). A short agrin form consisting of its MuSK-activating and laminin-binding domains is sufficient to restore NMJs in *agrin* mutant mice when expressed by muscle, suggesting that agrin function does not depend on its local deposition at synapses (Lin et al. 2008).

Agrin, other HSPs, and nidogens stabilize networks of laminin, the most prominent non-collagenous glycoprotein of the BL at the NMJ

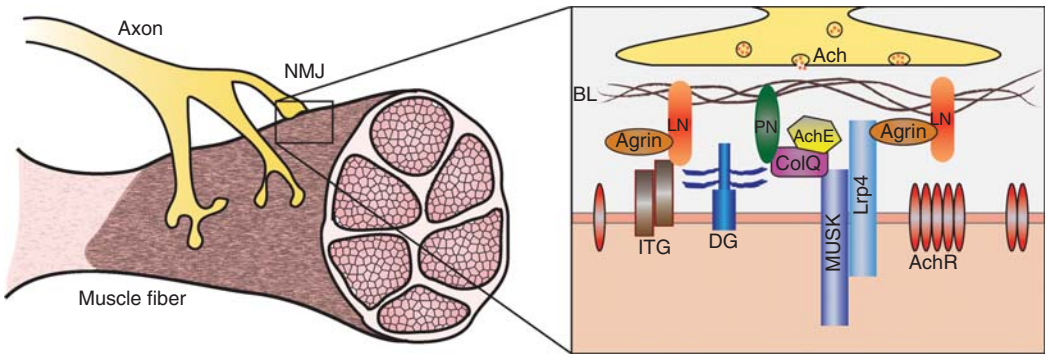

Figure 3. ECM molecules at the neuromuscular junction. ECM molecules (BL) are required for NMJ development and function. The heparan sulfate proteoglycan agrin binds to its receptor, Lrp4, and regulates postsynaptic NMJ development through the receptor tyrosine kinase, MuSK. Laminins (LN) are required at the NMJ to promote presynaptic differentiation, as well as postsynaptic maturation via integrin (ITG) and α-dystroglycan (DG) receptors. ITG and DG receptors also bind perlecan (PN) in the BL, which recruits collagen Q (ColQ). ColQ can also bind MuSK and is important for AchR clustering and regulation of Ach levels via recruitment of acetylcholinesterase (AchE) to the NMJ.

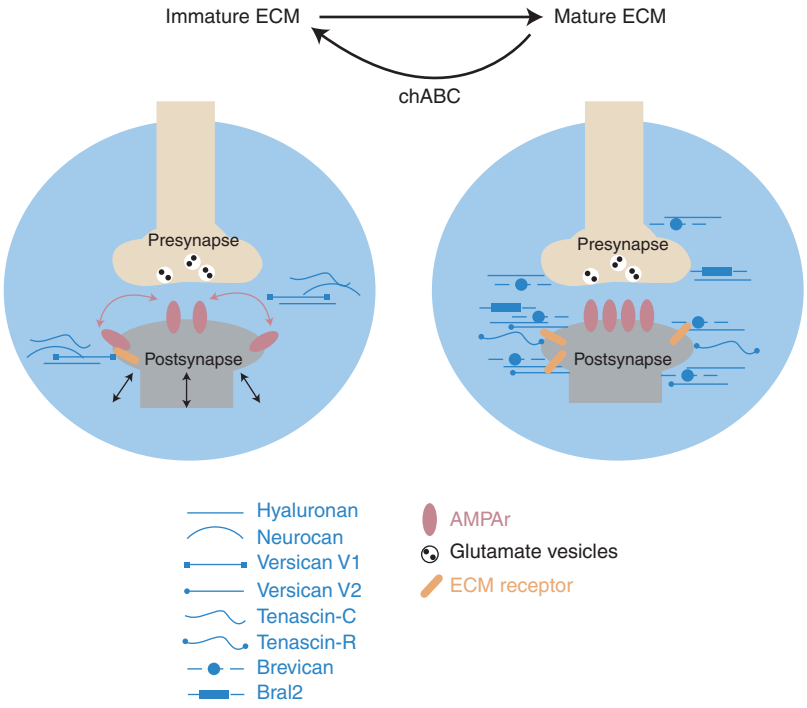

Figure 4. ECM changes at CNS synapses**.** Synapses are embedded into an ECM meshwork (blue) composed of hyaluronan, chondroitin sulfate proteglycans (CSPGs), tenascins, and others. The composition of the ECM changes during development. For example, neurocan, versican V1, and tenascin-C are abundant in the immature CNS, whereas tenascin-R, versican V2, and Bral1 are prominent in the mature CNS. The mature ECM is thought to restrict dendritic spine motility and lateral diffusion of AMPA receptors (AMPAr). Chondroitinase ABC (chABC) digestion of CSPGs can restore juvenile spine dynamics.

(Fig. 3) (Massoulie and Millard 2009). β2-containing laminins bind calcium channels, inducing their clustering and consequent assembly of presynaptic proteins. Deletion of laminin β2 results in loss of NMJ presynaptic active zones where neurotransmitters are released (Noakes et al. 1995; Knight et al. 2003; Nishimune et al. 2004; Miner et al. 2006; Fox et al. 2007). Laminin α4 is also required for presynaptic differentiation (Ichikawa et al. 2005) and for the correct apposition between active zones and postsynaptic sites (Patton et al. 2001). Laminins play additional roles in postsynaptic maturation. Clustering of AChr is delayed in muscles of laminin α5 mutant mice and arrested in α4/α5 double mutants (Nishimune et al. 2008). Furthermore, agrin-induced aggregation of AChr in myotubes correlates with laminin recruitment (Montanaro et al. 1998). This laminin-mediated effect is MuSK-independent, occurring instead via the dual agrin/laminin receptor α-dystroglycan (Montanaro et al. 1998; Nishimune et al. 2008), which plays vital roles in maturation of the NMJ and central synapses (Grady et al. 2000; Jacobson et al. 2001; Pilgram et al. 2010). Integrins are additional laminin receptors at the NMJ (Barros and Muller 2005). β1-integrins modulate AChr clustering in cultured myotubes (Martin and Sanes 1997). In vivo, ablation of β1-integrins in motoneurons has little effect on NMJ formation, but its loss in muscle leads to defective motoneuron-muscle interactions, resulting in excessive nerve branching and preventing normal NMJ presynaptic differentiation (Schwander et al. 2004). These defects resemble the phenotype of agrin-null mice, indicating β1-integrins may be required for the presentation of agrin

and/or laminin to motor nerve terminals (Schwander et al. 2004).

Collagens

The most abundant BL protein at NMJs is collagen IV (Sanes 2003). Collagen IV chains α1 and 2 are implicated in NMJ nerve terminal maturation, while α3/6 chains are required for their maintenance (Fox et al. 2007). CollagenQ (ColQ), another collagen at the NMJ, anchors acetylcholinesterase (AChE), a serine hydrolase controlling ACh levels, to the ECM (Bon et al. 1997; Sigoillot et al. 2010b), and it is required for AChr clustering and synaptic gene expression via its interaction with MuSK (Sigoillot et al. 2010a; Sigoillot et al. 2010b). ColQ binds perlecan, which associates with dystroglycan, laminin and β1-integrins (Talts et al. 1999; Bix et al. 2004). Perlecan also stabilizes AChE to NMJs (Peng et al. 1999; Arikawa-Hirasawa et al. 2002), but it is unclear if it cooperates with ColQ in this function.

Central Synapses

In the CNS, the carbohydrate hyaluronan (HA) forms the backbone of PNNs. During nervous system maturation, many ECM molecules at PNNs are replaced by others of the same family, allowing for maintenance of overall ECM structure (Rauch 2004). For example, neurocan, versican V1, and tenascin-C are abundant in the juvenile rodent CNS, whereas brevican, versican V2, tenascin-R, Bral2, and HA synthases are prominent in the mature CNS (Bruckner et al. 2000; Bekku et al. 2003; Carulli et al. 2006; Carulli et al. 2007; Galtrey et al. 2008) (Fig. 4). Because some ECM components are inhibitory for cell adhesion and fiber outgrowth (Pesheva et al. 1989; Morganti et al. 1990; Angelov et al. 1998), the ECM has originally been thought of as inhibiting synaptogenesis, a view that has recently changed.

Chondroitin Sulfate Proteoglycans

In the model of ocular dominance plasticity, monocular deprivation leads to an ocular dominance shift in young animals that is not observed in adults. Reactivation of ocular dominance plasticity in adults can be achieved following enzymatic degradation of CSPGs (Pizzorusso et al. 2002). Brief monocular deprivation increases dendritic spine motility and occludes subsequent effects of ECM degradation, indicating that this mechanism may act to permit synapse remodeling during ocular dominance plasticity (Oray et al. 2004). Degradation of CSPGs at PNNs also renders subsequently acquired fear memories susceptible to erasure, implicating PNNs in the formation of stable memories (Gogolla et al. 2009). Finally, ECM removal restores juvenile AMPA-type neurotransmitter receptor (AMPAr) mobility in mature neurons, suggesting that PNNs compartmentalize neuronal surfaces and participate in short-term synaptic plasticity (Frischknecht et al. 2009). In sum, PNNs contribute to the formation of neural circuitry by restricting structural changes at synapses (Fig. 4), and by modulating experience-dependent synaptic plasticity. Key players are likely molecules regulating perisynaptic ECM proteolysis in an activity-dependent manner (Nakamura et al. 2000; Berardi et al. 2004; Lochner et al. 2006; Frischknecht et al. 2008; Lee et al. 2008).

Reelin

Reelin regulates not only neuronal migration but also synapse development and function (Dityatev and Schachner 2006; Rogers and Weeber 2008). In the adult neocortex, reelin is secreted by GABAergic interneurons (Alcantara et al. 1998; Sinagra et al. 2005). Reduction or loss of reelin signaling hampers arborization of hippocampal and frontal cortex neuronal dendrites, and reduces dendritic spine density (Liu et al. 2001; Niu et al. 2004; Matsuki et al. 2008; Niu et al. 2008). Conversely, transgenic mice overexpressing reelin show increased synaptic contacts and hypertrophy of hippocampal dendritic spines (Pujadas et al. 2010). Reelin signaling is also involved in synaptic plasticity; mice heterozygous for *reelin* or *ApoER2* show impaired hippocampal long-term potentiation (LTP) (Weeber et al. 2002; Beffert et al. 2005; Chen et al. 2005; Qiu et al. 2006; Rogers and

Weeber 2008). Reelin signals through ApoER2 to enhance LTP via a mechanism involving the activity-dependent splicing of an *ApoER2* exon that encodes a domain required for reelin-induced tyrosine phosphorylation of NMDA-type receptors (NMDAr) (Beffert et al. 2005; Beffert et al. 2006). Additionally, reelin participates in the recruitment, trafficking, and composition of NMDAr, contributing to the developmental switch of NMDAr subunits from NR2B to NR2A (Sinagra et al. 2005; Groc et al. 2007; Campo et al. 2009).

Thrombospondins

Astrocytes play an integral role in the development of synapses (Stevens 2008), and TSPs are key astrocyte-derived molecules regulating synaptogenesis. TSP1 and 2 are secreted by immature astrocytes, correlating with the onset of synaptogenesis (Ullian et al. 2001; Christopherson et al. 2005). Applying TSP1 and 2 to cultured retinal ganglion cells increases the number of excitatory synapses. Conversely, *TSP1/2* double KO mice show reduced cortical synapse density (Christopherson et al. 2005). TSP1/2 interact with the gabapentin receptor α2γ-1, which can mediate their synaptogenic activity (Eroglu et al. 2009). TSP1/2 induced synapses are presynaptically active but postsynaptically silent (Christopherson et al. 2005), suggesting that other signals are required to convert these immature synapses into functional ones. TSP1 also accelerates formation of immature synapses in cultured hippocampal neurons (Xu et al. 2010). This effect depends on neuroligin1 (NL1) (Xu et al. 2010), which together with its neurexin ligands induces formation of synapses lacking AMPAr (Graf et al. 2004). TSP1 also binds to the reelin receptors ApoER2 and VLDLR (Blake et al. 2008). In addition, production of TSP-1 by astrocytes is enhanced by type IV collagen, an effect that depends on α1β1 integrins (Yonezawa et al. 2010). Given that type IV collagen plays important roles in presynaptic specialization at NMJs (Fox et al. 2007) and that β1 integrins are required for hippocampal LTP (Chan et al. 2006; Huang et al. 2006), it will be interesting to examine if these molecules have coordinated functions with TSPs at central synapses.

Other ECM Proteins

Other ECM molecules have been implicated in the formation and plasticity of central synapses (Dityatev and Schachner 2006; Galtrey and Fawcett 2007; Lee et al. 2008; Faissner et al. 2010), such as neuronal pentraxins (NPs) and tenascins. The neuronal activity-regulated pentraxin (Narp) and the neuronal pentraxin NP1 are axonal-derived lectins enriched at excitatory synapses. The neuronal pentraxin receptor (NPR) associates with Narp and NP1, and its extracellular domain is released into the ECM. NP proteins contribute to synaptogenesis by clustering AMPAr (Xu et al. 2003; Bjartmar et al. 2006; Sia et al. 2007). In addition, NPR ectodomain cleavage by TACE is essential for metabotropic glutamate receptor-dependent long-term depression (LTD) (Cho et al. 2008). TN-R and TN-C have also been implicated in forms of synaptic plasticity. Although TN-C affects LTP and LTD in the CA1 hippocampal area via L-type calcium channels (Evers et al. 2002; Strekalova et al. 2002), loss of TN-R leads to elevated basal excitatory synaptic transmission and reduced perisomatic GABAergic inhibition (Bukalo et al. 2001; Bukalo et al. 2007). Therefore, ECM components affect synapse development and function in complex ways, in which different ECM molecules have specific effects that are likely mediated by distinct receptors.

CONCLUDING REMARKS

The genome of mammals encodes a vast range of different ECM glycoproteins that affect nearly all aspects of nervous system development and function. Although substantial progress has been made to define the functions of specific ECM molecules in the nervous system, many challenges remain. For example, which mechanisms control the composition and structure of ECM assemblies in different parts of the nervous system? How do these assemblies affect the activity of secreted growth factors

and morphogens, and how do cells integrate information provided by complex ECM mixtures? Finally, how does the three-dimensional ECM architecture and its mechanical properties affect cell behavior? Advances in genomics, proteomics, genetics, and systems level approaches will undoubtedly help provide answers to these questions.

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