Extracellular Matrix Functions During Neuronal Migration and Lamination in the Mammalian Central Nervous System

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ABSTRACT: **Extracellular matrix (ECM) glycoproteins are expressed in the central nervous system (CNS) in complex and developmentally regulated patterns. The ECM provides a number of critical functions in the CNS, contributing both to the overall structural organization of the CNS and to control of individual cells. At the cellular level, the ECM affects its functions by a wide range of mechanisms, including providing structural support to cells, regulating the activity of second messenger systems, and controlling the distribution and local concentration of growth and differentiation factors. Perhaps the most well known role of the ECM is as a substrate on which motile cells can migrate. Genetic, cell biological, and biochemical studies provide strong evidence that ECM glycoproteins such as laminins, tenascins, and proteoglycans control neuronal migration and positioning in several regions of the developing and adult brain. Recent findings have also shed important new insights into the cellular and molecular mechanisms by which reelin regulates migration. Here we will summarize these findings, emphasizing the emerging concept that ECM glycoproteins promote different modes of neuronal migration such as radial, tangential, and chain migration. We also discuss several studies demonstrating that mutations in ECM glycoproteins can alter neuronal positioning by cell nonautonomous mechanisms that secondarily affect migrating neurons.** Develop Neurobiol 71: 889–900, 2011

Keywords: **extracellular matrix; nervous system; neuronal migration**

INTRODUCTION

Critical for many aspects of nervous system development is the migration of cells from their origin of birth to defined target areas where they terminally differentiate and are integrated into neuronal circuits. Nervous system development is initiated with the formation of the neural tube, a single layered epithelium that forms during gastrulation. Neural crest cells (NCCs) emigrate from the dorsal aspect of the neural tube, disseminate throughout the developing body to defined target areas and then form various structures of the peripheral nervous system such as sensory, sympathetic, and enteric neurons. Some NCCs also generate Schwann cells, the myelinating glial cells of the periphery (Woodhoo and Sommer, 2008; Krispin et al., 2010). The central nervous system (CNS) forms from the anterior part of the neural tube where progenitor cells divide to give rise to distinct neuronal subtypes and glial cells that can migrate over large distances before they terminally differentiate (Hatten, 1999; Marín et al., 2010). Precursors for neurons are also maintained in specialized niches of the adult nervous system, such as the dentate gyrus and lateral walls of the lateral ventricles (Altman, 1962, 1963,

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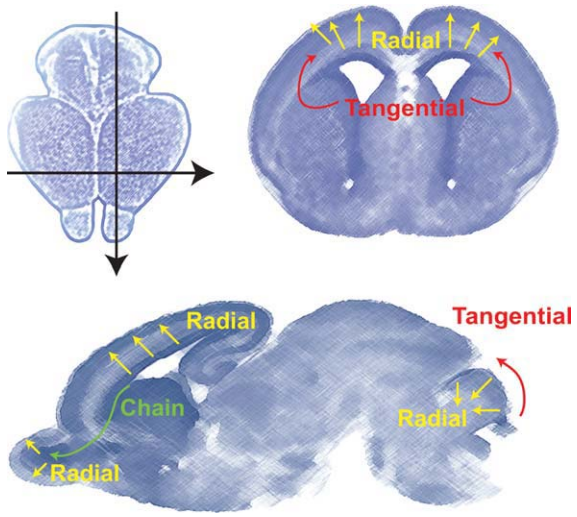

Figure 1 Principle types of cell migration in the CNS. Coronal (right arrow) and sagittal (down arrow) sections through a developing brain illustrate the primary classes of neuronal migration. In the forebrain (right), interneurons generated in the ganglionic eminences migrate dorsally and tangentially into the neocortex. Many then switch to a radial mode of migration to settle into the appropriate layers. Excitatory neurons of the neocortex also migrate radially, moving from their birthplace in the ventricular zone up toward the pial surface to form the cortical plate. A sagittal view (bottom) also illustrates radial migration in the neocortex, in addition to the different migratory routes in other brain regions. In the developing cerebellum, granule cell precursors generated in the rhombic lip first migrate tangentially within the external granular layer (EGL) to cover the surface of the cerebellar cortex. After a secondary proliferation period in the EGL, postmitotic granule cells then switch to a radial migration mode to move into the internal granular layer. In the postnatal brain, neuronal precursors born in the SVZ of the lateral ventricles migrate in chains along the RMS to the olfactory bulb, where they detach and migrate radially as individual cells.

1969; Altman and Das, 1965). These precursors generate neurons throughout life that subsequently migrate, sometimes over considerable distances, before they terminally differentiate and are integrated into preexisting neuronal circuits of the hippocampus and olfactory bulb, respectively (Lois and Alvarez-Buylla, 1994; Luskin and Boone, 1994; Curtis et al., 2009).

Within the CNS, several principle types of migration have been distinguished based on the route of migration and the ways in which cells interact during migration. Some of the best-described forms of migration are radial migration, tangential migration, and chain migration (see Fig. 1). The cerebral and cerebellar cortices provide good examples of both radial and tangential migration. Excitatory neurons of the neocortex are born in the cortical ventricular zone (VZ) (Alvarez-Buylla et al., 1990; Chanas-Sacre et al., 2000; Malatesta et al., 2000; Hartfuss et al., 2001; Noctor et al., 2001; Tamamaki et al., 2001) and migrate into the developing cortical wall in a radial direction (Rakic, 1972; Levitt and Rakic, 1980). Many, but not all, of these neurons migrate along the processes of radial glia cells (RGCs) that extend radially from the cortical VZ to the cortical marginal zone (MZ) (Morest, 1970; Rakic, 1972; Shoukimas and Hinds, 1978; Nadarajah et al., 2001; Tabata and Nakajima, 2003; Noctor et al., 2004; Rakic, 2007). Purkinje cells and granule neurons in the cerebellum employ a similar radial migration mode to move along radial glial fibers and Bergman glial fibers, respectively (Edmondson and Hatten, 1987; Gregory et al., 1988; Hatten, 1999; Wingate, 2005). During early stages of their migration, cerebellar granule neurons also undergo tangential migration as they move through the external granular layer along the surface of the developing cerebellum (Alder et al., 1996; Hatten, 1999; Wingate and Hatten, 1999; Wingate, 2005). Another well-studied example of tangentially migrating neurons is the interneurons of the neocortex. Neocortical interneurons are generated within the subcortical ganglionic eminences, from where they migrate along well-defined tangential routes into the developing cortical wall (Van Eden et al., 1989; Parnavelas et al., 1991; DeDiego et al., 1994; Tamamaki et al., 1997; Tan et al., 1998; Anderson et al., 2001; Wichterle et al., 2001). Some interneurons then switch their migratory direction and invade the cortical plate radially to populate defined neuronal cell layers, where they establish connections with excitatory neurons (Marín and Rubenstein, 2001; Ang et al., 2003; Kriegstein and Noctor, 2004; Yokota et al., 2007). Finally, neurons that are born in the subventricular zone (SVZ) of the lateral ventricles in adult animals migrate along the rostral migratory stream (RMS) into the olfactory bulbs by a special mode of migration that is called chain migration (Lois and Alvarez-Buylla, 1994; Lois et al., 1996). During chain migration, neuronal precursors are in close contact with each other and appear to migrate along the surface of other neurons (Lois et al., 1996). These migrating chains are ensheathed by a glial tube, which may provide additional guidance information for these neurons (Lois et al., 1996). Once the neurons have reached the olfactory bulb, the chains are disassembled and the neurons migrate radially to populate the olfactory bulbs (Petreanu and Alvarez-Buylla, 2002; Curtis et al., 2009). These examples highlight different modes of migration within the nervous system and indicate that neurons often switch

between distinct types of migration, suggesting that besides cell-intrinsic mechanisms, extracellular cues may be important determinants for the choice of a particular migration mode.

In the peripheral and CNSs, NCCs and neurons often migrate through territories rich in extracellular matrix (ECM) glycoproteins, indicating that the ECM may play important roles in regulating cell migration in the nervous system. In the developing and adult CNS, ECM glycoproteins are often assembled into basement membranes that demarcate tissue boundaries, but are also deposited in structurally less well-defined networks that are encountered by neurons and glia alike. In this review, we will summarize some of the findings on the roles of ECM molecules in regulating different modes of migrations in the CNS by cell autonomous and nonautonomous mechanisms, and by controlling the transitions between different migratory modes. We will focus here on the function of bona-fide ECM glycoproteins such as laminins, proteoglycans, tenascins, and reelin. Other secreted glycoproteins such as netrins and semaphorins share features with ECM glycoproteins, but have been extensively reviewed (Livesey, 1999; Bagri and Tessier-Lavigne, 2002; de Wit and Verhaagen, 2003) and will not be further considered here. Likewise, studies on the function of ECM molecules in neural crest migration have been reviewed elsewhere (Krull, 2001) and will not be addressed here.

ECM Molecules Involved in Neuronal Migration and Lamination in the Developing Neocortex

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). The BL is known to contribute critically to formation and function of the blood-brain barrier (Baeten and Akassoglou, 2011), but a number of studies have demonstrated that the BL is also crucial for layer formation in laminated brain structures. For example, removal of the pial BL leads to layering defects in the cerebellum and neocortex (Sievers et al., 1986, 1994; von Knebel Doeberitz et al., 1986; Radakovits et al., 2009). Mutations affecting laminins, a major component of the BL (Timpl et al., 1979), also cause lamination defects. Mice lacking laminin γ1 die during embryogenesis (Smyth et al., 1999), but those bearing a mutation affecting solely the laminin γ1 nidogen-binding domain survive until birth and display disruptions of the pial BL accompanied by disorganized collections of mispositioned neurons, called ectopias (Halfter et al., 2002). Inactivation of laminin γ1 in a subset of cortical neurons also causes neocortical lamination defects (Chen et al., 2009).

Additional evidence supporting a role for laminins in controlling lamination of brain structures comes from studies of their dystroglycan and integrin receptors. Human patients with mutations in enzymes that glycosylate dystroglycans exhibit brain abnormalities resulting from defects in neuronal positioning (Kobayashi et al., 1998; Yoshida et al., 2001; Beltran-Valero de Bernabe et al., 2002; Longman et al., 2003; Topaloglu et al., 2003; van Reeuwijk et al., 2005). Likewise, mice lacking dystroglycan in the CNS or bearing mutations in dystroglycan glycosyltransfserases display BL disruptions and neuronal positioning defects (Grewal et al., 2001; Michele et al., 2002; Moore et al., 2002; Qu and Smith, 2005; Qu et al., 2006). Similarly, inactivation of β1 integrins in the CNS results in abnormal neocortical lamination and fusion of cerebellar folia (Graus-Porta et al., 2001; Blaess et al., 2004).

Importantly, although disfunction in ECM glycoproteins and their receptors in the developing CNS disrupts cortical lamination, a number of studies suggest that these defects are not caused by a direct effect on migrating neurons. Instead, aberrant neuronal positioning and defective lamination are secondary consequences of disrupted interaction between radial glial cells and the BM in the cortical MZ. This has been documented most thoroughly for ECM receptors of the integrin family. Accordingly, disrupted cortical lamination in integrin β1-deficient animals is a consequence of disorganization of the pial BL and cortical MZ and detachment of RGCs from the pia (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 normally, but form ectopias near the MZ in areas where RGC endfeet have detached from the BL (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). However, deletion of β1 integrin solely in migrating neurons does not affect neuronal positioning and 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,b).

Interestingly, laminins are also found in the VZ of the developing neocortex (Campos et al., 2004; Lathia et al., 2007) and disruption of β1 integrin function specifically 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.

Some insight has been gained into the signaling pathways by which β1 integrins exert their function during the formation of neocortical cell layers. Studies with genetically modified mice have shown that inactivation of focal adhesion kinase (FAK) (Beggs et al., 2003) and integrin linked kinase (ILK) (Niewmierzycka et al., 2005), two prominent downstream effectors of β1 integrins, also cause aberrant neocortical lamination that is associated with primary defects in radial glial fibers. Although the mechanisms by which these signaling molecules act still need to be defined, it seems likely that FAK and ILK act in radial glial endfeet during assembly and maintenance of adhesion complexes at the BL, the structure and composition of which may resemble focal adhesion complexes of non-neuronal cells (Legate et al., 2006; Schaller, 2010).

While the preponderance of evidence indicates that laminins affect the motility and positioning of radially migrating neurons indirectly, some lines of evidence suggest additional roles for laminins during neuronal migration. 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. Thus, some laminin isoforms might affect cell migration more directly, possibly by binding cell surface receptors other than β1 integrins. For example, β4 and β8 integrins have been implicated in neural stem cell development, neocortical lamination and/or neuronal migration (Murgia et al., 1998; Mobley et al., 2009). In addition, β1 integrins and their laminin ligand might have more active roles in promoting modes of migration different from glial-guided radial migration. Integrin α3β1, a receptor for laminins, has been shown to regulate tangential migration of interneurons into the cortical wall (Stanco et al., 2009). In the adult brain, β1 integrins and laminins α2/α4 are required for the formation of cell chains that migrate tangentially within the RMS (Belvindrah et al., 2007a,b). Therefore, it will be interesting to determine the extent to which integrin effectors such as FAK and ILK are required cell-autonomously in tangentially migrating neurons.

Proteoglycans. Proteoglycans are a major component of the ECM in the nervous system (Gu et al., 2007, 2009; Abaskharoun et al., 2010). They consist of a core protein that is highly glycosylated by attachment of glycosaminoglycan side chains (Nadanaka and Kitagawa, 2008; Kirn-Safran et al., 2009). Expression patterns and functional studies of the core proteins and enzymes responsible for glycosaminoglycan biosynthesis indicate that proteoglycans are critical regulators of various aspects of CNS development (Kawano et al., 1995; Toba et al., 2002; Inatani et al., 2003). However, *in vivo* evidence for proteoglycans specifically regulating neuronal migration is limited. Genetic ablation of the heparan sulfate proteoglycan (HSPG) perlecan results in massive BL disruptions that cause the brain to extrude outside of the skull (exencephaly), or in neuronal ectopias in the neocortex of mutants with less severe BL defects (Costell et al., 1999; Haubst et al., 2006; Girós et al., 2007). Perlecan mutants are also microcephalic and exhibit distorted lamination of the neocortex, but these phenotypes are likely secondary to defects in neurogenesis and BL integrity (Girós et al., 2007) rather than neuronal migration *per se*. Results from various other mutant mice are consistent with the idea that HSPGs regulate neurogenesis, but are not critical for neuronal migration. For example, mice lacking the glycosyltransferase Ext1, which is essential for all heparin sulfate biosynthesis, are microcephalic as a result of abnormal neurogenesis, yet exhibit normal neocortical layering (Inatani et al., 2003). Likewise, genetic ablation of the HSPG glypican-1 causes microcephaly, but not lamination defects (Jen et al., 2009). One exception is the HSPG N-syndecan. N-syndecan knockout mice exhibit moderate neocortical lamination defects in which some upper-layer neurons are found ectopically in deep layers (Hienola et al., 2006). Since neural proliferation and differentiation occurs normally in these mutants, the positioning phenotype is thought to arise from defective radial migration of newborn neurons. Consistent with N-syndecan directly regulating migration, neurons from null mice also exhibit defective migration from the VZ into the olfactory bulb (OB) via the RMS, as well as decreased epidermal growth factor (EGF)- and heparin binding growth-associated molecule (HB-GAM)-induced migration *in vitro* (Hienola et al., 2006).

Some experimental evidence suggests that chondroitin sulfate proteoglycans (CSPGs) influence neuronal migration. The functional side chains of CSPGs comprise sulfated structures generated by a family of sulfotransferases, of which several members and their associated sulfated structures are found in the developing neocortex (Akita et al., 2008; Ishii and Maeda, 2008). When a number of sulfotransferases are knocked down individually in the neocortex by in utero electroporation of short hairpin RNAs, neuronal migration is blocked at the multipolar-to-bipolar transition while RGCs are unaffected (Ishii and Maeda, 2008), suggesting that specific sulfated side chains

are important for radial migration in the neocortex. The mechanism by which sulfation regulates migration is not known, but may involve the ability of chondroitin sulfate side chains to act as binding sites for various growth factors and guidance molecules (Emerling and Lander, 1996; Deepa et al., 2002; Maeda et al., 2006; Catlow et al., 2008). Indeed, this is the case for the regulation of tangential migration of interneurons from the ganglionic eminences into the neocortex, where chondroitin-4-sulfate acts in concert with the repulsive cue semaphorin 3A (Sema 3A) to influence the migratory route of interneurons (Zimmer et al., 2010). Secreted Sema 3A binds to chondroitin sulfate in the non-target regions flanking the migration path of cortical interneurons, thereby localizing Sema 3A to regions that should be non-permissive to the migrating interneurons (Zimmer et al., 2010). Moreover, either degradation of chondroitin sulfate side chains or disruption of Sema 3A signaling causes migrating interneurons to invade non-target regions (Zimmer et al., 2010), suggesting CSPGs and Sema 3A act in concert to repel tangentially migrating cortical interneurons. This is further supported by the ability of chondroitin sulfate to act as a repellent for interneurons *in vitro*, an effect that is enhanced by addition of soluble Sema 3A (Zimmer et al., 2010).

Reelin. Reelin is one of the most widely studied ECM molecules in the CNS. Reelin is a large ECM glycoprotein comprising an N-terminal domain with similarity to F-spondin, followed by 8 so-called reelin repeats that each contains an EGF-like repeat at its center, and a C-terminus containing a highly basic domain (D'Arcangelo et al., 1995). During development, reelin is secreted by specific cell types in several laminated brain structures, where it controls neuronal migration and the formation of cell layers. Secreted reelin binds to the transmembrane lipoprotein receptors Apoer2 and Vldlr (D'Arcangelo et al., 1999), which are expressed by migrating neurons and RGCs (Luque et al., 2003). The cytoplasmic domains of Apoer2 and Vldlr bind to the adaptor protein Dab1, which is phosphorylated by Src-family kinases upon reelin binding to its receptors (Howell et al., 1999; Arnaud et al., 2003). Phosphorylated Dab1 recruits several 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), thereby initiating diverse signaling pathways downstream of reelin. Mutations in the reelin signaling pathway in humans cause lissencephaly (smooth brain surface) and cerebellar hypoplasia (underdevelopment of the cerebellum) (Hong et al., 2000), and in mice cause the *reeler* phenotype characterized by widespread neuroanatomic defects. The *reeler* cerebellum is significantly reduced in size and lacks normal folia and cell layers, resulting in severe motor defects that include ataxia and tremors (Mariani et al., 1977; Goffinet, 1983; Goffinet et al., 1984). Cell layers are also disrupted in both the hippocampus and neocortex of *reeler* mutants (Caviness and Korde, 1981; Caviness, 1982; Hoffarth et al., 1995), indicating that the reelin pathway is essential for neocortical, hippocampal, and cerebellar lamination. Neocortical lamination defects in the *reeler* mutant are characterized by failure of newborn neurons to move past their predecessors, creating a disorganized cytoarchitecture that lacks the typical inside-out layering pattern of the normal neocortex. Since the number and types of neocortical neurons generated appears to be conserved in the *reeler* mutant (Caviness, 1973), it is thought that the primary function of reelin signaling is to control neuronal migration.

A number of contrasting models have been proposed to explain the cellular mechanisms by which reelin regulates migration and positioning during neocortical development. For example, reelin has been proposed to act as 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 radially migrating neurons. However, a number of recent studies suggest that none of these models sufficiently explain reelin function (Magdaleno et al., 2002; Jossin et al., 2004; Belvindrah et al., 2007a,b). Furthermore, these models have mostly been based on the assumption that all radially migrating neurons move along RGC fibers, but time-lapse imaging experiments demonstrate that radial migration is more complex than originally appreciated (see Fig. 2). After leaving the VZ, newly born neurons adopt a multipolar morphology and migrate through the SVZ independently of RGC processes (Tabata and Nakajima, 2003). In the intermediate zone (IZ), migrating neurons assume a bipolar morphology, attach to RGCs and migrate into the CP by glia-guided locomotion (Noctor et al., 2004). Near the MZ, migrating neurons attach their leading processes to the MZ and switch to glia-independent somal translocation (Nadarajah et al., 2001). During somal translocation, neurons shorten their leading processes to move their cell bodies to their final positions. Importantly, during early stages of neocortical development the CP is sufficiently thin that migrating neurons can extend leading processes to the MZ and migrate by glia-independent somal translocation alone (Morest, 1970; Shoukimas and Hinds, 1978; Nadarajah et al., 2001).

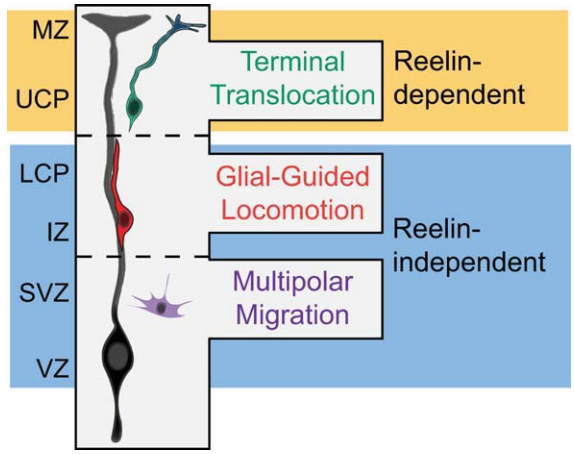

Figure 2 Modes of radial migration in the neocortex. Postmitotic neurons generated by RGCs (black) or intermediate progenitors (not shown) adopt a multipolar morphology and move through the SVZ by glia-independent multipolar migration (purple cell). In the IZ, migrating neurons assume a bipolar morphology, attach to RGCs and migrate into the CP by glia-guided locomotion (red cell). Near the MZ, migrating neurons attach their leading processes to the MZ and switch to glia-independent somal translocation (green cell). During terminal somal translocation, neurons shorten their leading processes to move their cell bodies to their final positions. Terminal translocation requires reelin signaling, whereas multipolar migration and glia-guided locomotion are independent of the reelin pathway. VZ, ventricular zone; SVZ, subventricular zone; IZ, intermediate zone; LCP, lower cortical plate; UCP, upper cortical plate; MZ, marginal zone.

Additionally, some neurons inherit the radial processes of their RGC precursors and translocate their cell bodies along these processes to settle in appropriate cell layers (Miyata et al., 2001).

Taking into account these observations that cortical neurons migrate by glia-dependent and -independent modes, an alternative model has been proposed for reelin function: that reelin causes detachment of neurons from RGCs and stimulates glia-independent somal translocation (see Fig. 2; Nadarajah et al., 2001; Luque et al., 2003; Cooper, 2008). Recently, our laboratory has provided experimental evidence in strong support of this model (Franco et al., 2011). Using timed inactivation of the reelin effector Dab1, we showed that reelin signaling is essential for glia-independent somal translocation of both early- and late-born neurons, but is dispensable for glia-guided motility (see Fig. 2). Furthermore, a *reeler* phenotype is also observed when Dab1 is deleted in neurons alone without affecting RGCs, demonstrating that cell-autonomous neuronal deficits in somal translocation are sufficient to disrupt completely layer formation. This function of reelin signaling during somal translocation is accomplished at least in part by a Rap1/cadherin pathway downstream of Dab1, which stabilizes leading neuronal processes that are attached to the cortical MZ (Franco et al., 2011). However, it is likely that this is not the only pathway involved, as glia-independent migration also requires cell body translocation and termination of migration. Studies demonstrating cross-talk between reelin and other well-known signaling pathways associated with Lis1 (Assadi et al., 2003), 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 the reelin signaling pathway belongs to a large and complex developmental paradigm. This complexity is also reflected in the fact that some components of the reelin pathway, for example the Apoer2 and Vldlr receptors, have different levels of importance in cerebellar, hippocampal and neocortical development (Trommsdorff et al., 1999; Benhayon et al., 2003; Beffert et al., 2006; Hack et al., 2007; Forster et al., 2010). Thus, it is likely that the cellular and molecular mechanisms of reelin function during development of different structures in the CNS have only begun to be elucidated.

Tenascins. Several members of the tenascin family of ECM glycoproteins are expressed in the developing CNS. Tenascin-C (TN-C) is found in regions of active neurogenesis (Bartsch et al., 1992; Jankovski and Sotelo, 1996) and is particularly prominent on radial and Bergmann glia in the neocortex and cerebellum (Grumet et al., 1985; Crossin et al., 1986; Yuasa, 1996; Yuasa et al., 1996). Tenascin-R (TN-R) is expressed by myelinating glia, subsets of interneurons and in the deepest layers of the OB (Saghatelyan et al., 2004; Huang et al., 2009). Tenascin-X has recently been shown to be expressed in the leptomeninges and choroid plexus (Imura and Sato, 2008, 2009). In neural stem cells (NSC) in culture, TN-C facilitates the switch from production of neuronal to glial progenitors (Garcion et al., 2004; Liao et al., 2008), while TN-R inhibits migration of NSC-derived neurons (Huang et al., 2009). The importance of tenascins for neuronal migration *in vivo* is less clear. While there is little evidence for a role of tenascins in regulating the radial migration of cortical neurons or tangential migration of interneurons in the developing and adult brain, TN-R has been shown promote detachment of chain-migrating neuroblasts in the RMS and their migration within the OB (Saghatelyan et al., 2004). Interestingly, OB expression of TN-R is activity-dependent and reduced upon odor depriva-

tion (Saghatelyan et al., 2004). Taken together, these findings suggest that a least one tenascin, TN-R, has a specific role in controlling the switch from tangential migration in the RMS to radial migration in the OB. At present, little is known, however, about the mechanisms and signaling pathways by which TN-R affects the migrating neurons.

Thrombospondin Type-1 Repeat Proteins. Proteins containing thrombospondin type-1 repeats (TSR), known as the TSR superfamily (Adams and Tucker, 2000), are another class of ECM molecules expressed widely during embryonic development. The TSR superfamily comprises thrombospondins, F-spondins, Unc5, SCO-spondin, and members of the ADMATS and semaphorin five families, many of which are expressed in the developing brain, spinal cord and peripheral nerves. Expression patterns and *in vitro* studies of TSR-containing proteins suggest functions in neuronal and axonal motility, although evidence that TSR family members regulate neuronal migration *in vivo* is sparse. One exception is thrombospondin-1 (THBS-1), which regulates chain migration of interneuron precursors migrating in the postnatal RMS to the OB (Blake et al., 2008). Although THBS-1 knockout mice do not have widespread overt brain abnormalities (Lawler et al., 1998), they do exhibit a widening of the RMS and subsequent reduction in the number of neuronal precursors that reach the OB (Blake et al., 2008). Consistent with this phenotype, THBS-1 is expressed in the postnatal SVZ and along the RMS and increases the stability of neuronal precursor chains migrating *in vitro* (Blake et al., 2008). Interestingly, THBS-1 was shown to be a novel ligand of the reelin receptors ApoER2 and Vldlr, and to induce phosphorylation of the reelin downstream effector Dab1 (Blake et al., 2008). However, the effects of THBS-1 on chain migration appear to be independent of and opposite those of reelin, which promotes disassembly of neuroblast chains (Hack et al., 2002). It will be of interest to both the THBS-1 and reelin fields to elucidate the molecular pathways by which these two molecules elicit distinct cellular behaviors via the same immediate downstream effectors.

CONCLUDING REMARKS

The mammalian genome encodes a vast array of ECM glycoproteins that affect nearly all aspects of nervous system development and function, including neuronal migration and lamination. Several conclusions can be drawn regarding the role of ECM molecules during migration and lamination. First, a particular ECM glycoprotein can affect different modes of migration, such as radial, tangential, and chain migration, in distinct ways. For example, laminins regulate radial migration in the embryonic neocortex and tangential migration in the RMS of adult mice. However, radially migrating neurons do not require laminins directly for their motility. Instead, laminins mediate attachment of RGC endfeet at the cortical marginal zone, thereby regulating the assembly and maintenance of the glial scaffold along which the neurons migrate. In contrast, laminins have a more direct role in the RMS, where they directly stimulate the formation of migratory cell chains. Interestingly, different ECM molecules can control different types of migration via the same set of downstream effectors, as evidenced by THBS-1 and reelin controlling chain migration and radial migration, respectively, both via phosphorylation of Dab1. Second, different ECM molecules can control specific aspects of neuronal migration. This is highlighted by studies on the functions of CSPGs and reelin in radially migrating neurons in the neocortex, where the former regulate the multipolar-to-bipolar transition while the latter regulates glia-independent somal translocation. Finally, ECM glycoproteins often function together with other signaling molecules, as highlighted by the observation that CSPGs and Sema 3A act in concert to repel tangentially migrating cortical interneurons.

Of course, many challenges still remain for future study on ECM functions during neuronal migration and lamination in the CNS. For example, which mechanisms control the composition and structure of ECM assemblies in different parts of the nervous system? How do these distinct compositions affect the motility of neurons migrating by different modes and the transitions between these modes? What are the molecular signaling mechanisms by which neurons integrate instructional information provided by complex ECM assemblies? Finally, how do the mechanical properties of three-dimensional ECM structures regulate neuronal migration? Advances in genomics, proteomics, genetics, and systems level approaches will undoubtedly help provide answers to these questions.

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