

FEATURE ARTICLE

Role of Integrins in the Development of the Cerebral Cortex

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Spatial and temporal changes in expression and function of integrin receptors in the developing cerebral wall parallel neurogenesis, radial glial differentiation, neuronal migration and the emergence of neuronal layers in the cerebral cortex. The distinct outcomes of integrin and extracellular matrix ligand mutations underscore the dynamic role they play in these processes during corticogenesis. The changing patterns of adhesive interactions mediated by integrins and their ligands across the cerebral wall during embryogenesis may set in motion developmental programs needed for progressive acquisition of different neuronal or glial phenotypes in the cerebral cortex. Here we discuss the role of integrins during cortical layer formation.

Introduction

The functionally critical laminar organization of the cerebral cortex emerges as a result of appropriate migration and placement of neurons during cortical development. Post-mitotic neurons migrate radially from the ventricular zone towards the pial surface, past previously generated neuronal layers (Rakic, 1971, 1972) to reach the top of the cortical plate, where they terminate their migration and assemble into layers with distinct patterns of connectivity. Radial migration of cortical neurons can occur in two distinct modes: locomotion or somal translocation (Nadarajah *et al.*, 2001, 2002). In contrast, populations of GABAergic interneurons, originating from the lateral ganglionic eminence, migrate tangentially into the neocortex (Anderson *et al.*, 1997; Letinic and Rakic, 2001; Maricich *et al.*, 2001). Some of these neurons migrate ventrally towards the cortical ventricular zone prior to radial migration towards the pial surface (Nadarajah *et al.*, 2002). Specific cell-cell recognition and adhesive interactions between neurons, glia and the surrounding extracellular matrix (ECM) are likely to play an important role in distinct patterns of neuronal migration, placement and differentiation within the cortex.

The integrin family of cell surface receptors is a major mediator of cell-cell and cell-ECM interactions. Integrins can efficiently transduce signals to and from the external cell environment to the intracellular signaling and cytoskeletal compartments, while modulating signaling cascades initiated by other cellular receptors. Functional integrin receptors are formed by membrane spanning heterodimers of α and β subunits. There are at least 18 α and 8 β subunits that can form >20 different integrin receptors (Juliano, 2002). The α subunits play a determinant role in ligand specificity and physiological response of the individual integrin receptor. ECM ligands and other cell surface molecules, such as receptor tyrosine kinases (RTKs), G-protein coupled receptors (GPCRs), growth factor receptors, L1-CAM, or members of the tetraspanin family of proteins, can bind to or associate with integrin receptors. These interactions activate, directly or indirectly, intracellular signal transduction cascades involving focal adhesion kinase (FAK), the Src family kinase *fyn*, MAP kinase, protein phosphatases,

SH2-SH3 adaptors, Rho-family GTPases and phospholipid mediators (Clark and Brugge, 1995; Boudreau and Jones, 1999; Giancotti and Ruoslahti, 1999; Juliano, 2002). The activation of these signaling cascades ultimately results in a number of changes of integrin characteristics, such as spatial localization, internalization, ligand affinity, intracellular association with signaling proteins, interaction with the cytoskeleton and, finally, transcriptional modulation.

Differential Distribution of Integrin Receptors and their Ligands in the Developing Cerebral Wall

During the course of cortical development, spatial and temporal expression of different integrin subunits and their ligands suggests a critical role in cortical layer formation and plasticity. As summarized in Table 1, the expression of integrin receptor subunits in the developing cortex can be grouped into three different categories: ubiquitous; spatially and temporally regulated; and cell-type specific.

Of the β integrins, β_1 and β_5 integrin are expressed in all regions of the developing cerebral wall and their expression persists in the adult cortex (Cousin *et al.*, 1997; Pinkstaff *et al.*, 1999; Graus-Porta *et al.*, 2001). β_2 , β_3 and β_4 integrins are not expressed in the cerebral cortex (Pinkstaff *et al.*, 1999). β_6 integrin was observed in the adult cortex primarily on neurons and oligodendrocytes (Cousin *et al.*, 1997), whereas β_8 is diffusely distributed throughout the neuropil (Nishimura *et al.*, 1998). α_1 and α_3 integrins are expressed across the developing cerebral wall (Gardner *et al.*, 1999; Dulabon *et al.*, 2000), but in the adult cortex, α_1 integrin appeared prominently only in layer V, whereas α_3 integrin is expressed in layers II-VI (Pinkstaff *et al.*, 1999; Rodriguez *et al.*, 2000). α_2 integrin is not detected in the mature brain (Pinkstaff *et al.*, 1999). α_4 integrin is expressed in layers II and III of the cerebral cortex (Pinkstaff *et al.*, 1999). In contrast, α_5 integrin can be found throughout the cortex on cell bodies and apical dendrites (Bi *et al.*, 2001). α_6 integrin is highly expressed in the ventricular zone and cortical plate of the developing cerebral wall (Georges-Labouesse *et al.*, 1998) and its expression is restricted to layer VI in the mature cortex. α_7 integrin is diffusely expressed, primarily in the adult cortex (Pinkstaff *et al.*, 1999). α_8 integrin appears in dendrites of layer V-VI of the cerebral cortex as early as embryonic day 16 (Einheber *et al.*, 1996; Pinkstaff *et al.*, 1999). α_v integrin is expressed on radial glia fibers of the developing cerebral cortex and in glial fibrillary acidic protein (GFAP) positive astroglial cells in mature cortex (Hirsch *et al.*, 1994; Anton *et al.*, 1999). Developmental changes in the cell surface integrin repertoire and function may modulate neural cell behavior in the developing cerebral cortex by altering the strength and ligand preferences of cell-cell adhesion during development.

Expression of integrins occurs in a continuously changing ligand environment during corticogenesis. These ligands are ECM

Table 1
Distribution of integrin subunits in cerebral cortex

	α_1	α_2	α_3	α_4	α_5	α_6	α_7	α_8	α_9	α_{10}	α_v	β_1	β_2	β_3	β_4	β_5	β_6	β_7	β_8
Dev. cerebral wall																			
Ventricular zone	+	-	+	n.d.	n.d.	+	n.d.	+	+	-	+	+	-	-	n.d.	+	-	-	n.d.
Intermediate zone	+	-	+	n.d.	n.d.	-	n.d.	+	+	-	+	+	-	-	n.d.	+	-	-	n.d.
Cortical plate	+	-	+	n.d.	n.d.	+	n.d.	+	-	-	+	+	-	-	n.d.	+	-	-	n.d.
Cortical layers	5	-	2-6	2-3	2-6	6	2-6	5-6	2-6	n.d. ^a	2-6	1-6	-	-	-	1-5	1-6	-	1-6 ^b
Cell types																			
Radial glia	+	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	+	n.d. ^a	+	+	-	-	-	+	n.d.	-	n.d.
Neurons	+	-	+	+	+	+	+	+	-	n.d. ^a	-	+	-	-	-	+	+	-	+
Oligodendroglia	-	-	-	-	-	+	-	+	+	n.d. ^a	+	+	-	-	-	+	+	-	+
Astrocytes	+	-	-	n.d.	+	+	n.d.	n.d.	+	n.d. ^a	+	+	-	-	-	+	n.d.	-	+

n.d., not determined.

^amRNA expression in adult brain.

^bDiffuse throughout neuropil.

components, such as fibronectin, tenascin, thrombospondin, glycosaminoglycans, laminins, reelin and integrin-associating molecules such as CD9 and L1-CAM (O'Shea *et al.*, 1990; Sheppard *et al.*, 1991; Dulabon *et al.*, 2000; Schmid and Maness, 2001). Laminin, though expressed primarily in the basement membrane associated with the pia matter of the cerebral cortex, is also thought to be present in the ventricular zone, subplate and marginal zone of the developing cerebral wall. Its expression along routes of migrating neurons implies that glial laminin may serve as a substratum for neuronal attachment (Liesi, 1990; Hunter *et al.*, 1992). Laminin-2 (merosin), which binds to β_1 integrin and whose deficiency causes muscular dystrophy in humans, is distributed punctately on cortical neuronal processes. Fibronectin is initially found in the ventricular zone throughout the telencephalic vesicle, where it may support cell division and cell fate during neurogenesis. Eventually, fibronectin is expressed in radial glia, migrating neurons and cortical plate neurons during layer formation (Sheppard *et al.*, 1991, 1995). Both laminin and fibronectin may associate with chondroitin-sulfate proteoglycans (CSPGs) and modulate neuronal adhesion (Snow *et al.*, 1996). CSPGs are highly expressed in the ventricular zone, preplate and preplate derivatives during cortical development. *In vitro* assays with thalamic neurons suggest that CSPGs may constitute barriers for neuronal migration and neurite extension, with different CSPGs functioning either as attractants or repellants (Emerling and Lander, 1996). Secondary deficits in CSPG expression in the developing cortex in mice deficient in MARCKS (a neural substrate for protein kinase C) result in widespread neuronal ectopia in the forebrain (Blackshear *et al.*, 1997). Expression of both fibronectin and CSPGs declines rapidly as the cortex matures. In contrast, tenascins are not expressed in cortex until late in development, when radial glia start to differentiate into astrocytes (Sheppard *et al.*, 1991). The significance of the assembly of different ECM proteins in the basement membranes of the developing cortex is evident in the disrupted corticogenesis seen in mice deficient in the ECM components perlecan (Costell *et al.*, 1999), laminin α_5 chain (Miner *et al.*, 1998), or laminin γ_1 nitrogen binding site (Halfter *et al.*, 2002). They are characterized by abnormal basal lamina assembly, altered radial glial development and dysplasia of neurons in the developing cortical plate. In humans, secondary deficiencies in basal lamina assembly may lead to cobblestone lissencephaly, where gaps in basal lamina enable neurons to migrate out of the developing brain to form ectopias (Buxhoeveden and Casanova, 2002; Moore *et al.*, 2002; Olson and Walsh, 2002).

Integrins are also capable of synergizing with other cell

surface receptor systems in order to finely modulate a cell's adhesive behavior in response to multiple environmental cues. Members of the tetra-membrane-spanning (tetraspanin) protein superfamily, including Tspan-5, CD9, CD63, CD81, CD82 and CD151, can associate with integrins and regulate their activity (Berditchevski and Odintsova, 1999; García-Frigola *et al.*, 2001). Low levels of CD9 are diffusely expressed in the developing brain in cell types including neuronal progenitor cells, astrocytes, microglia and oligodendroglia. CD9 associates with β_1 integrins to modulate cell motility and adhesion. CD63 is expressed on both CNS neurons and astrocytes, whereas CD81 is localized to the ependyma, choroid plexus, astrocytes and oligodendrocytes of the developing cortex (Kelic *et al.*, 2001). CD151 is present only at very low levels in the developing brain (Hasegawa *et al.*, 1997). β_1 integrins can also interact with the membrane spanning neural cell adhesion molecule L1-CAM (Silletti *et al.*, 2000), which is expressed on neurons in the intermediate and marginal zones and the subplate of developing cortex (Demyanenko *et al.*, 1999). L1-integrin interactions are critical for modulation of neuronal migration during development (Thelen *et al.*, 2002).

The combination of distinct integrin receptor subunit expression and changing availability of types and levels of ligands may enable developing cortical neural cells to display different adhesive properties and activate different intracellular signal transduction pathways specific to particular integrin-ligand combinations. Distinct changes in neuronal function, shape, process extension, orientation, neuron-glia interactions and glial differentiation thus generated may lead ultimately to the emergence of neuronal layers in the cerebral cortex. This is evident in the cortical phenotypes of different integrin mutants.

Cortical Abnormalities in Mice Deficient in Integrin Subunits

Different α integrin subunits dimerize preferentially or exclusively with β_1 integrin, which is ubiquitously expressed in the developing cerebral cortex. Knockout mice have been created for nine of the α subunits that can dimerize with β_1 . Of these, early embryonic lethality (before E9) of α_2 and α_5 mutants precludes analysis of cortical development. Cortical phenotypes of α_1 , α_4 , α_7 , α_8 and α_9 deficient mice are either normal or yet to be characterized carefully. However, distinct cortical malformations were found in α_3 , α_6 and α_v knockout mice (Table 2).

Mice homozygous for a targeted mutation in the α_3 integrin gene die soon after birth with severe defects in the development of the cerebral cortex, lungs, skin and kidneys (Kreidberg *et al.*, 1996; Anton *et al.*, 1999). In the cerebral cortex, laminar

Table 2

Phenotypes of integrin deficient mice

Genotype	Phenotype	References
$\alpha_1^{-/-}$	No overt cortical phenotype Deficits in collagen synthesis and collagen-mediate cell proliferation	(Pozzi <i>et al.</i> , 1998; Gardner <i>et al.</i> , 1999)
$\alpha_2^{-/-}$	Die around E5.5	(Sheppard, 2000)
$\alpha_3^{-/-}$	Abnormal neuronal migration and laminar organization of cortex Abnormal radial glia differentiation Neuron–glia interaction impaired Abnormal kidney and lung development	(Kreidberg <i>et al.</i> , 1996; Anton <i>et al.</i> , 1999)
$\alpha_4^{-/-}$	Die at E11–14 from detachment and rupture of epicardium and coronary arteries ^a	(Yang <i>et al.</i> , 1995)
$\alpha_5^{-/-}$	Die at E10–11 due to defects in posterior trunk, yolk sac and mesodermal structures ^a	(Yang <i>et al.</i> , 1993)
$\alpha_6^{-/-}$	Lethal at birth Disorganized cortical plate Ectopic neuroblasts in embryonic cortex Disorganized basal lamina assembly	(Georges-Labouesse <i>et al.</i> , 1996, 1998)
$\alpha_3, \alpha_6^{-/-}$	No neural tube closure Abnormal basal lamina assembly Multiple neuroblast ectopias in cortex	(De Arcangelis <i>et al.</i> , 1999)
$\alpha_7^{-/-}$	Muscular dystrophy shortly after birth PNS axonal outgrowth and target reinnervation impaired ^a	(Mayer <i>et al.</i> , 1997; Werner <i>et al.</i> , 2000)
$\alpha_8^{-/-}$	Abnormal kidney development ^a	(Muller <i>et al.</i> , 1997)
$\alpha_9^{-/-}$	Death from bilateral chylothorax at 6–12 days of age ^a	(Huang <i>et al.</i> , 2000b)
$\alpha_v^{-/-}$	80% die before E11.5, rest die at birth Intra-cortical and gastrointestinal hemorrhage	(Bader <i>et al.</i> , 1998)
$\beta_1^{-/-}$	Lethal at E5.5	(Fassler and Meyer, 1995; Stephens <i>et al.</i> , 1995)
β_1 cond. $^{-/-}$	Disrupted cortical laminar organization Radial glia endfeet and pial basement membrane abnormalities	(Graus-Porta <i>et al.</i> , 2001)
$\beta_2^{-/-}$	Leukocyte and T-cell abnormalities ^a	(Scharffetter-Kochnek <i>et al.</i> , 1998)
$\beta_3^{-/-}$	Placental defects and pre-natal hemorrhages ^a	(Hodivala-Dilke <i>et al.</i> , 1999)
$\beta_4^{-/-}$	Lethal at birth Disorganized cortical plate with neuronal ectopias Basal lamina disorganization	(Murgia <i>et al.</i> , 1998)
$\beta_5^{-/-}$	Normal	(Huang <i>et al.</i> , 2000a)
$\beta_6^{-/-}$	Inflammatory baldness and lung inflammation ^a	(Huang <i>et al.</i> , 1996)
$\beta_7^{-/-}$	Normal, except abnormal development of Peyer's patches ^a	(Wagner <i>et al.</i> , 1996)

^aTelencephalic or cortical phenotype not reported.

organization of neurons is lost and neurons are positioned in a disorganized pattern. α_3 integrin modulates neuron–glia recognition cues during neuronal migration and maintains neurons in a gliophilic mode until glial-guided neuronal migration is over and layer formation begins (Anton *et al.*, 1999). The gliophilic to neurophilic switch in the adhesive preference of developing neurons and premature radial glia differentiation in the absence of α_3 integrin were hypothesized to underlie the abnormal cortical organization of α_3 integrin mutant mice. Reelin, an ECM protein released from the layer I cortical neurons, has been shown to interact with $\alpha_3\beta_1$ integrin by several independent methods (Dulabon *et al.*, 2000). During glial-guided migration to the cortical plate, neuronal α_3 integrin may interact with glial cell surface molecules such as laminin-2 or fibronectin and at the top of the cortical plate, the ligand preference of α_3 integrins may change from radial glial cell surface ECM molecules to reelin. Proteolytic activity of reelin may also degrade fibronectin or laminin at the top of the cortical plate (Quattrocchi *et al.*, 2002). Different ligands or ligand concentration can determine the surface levels of integrins by regulating the rate at which integrin receptor is removed from the cell surface. Ligands can also regulate polarized flow of integrins towards or away from growth cone membranes (Lawson and Maxfield, 1995; Condic and Letourneau, 1997; Grabham and Goldberg, 1997). Thus, changes in the availability, function and ligand preference of α_3 integrins may trigger the decrease in a migrating neuron's bias for gliophilic adhesive interactions and promote neurophilic

interactions needed for neurons to detach from radial glial guides and organize into distinct layers. Interestingly, deficiencies in α_3 integrin ligands, laminin-2 and reelin lead to cortical anomalies such as polymicrogyria or lissencephaly in humans (Sunada *et al.*, 1995; Hong *et al.*, 2000).

In contrast to α_3 integrin, α_v integrins appear to provide optimal levels of basic cell–cell adhesion needed to maintain neuronal migration and differentiation. Substantial disruption of cellular organization in cerebral wall and lateral ganglionic eminence is seen at E11–12 in α_v null mice. Extensive intracerebral hemorrhage in α_v deficient mice, beginning at E12–13, prevents further evaluation of cortical development in late surviving (until birth) α_v null mice (Bader *et al.*, 1998). α_v integrins expressed on radial glial cell surface can potentially associate with at least five different β subunits: β_1 , β_3 , β_5 , β_6 and β_8 . Adhesive interactions involving fibronectin, vitronectin, tenascin, collagen, or laminin, ECM molecules that are found in the developing cerebral wall, can be mediated through these α_v containing integrins (Moyle *et al.*, 1991; Hirsch *et al.*, 1994). Both transient cell–matrix interactions and cell anchoring mechanisms that are mediated by different α_v containing integrins and their respective ligands are likely to modulate the process of glial development, neuronal translocation and differentiation in cerebral cortex.

In addition to α_3 integrin, laminin isoforms in the developing cerebral cortex can also interact with α_6 integrin dimers (Georges-Labouesse *et al.*, 1998). α_6 null mice die at birth

(Georges-Labouesse *et al.*, 1996), with abnormal laminar organization of the cerebral cortex and retina (Georges-Labouesse *et al.*, 1998). Chain migration of neurons in the post-natal rostral migrational stream, from the subventricular zone to the olfactory bulb, also depends on α_6 integrin signaling (Jacques *et al.*, 1998). Analysis of α_6 integrin deficient embryos revealed ectopic neuronal distribution in the cortical plate, protruding out to the pial surface. The cortical plate was further disorganized by wavy neurite outgrowth of ectopic neuroblasts. Coinciding abnormalities of laminin synthesis and deposition also occur in the mutant brain. Persistence of glial laminin throughout development may have prevented neuroblasts from appropriately arresting their migration in the developing cortical plate in α_6 null mice. Since cerebral cortex still formed in α_6 mutants, albeit abnormally, other integrin dimers may have overlapping functions with α_6 integrins during early cortical development. The similarities in the ligand preferences of α_3 and α_6 integrins are suggestive of potential functional overlap. The severe and novel cortical abnormalities in α_3, α_6 double knock-out mutants, i.e. disorganization of cortical plate with large collection of ectopias, aberrant basal lamina organization and abnormal choroid plexus, support a synergistic role for α_3 and α_6 integrins during cortical development (De Arcangelis *et al.*, 1999). Deficiency in β_4 integrin, which only associates with α_6 , leads to an identical cortical phenotype. Mutations in either α_6 or β_4 integrin in humans results in skin blistering (epidermolysis bullosa). However, the brain phenotype of the affected patients is unknown.

β_1 integrin in the cerebral cortex can dimerize with at least 10 different α subunits, including α_3 , α_6 and α_v . Most of the cortical specific α subunits seem to dimerize only with β_1 integrin and β_1 integrin deficiency leads to lethality around E5.5 (Fassler and Meyer, 1995; Stephens *et al.*, 1995). In an attempt to study the role of β_1 integrin in the developing cortex, β_1 integrin-floxed mice were crossed with nestin-cre mice, resulting in widespread inactivation of β_1 integrins in cortical neurons and glia from \sim E10.5 (Graus-Porta *et al.*, 2001). Cortical layer formation is disrupted in these mice, in large part as a result of defective meningeal basement membrane assembly, marginal-zone formation and glial end feet anchoring at the top of the cortex. BrdU birthdating studies suggest that glial-guided neuronal migration is not significantly impaired. However, perturbed radial glial end feet development may contribute to the defective placement of neurons in the cortex. Determination of the onset of radial glial abnormalities in β_1 integrin deficient cortex (i.e. whether they occur prior to E18) and the use of quantitative bioassays for neuron-radial-glia interactions may clarify whether lack of pial anchoring of radial glial cells in β_1 deficient cortex affects their ability to function concurrently as neuronal precursors and neuronal guides and contributes to the observed cortical phenotype. Furthermore, cortical neurons in β_1 deficient mice invade the marginal zone in areas devoid of reelin producing Cajal-Retzius (CR) cells and in regions with CR cell ectopias, accumulate underneath them. Invasion of neurons only into areas devoid of reelin producing CR cells supports a role for reelin in normal termination of neuronal migration. Since $\alpha_3\beta_1$ integrin has been shown to regulate reelin mediated detachment from glial guides, it was expected that β_1 deficient neurons would continue to migrate past CR cell ectopias, instead of accumulating underneath them (Graus-Porta *et al.*, 2001). However, the absence of this phenotype indicates redundant functions for other known or novel reelin receptors in neuronal placement in the β_1 deficient cortex. Alternatively, since β_1 integrin is thought to modulate the gliophilic-neurophilic adhesive balance *in vitro* (Galileo *et al.*, 1992; Anton *et al.*, 1999;

Hatten, 1999) and reelin mediated radial glial differentiation (Forster *et al.*, 2002), β_1 deficient neurons may have accumulated under CR cell ectopia due to an inability to regulate appropriate neuron-neuron or neuron-glia adhesion in response to reelin in the absence of β_1 integrin. Given the varied cortical phenotypes of α_3 , α_6 and α_v null mice and the ability of β_1 to associate with multiple other cortical α integrins, it is surprising that the β_1 conditional phenotype is not more severe. This may reflect the transdominant, transnegative, or compensatory influences distinct integrin receptor dimers exert over each other and the ECM ligands in the developing cerebral cortex. For example, an increase in fibronectin and collagen IV activity is seen in α_3 null keratinocytes (Hodivala-Dilke *et al.*, 1998). *In vitro*, binding of a ligand to a signal transducing integrin can initiate a unidirectional signaling cascade affecting the function of a different target integrin in the same cell (Simon *et al.*, 1997; Blystone *et al.*, 1999). Elucidation of whether such integrin crosstalk regulates patterns of neuronal development and interactions with specific ECM molecules in the developing cortices of various integrin null mice will be informative in understanding the role of integrins in corticogenesis.

Pathways that are hypothesized to be activated downstream of integrins in developing cortical neurons include the CDK5/p35 complex and dab1. Mutant mice deficient in p35, CDK5, or dab1 exhibit major defects in laminar organization of the cerebral cortex (Feng and Walsh, 2001; Olson and Walsh, 2002). CDK5 is a neuron-specific cyclin dependent kinase, whose activation is dependent on association with its p35 cofactor (Tsai *et al.*, 1994). The p35/CDK5 complex has been shown to interact with Rac, a member of the Rho family of GTPases, the Lis1-interacting protein NUDEL and the microtubule-associated protein tau (Nikolic *et al.*, 1998; Feng *et al.*, 2000; Niethammer *et al.*, 2000), thus providing several avenues through which it may affect cytoskeletal reorganization involved in distinct aspects of neuronal development. dab1 is a cytoplasmic adapter protein containing a PTB domain, which may interact with the NPxY motif in the cytoplasmic domains of β_1 receptors. Filamin1, a cytoskeletal protein whose mutation results in periventricular heterotopia, can also bind to β_1 and β_2 integrins (Sharma *et al.*, 1995; Loo *et al.*, 1998). Furthermore, integrin signaling can also switch distinct responses of migration modulating growth factors, such as neuregulin (NRG) (Colognato *et al.*, 2002). At present, the mechanisms of activation and regulation of these signaling pathways downstream of integrins during cortical development remain incompletely understood.

Concluding Remarks

Development of cortical cells occurs as they adhere to a diverse array of ECM matrix ligands via multiple integrins. Glial progenitors and neurons undergo distinctly different sets of adhesive interactions with their environment during corticogenesis. This may serve as an essential mechanism for the acquisition of distinct cortical neuronal or glial phenotypes. The functional hierarchy and diversity observed within integrins during the process of laminar organization in the cerebral cortex may have resulted from their effects on ECM organization, differences in their modes of association with the cytoskeleton, interactions with non-ECM neuronal cell surface molecules such as tetraspanin proteins or EGF receptors, integrin crosstalk and the distinct intracellular signaling cascades induced in response to ligand binding. Molecular analysis of human and mouse cortical malformations has uncovered several critical links between ECM, integrins and downstream signaling molecules during corticogenesis. Further profiling of developmental distribution

of integrin receptors using BAC-mediated transgenic approaches (Heintz, 2001), generation of mutant lines lacking multiple, functionally related integrin receptors and the use of cell type specific or inducible gene manipulation methods will enable the determination of the relative contributions of different integrins to the assembly of the cerebral cortex.

Notes

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