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Neuronal Migration in the Developing Brain

Franck Polleux and E. S. Anton

INTRODUCTION

The way in which a nervous system is constructed predisposes and constrains its functions. Thus the study of neuronal cell migration, an elementary step in the histogenesis of any nervous system, is critical if we are to understand how the structure and function of a nervous system come about. Specific neuronal networks emerge as a result of appropriate migration and final placement of neurons during development. In the developing nervous system, most, if not all, neurons undergo their terminal division and terminal differentiation in distinct locations. Specific neuronal populations have to migrate in distinct pathways and patterns over extensive distances to reach their final position. Two main types of migration predominate during the development of the central nervous system: radial vs tangential. Radial migration is characterized by close interactions between migrating neurons and the processes of radial glial cells, which constitute a scaffold bridging the proliferating neuroepithelium and the differentiating zone. Postmitotic neurons migrate radially from the ventricular zone toward the pial surface past previously generated neuronal layers (Rakic, 1971b, 1972a) to reach the top of the cortical plate (CP), 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; Nadarajah and Parnavelas, 2002; Nadarajah *et al*., 2002). In contrast, tangential migration is referred to as a nonradial mode of neuronal translocation that does not require specific interaction with radial glial cell processes. Observations of tangential dispersion of precursors or postmitotic neurons in the developing cortex suggested the possibility of nonradial migration in the cortex (O'Rourke *et al*., 1992, 1995, 1997; Walsh and Cepko, 1992; Fishell *et al*., 1993; Tan and Breen, 1993; Tan *et al*., 1995; de Carlos *et al*., 1996). Analysis of *Dlx1/2* double knockout mice has demonstrated for the first time that subpopulations of GABAergic interneurons, originating from the ventral telencephalon (also called the ganglionic eminence [GE]), indeed migrate tangentially into the neocortex (Anderson *et al*., 1997). Therefore, there is a tight correlation between neuronal subtype identity (glutamaergic vs GABAergic) and the mode of migration (radial vs tangential) in the developing cortex of mammals (Parnavelas, 2000).

Specific cell–cell recognition and adhesive interactions between neurons, glia, and the surrounding extracellular matrix (ECM) appear to modulate distinct patterns of neuronal migration, placement, and eventual differentiation within cortex. A fundamental challenge in the study of cortical development is the elucidation of mechanisms that determine how neurons migrate and coalesce into distinct layers or nuclei in the developing cerebral cortex. In this regard, several related questions need specific attention: (1) What are the cell-intrinsic and extracel-lular cues that trigger the onset of neuronal migration following last mitotic cell division? (2) What is the molecular basis and role of glial-independent and glial-guided neuronal migration in cortical development? (3) How do migrating neurons know where to end? and (4) What are the stage-specific genes that determine distinct aspects of neuronal migration in developing mammalian brain? In combination, analysis of these questions may elucidate some of the fundamental rules guiding the development of cerebral cortex.

PATTERNS OF NEURONAL MIGRATION

Extensive observations of neuronal migration in the past several decades in mammalian cerebral cortex and recent molecular characterization of migration deficits in mice and humans have raised the cerebral cortex as a prototype model for the analysis of migration in the developing mammalian central nervous system. Radial glial cells play a critical role in the construction of the mammalian brain by contributing to the formation of neurons and astrocytes and by providing a permissive and instructive scaffold for neuronal migration. The establishment of radial glial cells from an undifferentiated sheet of neuroepithelium precedes the generation and migration of neurons in the cerebral cortex. During early stages of corticogenesis, radial glial cells can give rise to neurons (reviewed in Fishell and Kriegstein, 2003; Rakic, 2003). Subsequent neuronal cell movement in the developing mammalian cerebral cortex occurs

Franck Polleux • Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, NC 27599. E. S. Anton • Department of Cell and Molecular Physiology, University of North Carolina School of Medicine, Chapel Hill, NC 27599.

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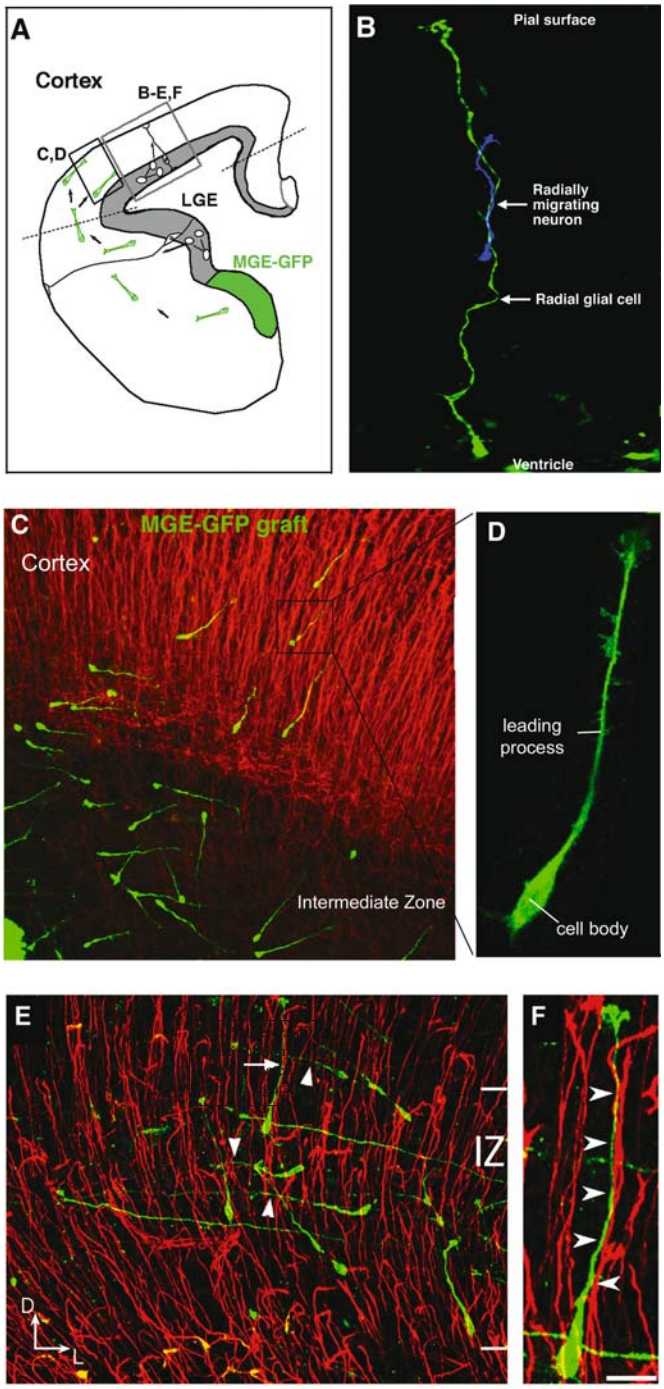

FIGURE 1. Radial vs tangential patterns of neuronal migration. In the developing embryonic cortex (A), radially (B) and tangentially (C) migrating neurons display a unipolor morphology characterized by a prominent leading process (D). These neurons are in intimate contact with either radia glial cells (B, green) or with neurites (C, red) within the developing cortex. Tangentially migrating neurons (arrowhead, E) eventually turn radially (arrow, E) in the intermediate zone and associate with radial fibers (F, red) during final stages of translocation to the cortical plate. Cells shown in B were electroporated with GFP, whereas tangentially migrating neurons (C–F) were isolated from GFP-expressing MGE graft on a slice co-culture assay (Polleux *et al*., 2002).

mainly along radial glial fibers, though nonpyramidal neurons initially migrate into the cortex in a radial glial-independent manner (Fig. 1). Neurons migrate from the ventricular zone toward the pial surface past previously generated neuronal layers (Rakic, 1971a, b; 1972a, b) to reach the top of the CP, 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; Nadarajah and Parnavelas, 2002; Nadarajah *et al*., 2002). Somally translocating neurons, prevalent during early phases of corticogenesis, appear to move toward the pial surface by maintaining pial attachment while losing their ventricular attachments. In contrast, radial glial cell fibers serve as the primary migratory guides for locomoting neurons (Rakic, 1971a, b, 1972a, b, 1990; Gray *et al*., 1990; Hatten and Mason, 1990; Misson *et al*., 1991). These neurons form specialized membrane contacts variably referred to as junctional domains, interstitial junctions, or punctae adherentia with the underlying radial glial cell substrate (Gregory *et al*., 1988; Cameron and Rakic, 1994; Anton *et al*., 1996). Such specialized membrane contacts are hypothesized to be critical elements in the maintenance of directed neuronal cell migration along radial glial cell fibers (Rakic *et al*., 1994). The radial movement of neurons stops abruptly at the interface between CP and cell sparse marginal zone. The signal to end neuronal cell migration is thought to be provided either by the afferent fibers that migrating neurons encounter near their target location or by the ambient neuronal cell population that had already reached its final position (Sidman and Rakic, 1973; Hatten, 1990, 1993; Hatten and Mason, 1990; D'Arcangelo *et al*., 1995; Ogawa *et al*., 1995). Alternately, a change in the cell surface properties of the radial glial substrate may signal a neuron migrating on it to stop, detach, and differentiate.

In contrast to radially migrating neurons, populations of GABAnergic interneurons, originating from the GE, migrate tangentially into the neocortex (Anderson *et al*., 1997; Letinic and Rakic, 2001; Maricich *et al*., 2001; Tamamaki *et al*., 1997; Wichterle *et al*., 2001; see Fig. 1). Some of these neurons migrate ventrally toward the cortical ventricular zone prior to radial migration toward the pial surface (Nadarajah *et al*., 2002). These distinct patterns of neuronal migration enables several generations of neurons to reach their appropriate areal and laminar positions in the developing CP. Analysis of mutations in mice and humans have revealed several molecular cues controlling different aspects of neuronal migration. Evidently, a dynamic regulation of multiple cellular events such as cell–cell recognition, adhesion, transmembrane signaling, and cell motility events underlies the process of neuronal migration.

MECHANISMS UNDERLYING RADIAL MIGRATION

Initiation of Migration

Movement of neuronal cells from their site of birth in the ventricular areas to the specific laminar location involves

a progressive unraveling of three interrelated cellular events: initiation of migration along appropriate pathways or substrates, maintenance of migration through a complex cellular milieu, and termination of migration in the CP at the appropriate laminar location.

In humans with periventricular heterotopia, mutations in actin-binding protein filamin 1 (or filamin-α [FLNA]) results in failure of neuronal migration and accumulation of neuroblasts in the ventricular zone of cerebral cortex (Eksioglu *et al*., 1996; Fox *et al*., 1998; Sheen *et al*., 2001; Moro *et al*., 2002). FLNA co-localizes to actin stress fibers, highly expressed by neural cells in the ventricular surface, is thought to crosslink F-actin network to facilitate cell motility (Fox *et al*., 1998; Stossel *et al*., 2001). The inability of neurons to initiate migration following FLNA mutations is indicative of the significance of actin dynamics in initiation of migration. Whether FLNA's interactions with cell surface integrin receptors (β1 or β2), presenilin, and small GTPase RalA is part of the cascade that conveys extracellular signals from the ventricular zone to initiate migration still needs further examination (Sharma *et al*., 1995; Loo *et al*., 1998; Zhang and Galileo, 1998; Ohta *et al*., 1999). However, Filamin A interacting protein (FLIP) is expressed in the ventricular zone and degrades FLNA, thereby inhibiting premature onset of neuronal migration from the ventricular zone (Nagano *et al*., 2002).

Maintenance of Migration

Once initiated, a dynamic regulation of multiple cellular events such as cell–cell recognition, adhesion, transmembrane signaling, and cell motility events underlies the process of neuronal migration (Lindner *et al*., 1983; Grumet *et al*., 1985; Antonicek *et al*., 1987; Chuong *et al*., 1987; Rutishauser and Jessell, 1988; Edmondson *et al*., 1988; Sanes, 1989; Hatten and Mason, 1990; Stitt and Hatten, 1990; Takeichi, 1991; Misson *et al*., 1991; Galileo *et al*., 1992; Grumet, 1992; Komuro and Rakic, 1992, 1993, 1995; Shimamura and Takeichi, 1992; Fishman and Hatten, 1993; Hatten, 1993; Cameron and Rakic, 1994; Rakic *et al*., 1994; Stipp *et al*., 1994; Rakic and Komuro, 1995). A migrating neuron attaches itself to the radial glial substrate primarily by its leading process and cell soma. Only the actively migrating neurons form the specialized junctional domains or the interstitial densities with the apposing glial fibers (Gregory *et al*., 1988; Cameron and Rakic, 1994), whereas the stationary neurons form desmosomes or puncta adherentia. The specialized subcellular accumulations of membrane proteins, such as radial glial based neuron–glial junctional protein 1 (NJPA1) or neuronal astrotactin, at the apposition of migrating neurons and radial glial cells may function in migration by orchestrating cell–cell recognition, adhesion, transmembrane signaling, and or motility. The homophilic or heterophilic nature of the junctional domain antigen interactions are unclear. However, the integrity of neuron–glial junctional complexes appears to depend on their association with microtubule cytoskeleton (Gregory *et al*., 1988; Cameron and Rakic, 1994). Disruption of microtubules, but not actin filaments, adversely affect neuron–glial adhesion (Rivas and Hatten, 1995). Junctional domain associated microtubules are thought to play a role in force generation during cell movement, in addition to being vital for the elaboration and maintenance of junctional domains (Gregory *et al*., 1988). Furthermore, specific cell–cell interactions between migrating neurons and radial glial cells mediated by the junctional domain antigens may also modulate the properties of each other's cytoskeleton, akin to that observed between developing peripheral axons and Schwann cells (Kirkpatrick and Brady, 1994). It is argued that an increase in class III β-tubulin content leads to enhanced microtubule lability, thus allowing the continuous assembly and disassembly of microtubules needed to generate a forward force during cell movement (Falconer *et al*., 1992; Moskowitz and Oblinger, 1995; Rivas and Hatten, 1995; Rakic *et al*., 1996).

Significant deficits in neuronal migration were seen following mutations in genes regulating microtubule cytoskeleton (see Table 1 and Fig. 2). In humans, mutations in Lis1 (noncatalytic subunit of platelet-activating factor acetylhydrolase isoform 1b) Miller–Dieker syndrome, a severe form of lissencephaly (Reiner *et al*., 1993; Hattori *et al*., 1994). In mouse, truncation of Lis1 leads to slower neuronal migration and cortical plate disorganization characterized by unsplit preplate (Cahana *et al*., 2001). Partial loss of Lis1 (i.e., mice with one inactive allele of Lis1) also results in retarded neuronal migration (Hirotsune *et al*., 1998). Lis1 binds to microtubules, microtubule based motor protein, dyenin, and related microtubule interactors such as dynactin, NUDEL, and mNudE (Sapir *et al*., 1997; Efimov and Morris, 2000; Faulkner *et al*., 2000; Kitagawa *et al*., 2000; Niethammer *et al*., 2000; Sasaki *et al*., 2000; Smith *et al*., 2000). Loss of Lis1 leads to concentration of microtubules around the nucleus and failed dynein aggregation, whereas overexpression of Lis1 causes transport of microtubule to edges of the cell and aggregation of dynein and dynectin (Sasaki *et al*., 2000; Smith *et al*., 2000). NUDEL and mNudE appear to control cellular localization of dynein and the microtubule network around the microtubule-organizing centrosome, respectively (Feng *et al*., 2000; Niethammer *et al*., 2000; Sasaki *et al*., 2000). How these associations of Lis1 modify the microtubule network to enable the nuclear translocation of neurons in the developing cortex remains to be elucidated.

Mutations in another microtubule-associated protein in migrating neurons, doublecortin (Dcx), leads to X-linked lissencephaly (double cortex syndrome) in humans (des Portes *et al*., 1998; Gleeson *et al*., 1998). In these patients, neurons that migrated aberrantly are deposited in a broad band in subcortical layers. Dcx is critical for the stabilization of microtubule network (Francis *et al*., 1999; Gleeson *et al*., 1999; Horesh *et al*., 1999). Dcx can associate with Lis1 and promote tubulin polymerization *in vitro* (Gleeson *et al*., 1999; Caspi *et al*., 2000; Feng and Walsh, 2001). Overexpression of Dcx results in aggregates of thick microtubule bundles resistant to depolymerization (Gleeson *et al*., 1999). Structural analysis of Dcx indicates that it contains a β-grasp superfold motif that can bind to tubulin and facilitate microtubule polymerization and stabilization (Taylor *et al*., 2000). Point mutations within this tubulin-binding motif were seen in patients with double cortex syndrome (Gleeson *et al*., 1999).

TABLE 1. Molecular Cues Affecting Radial and Tangential Neuronal Migration

Gene	Function and phenotype	References
Reelin	Essential for layer formation Inverted cortical layers	D'Arcangelo *et al*., 1995; Hirotsune *et al*., 1995; Ogawa *et al*., 1995; Hong *et al*., 2000
VLDLR/ ApoER2	Reelin receptors, critical for layer formation Inverted cortical layers	Trommsdorf *et al*., 1999
mDab1	Adopter protein component of reelin signaling cascade Inverted cortical layers	Howell *et al*., 1997; Sheldon *et al*., 1997; Ware *et al*., 1997
Astrotactin	Promotes neuron–radial glial adhesion Decreased rate of radial migration in mutants	Adams *et al*., 2002
Doublecortin	Critical for the stabilization of microtubule network Mutations lead to X-linked lissencephaly (double cortex syndrome) in humans	des Portes *et al*., 1998; Gleeson *et al*., 1998, 1999; Francis *et al*., 1999; Horesh *et al*., 1999
Lis1	Binds to microtubules, microtubule based motor protein, dyenin, and related microtubule interactors such as dynactin, NUDEL, and mNudE Mutations in Lis1 cause Miller–Dieker syndrome, a severe form of lissencephaly	Reiner *et al*., 1993; Hattori *et al*., 1994; Sapir *et al*., 1997; Efimov and Morris, 2000; Faulkner *et al*., 2000; Niethammer *et al*., 2000; Sasaki *et al*., 2000; Smith *et al*., 2000; Kitagawa *et al*., 2000
Cdk5	Facilitates neuronal migration to CP following splitting of the preplate Inverted layering in mutants	Oshima *et al*., 1996; Gilmore *et al*., 1998
p35/p39	Regulatory subunits of Cdk5 Similar in function to Cdk5	Chae *et al*., 1997; Kwon and Tsai, 1998; Ko *et al*., 2001
NRG1	Promotes radial migration Critical for the establishment of radial glial scaffold	Anton *et al*., 1999 Schmid *et al*., 2003
α_3 Integrin	Abnormal neuronal migration and laminar organization of cortex Neuron–glia interaction impaired Premature radial glial transformation	Anton *et al*., 1999; Kreidberg *et al*., 1996
α_6 Integrin	Lethal at birth Disorganized CP Ectopic neuroblasts in embryonic cortex Disorganized basal lamina assembly	Georges-Labouesse *et al*., 1996, 1998
α_3, α_6 Integrin	No neural tube closure Abnormal basal lamina assembly Multiple neuroblast ectopias in cortex	De Arcangelis *et al*., 1999
α_v Integrin	Survive until E14 or birth Intracortical hemorrhage Facilitates basic neuron–glial adhesion	Bader *et al*., 1998
β_1 Integrin (cond.)	Disrupted cortical laminar organization Radial glia end feet and pial basement membrane abnormalities	Graus-Porta *et al*., 2001
γ1 Laminin	Component of ECM in pial surface Misplaced neurons in CP	Halfter *et al*., 2002
Filamin α	Actin-binding protein, co-localizes to actin stress fibers, highly expressed by neural cells in the ventricular surface, crosslinks F-actin network to facilitate cell motility Needed to initiate migration from the ventricular zone Mutations cause periventricular heterotopia	Fox *et al*., 1998; Sheen *et al*., 2001; Moro *et al*., 2002
FILIP	Regulates degradation of Filamin α in the ventricular zone Prevents premature onset of migration	Nagano *et al*., 2002
Dlx1/2	Transcription factors regulating the differentiation of cortical and hippocampal interneurons from the subpallium Lateral ganglionic eminence (LGE)/medial ganglionic eminence (MGE)	Anderson *et al*., 1997; Pleasure *et al*., 2000

TABLE 1. (*Continued*)

Gene	Function and phenotype	References
Nkx 2.1	Transcription factor regulating the migration and differentiation of cortical interneurons from the MGE	Sussel *et al*., 1999; Anderson *et al*., 2001
TAG1	Neural cell-adhesion molecule expressed in corticofugal fibers Motogenic cue for tangentially migrating interneurons	Wolfer *et al*., 1994; Denaxa *et al*., 2001
HGF	Motogenic factor expressed in GE Promotes movement of cortical interneurons from MGE toward dorsal pallium	Powell *et al*., 2001
u-PAR	Urokinase-type plasminogen activator receptor Enables HGF activation	Powell *et al*., 2001
BDNF, NT-4	Motogenic factors for neuronal migration from MGE	Brunstrom *et al*., 1997; Ringstedt *et al*., 1998; Polleux *et al*., 2002
TrkB	Receptor for BDNF/NT-4 Mutation leads to reduced interneuronal migration into cortex	Brunstrom *et al*., 1997; Polleux *et al*., 2002
Slit 1/2	Chemorepellent for GABAergic interneurons in the GE	Zhu *et al*., 1999; Marin *et al*., 2003
Sema3A/3F	Chemorepellent expressed in striatal mantle region Helps to channel cortical interneurons toward the cortex	Marin *et al*., 2001; Tamamaki *et al*., 2003
Nrp1/2	Receptors for class 3 secreted semaphorins Enables cortical interneurons to migrate away from striatum into the cortex	Marin *et al*., 2001; Tamamaki *et al*., 2003

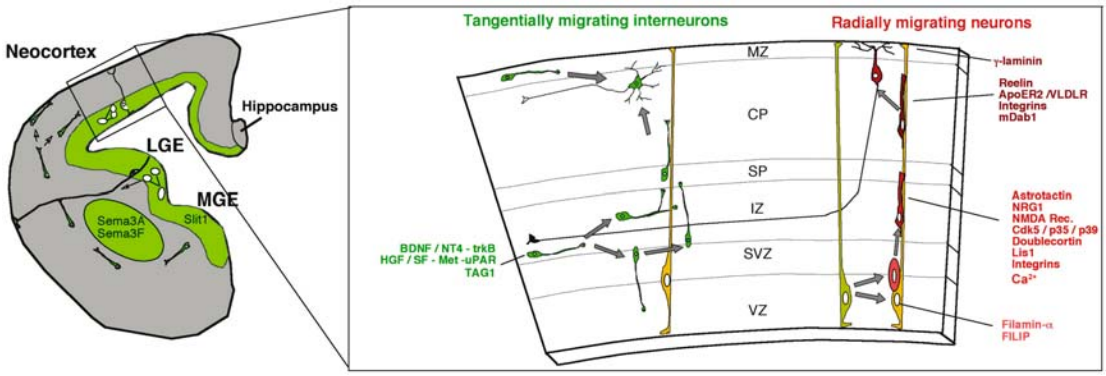

FIGURE 2. Molecular cues influencing distinct patterns of migration into the developing cerebral cortex. In the cerebral wall, neurons migrating tangentially into the cerebral cortex from ganglionic eminence and neurons migrating radially from the ventricular surface to the cortical plate are influenced by different sets of molecules on the right hand side panel. LGE-Lateral ganglionic eminence, MGE-medial ganglionic eminence, VZ-ventricular zone, SVZ-subventricular zone, IZ-intermediate, SP-subplate, CP-cortical plate, MZ-marginal zone.

Regulators of both actin and microtubule network associate with cyclin-dependent kinase-5 (Cdk5), expressed in migrating neurons and axon growth cones of the developing cortex (Nikolic *et al*., 1998). Both filamin 1 and NUDEL are putative substrates for Cdk5 phosphorylation (Fox *et al*., 1998; Niethammer *et al*., 2000; Feng and Walsh, 2001). Mice deficient in Cdk5 and its activating subunits, p35 and p39, display abnormal neuronal migration and placement in cerebral cortex (Ohshima *et al*., 1996; Chae *et al*., 1997; Gilmore *et al*., 1998; Kwon and Tsai, 1998; Ko *et al*., 2001). Deficits in Brn1 and 2, class III POU domain transcription factors regulating p35 and p39 expression, also lead to cortical migrational abnormalities (McEvilly *et al*., 2002). Interactions between p35 and β-catenin is thought to enable Cdk5 to regulate negatively *N*-cadherin-mediated adhesion and facilitate neuronal migration through the *N*-cadherin-rich developing cerebral wall up to the CP (Redies and Takeichi, 1993; Kwon *et al*., 2000).

Transient, intracellular calcium fluxes that modulate neuronal migration *in vitro* can significantly influence the actin and microtubule network of neurons undergoing oriented migration (Rakic *et al*., 1994). The link between extracelluar cues modulating migration and the internal cues involved in mechanics of migration is generated in a highly varied and redundant manner. For example, neurotransmitter receptors such as *N*-methyl-D-aspartate (NMDA) type glutamate receptors, and GABA receptors, or growth factors and their receptors such as neuregulins and its receptors erbB2, erbB3, and erbB4, or BDNF and its high-affinity receptor trkB, can promote radial-guided neuronal migration (Komuro and Rakic, 1993, 1996; Anton *et al*., 1997; Rio *et al*., 1997; Behar *et al*., 2000, 2001). The most direct transmission of external cues via membrane receptors to cytoskeletal changes during migration is provided by integrins. Integrins are heterodimeric cell surface receptors that serve as structural links between the ECM and the internal cytoskeleton. Different integrin receptors display different adhesive properties, regulate different intracellular signal transduction pathways, and thus, different modes of adhesion-induced changes in cell physiology. Integrins are also capable of synergizing with other cell surface receptor systems to finely modulate a cell's behavior in response to multiple environmental cues. Developmental changes in the cell surface integrin repertoire and function may thus modulate distinct aspects of neuronal migration in the developing cerebral cortex by altering the strength and ligand preferences of cell–cell adhesion during development. Different α integrin subunits dimerize preferentially or exclusively with β_1 integrin, which is ubiquitously expressed in the developing cerebral cortex. The varied, yet distinct, cortical phenotypes of integrin subunit null mice provide striking insights into the distinct roles that cell–cell, cell–ECM adhesive interactions play in neuronal migration.

Mice homozygous for a targeted mutation in the α_3 integrin gene die during the perinatal period with severe defects in the development of the kidneys, lungs, skin, and cerebral cortex (Kreidberg *et al*., 1996; Anton *et al*., 1999). In the cerebral cortex, the normal laminar organization of neurons is lost, and neurons are positioned in a disorganized pattern. The α_3 integrin modulates neuron–glial recognition cues during neuronal migration and maintain 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 in the absence of α_3 integrin was hypothesized to underlie the abnormal cortical organization of α_3 integrin mutant mice. 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 (LGE) 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). The 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 (Cheresh *et al*., 1989; Bodary and McLean, 1990; 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 neuronal translocation in cerebral cortex.

In addition to α_3 integrin, some laminin isoforms in the developing cerebral cortex can also interact with α_6 integrin dimers (Georges-Labouesse *et al*.,1998). The 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). Analysis of E13.5–E18.5 α_6 integrin-deficient embryos revealed ectopic neuronal distribution in the cortical plate, protruding out to the pial surface. The CP was further disorganized by wavy neurite outgrowth of ectopic neuroblasts. Coinciding abnormalities of laminin synthesis and deposition also occurs in the mutant brain. Persistence of glial laminin throughout development may have prevented neuroblasts from appropriately arresting their migration in the developing CP 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 knockout mutants, that is, disorganization of CP with large collection of ectopias, aberrant basal lamina organization, and abnormal choroid plexus, suggest 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 α_6 or β_4 integrin in humans results in skin blistering (epidermolysis bullosa). However, the brain phenotype of the affected patients is unknown.

The β_1 integrin in the cerebral cortex can dimerize with at least 10 different α subunits; thus β_1 integrin deficiency leads to lethality from around E5.5 (Fassler and Meyer, 1995; Stephens *et al*., 1995). Most of the cortical-specific α subunits seem to dimerize only with β_1 integrin. 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 around 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 affected significantly. However, perturbed radial glial end feet development may contribute to the defective placement of neurons in the cortex. The varied cortical phenotypes of α_1, α_3, α_6, α_v, and β_1 null mice may reflect the transdominant, transnegative, or compensatory influences distinct integrin receptor dimers may exert over each other and the ECM ligands in the developing cerebral cortex. *In vitro*, binding of a ligand to a signal transducing integrin or inactivation of signaling through a particular integrin can initiate a unidirectional signaling cascade affecting

the function of the target integrin in the same cell (Simon *et al*., 1997; Hodivala-Dilke *et al*., 1998; 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 different integrin null mice will be informative in fully characterizing the role of integrins in neuronal migration.

Termination of Migration

Once neurons reach the top of the CP, the movement of neurons stops abruptly at the interface between the CP and the cell sparse marginal zone and cohorts of neurons begin to assemble into their respective layers. This final stage of neuronal migration is the least explored aspect of neuronal migration, in spite of its significance for genetic and acquired cortical malformations (Rakic, 1988; Rakic and Caviness, 1995; Olson and Walsh, 2002). The signal to terminate neuronal cell migration is thought to be provided either by the afferent fibers that migrating neurons encounter near their target location or by the ambient neuronal cell population that had already reached its final position (Sidman and Rakic, 1973; Hatten and Mason, 1990; D'Arcangelo *et al*., 1995; Ogawa *et al*., 1995). Alternatively, a change in the cell surface properties of the radial glial substrate at the top of the CP may signal a migrating neuron to stop, detach, and differentiate.

In the *reeler* mouse, deficits in this phase of migration have led to disorganized, inverted cortex, with early-born neurons occupying abnormally superficial positions and later-born neurons adopting abnormally deep positions (Caviness *et al*., 1972; Caviness and Sidman, 1973; Lambert de Rouvroit and Goffinet, 1998). The inversion of final neuronal positions in the CP of the *reeler* mouse has made it a prototype model for the analysis of mechanisms controlling the final phase of neuronal migration, that is, how neurons disengage from a migratory mode to assemble into distinct layers. The *reeler* locus encodes Reelin, a 388 kDa secreted protein composed of a unique N-terminal sequence with similarity to F-spondin, followed by a series of eight 350–390 amino acid "Reelin repeats" each containing an EGF domain with homology to ECM proteins like Tenascin C (D'Arcangelo *et al*., 1995; Hirotsune *et al*., 1995). Reelin acts on noncell autonomously (Ogawa *et al*., 1997), and the protein is synthesized and secreted in the cerebral cortex predominantly by the Cajal–Retzius (CR) cell of the marginal zone, the outermost layer of the developing cortex (D'Arcangelo *et al*., 1995; Ogawa *et al*., 1995).

Mutations in three molecules, VLDLR, ApoER2, and Dab1, have been found to phenocopy almost exactly the effects of the *reeler* gene mutation, suggesting that the corresponding proteins represent a reelin regulated biochemical pathway that mediates proper termination of neuronal migration and formation of cerebral cortical lamination (Gonzalez *et al*., 1997; Howell *et al*., 1997; Sheldon *et al*., 1997; Ware *et al*., 1997). The *dab1* gene encodes a cytoplasmic adapter protein (Dab1) expressed by neurons in the developing CP, suggesting that Dab1 represents a link in the signaling pathway that receives the Reelin signal. This idea is confirmed by observation that Reelin expression is normal in the *dab1* mutant cortex (Gonzalez *et al*., 1997) but Dab1 protein accumulates in the *reeler* mouse brain (Rice *et al*., 1998) and Dab1 is phosphorylated in response to application of recombinant Reelin (Howell *et al*., 1999a). Mammalian Dab1 was identified through a two-hybrid screen using the non-receptor tyrosine kinase Src as "bait" (Howell *et al*., 1997) and found to have homology with Drosophila *disabled* (Gertler *et al*., 1993). Dab1 has an N-terminal alpha helical structure and the critical amino acids of a protein interaction/phosphotyrosine-binding domain (PI/PTB) (Kavanaugh and Williams, 1994; Borg *et al*., 1996; Margolis, 1996; Howell *et al*., 1997). The PI/PTB domain of Dab1 binds proteins that contain an NPXY motif (Howell *et al*., 1997, 1999b; Trommsdorff *et al*., 1998) a motif that has been implicated in clathrin-meditated endocytosis (Chen *et al*., 1990), and integrin signaling (Law *et al*., 1999).

More recently, mice with compound mutations in both VLDLR and ApoER2 have been found to have a phenotype indistinguishable from *reeler* and *dab1* mutants (Trommsdorff *et al*., 1999). VLDLR and ApoER2 are members of the low density lipoprotein (LDL) receptor superfamily that interacted with Dab1 in two-hybrid screens through the PI/PTB domain of Dab1 and the NPXY motif of LDL superfamily members (Trommsdorff *et al*., 1998). The NPXY motif of LDL receptor family members is essential for clathrin-mediated endocytosis (Chen *et al*., 1990). The implication of VLDLR and ApoER2 as potential Reelin receptors was surprising since LDL superfamily members are well characterized as mediating the endocytosis of specific ligands, but have never demonstrated a direct signaling function. Recent studies, however, have clearly demonstrated that both recombinant ApoER2 and the VLDLR bind Reelin and that this binding leads both to the tyrosine phosphorylation of Dab1 and in the case of VLDLR, the internalization of the receptor and Reelin (D'Arcangelo *et al*., 1999; Hiesberger *et al*., 1999). Thus there is compelling evidence that Reelin, VLDLR, ApoER2, and Dab1 function in a common signaling pathway between CR cells and CP neurons, but the downstream molecules that mediate Reelin signaling effect on either migration or adhesion of cortical neurons remains unclear.

Reelin's effect on cortical layering is hypothesized to result from three distinct cellular effects. First, reelin may regulate CP organization by initiating the splitting of preplate into marginal zone and subplate. Failure of this process in *reeler* mutants leads to the accumulation of cortical neurons underneath the preplate neurons. Second, a reelin gradient may act as an attractant for neurons to the top of the CP, thus enabling newly generated neurons to migrate past earlier generated ones in the developing CP. Third, reelin may induce detachment of neurons from their radial glial guides and thus end neuronal migration at the marginal zone-developing CP interface and initiate the differentiation of neurons into distinct layers.

Cortical neurons in β_1 integrin or laminin γ_1 nidogen-binding site (Halfter *et al*., 2002) deficient mice invade the marginal zone in areas devoid of reelin producing CR cells, and in regions with CR cell ectopias, accumulate underneath them, within the CP. Invasion of neurons into areas devoid of

reelin-producing CR cells supports a role for reelin in normal termination of neuronal migration. Furthermore, reelin appears to facilitate detachment of migrating neurons from glial guides *in vitro* and in the rostral migratory stream (RMS) (Hack *et al*., 2002). The reelin-induced detachment of embryonic cortical neurons from glial guides *in vitro* depends on α_3 integrin signaling. It is hypothesized that during glial-guided migration to the CP neuronal α_3 integrin may interact with glial cell surface molecules such as fibronectin or laminin-2, and at the top of the CP, the ligand preference of α_3 integrins may change from radial glial cell surface ECM molecules to reelin. 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 toward or away from growth cone membranes. Reelin can also function as serine protease and degrade fibronectin and laminin normally used to maintain glial-based migration (Quattrocchi *et al*., 2002). Thus changes in the availability, function, and ligand preference of α_3 integrins or reelin proteolytic activity 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 polymicrogyria or lissencephaly (Sunada *et al*., 1995; Hong *et al*., 2000).

TANGENTIAL MIGRATION IN THE FOREBRAIN

As introduced earlier in this chapter, two main types of migration are classically opposed during the development of the central nervous system: radial vs tangential migration. Radial migration is characterized by close interactions between migrating neurons and the processes of radial glial cells which constitute a scaffold bridging the proliferating neuroepithelium and the differentiating zone. By definition, tangential migration is referred to as a nonradial mode of neuronal translocation that does not require specific interaction with radial glial cell processes. Until recently, the predominant view was that the vast majority of neurons in the forebrain where generated through radial migration (Sidman and Rakic, 1973). The first evidence to suggest the need for a revised model came from observations of tangential dispersion of precursors or postmitotic neurons in the developing cortex (O'Rourke *et al*., 1992a, 1995; Fishell *et al*., 1993a; Tan and Breen, 1993; Tan *et al*., 1995; de Carlos *et al*., 1996). The widespread distribution of clonally related cells also suggested the possibility of non-radial migration in the cortex (Walsh and Cepko, 1992). In an elegant study, Parnavelas and collaborators coupled retroviral-mediated lineage-tracing studies with the determination of neuronal subtype identity and demonstrated a tight correlation between cell dispersion and neuronal subtype (Parnavelas *et al*., 1991): most excitatory, glutamatergic pyramidal neurons are produced locally by a set of precursors migrating radially in the cortex, whereas most GABAergic, nonpyramidal neurons were produced by a set of progenitors migrating tangentially (Parnavelas, 2000).

Origin of Tangentially Migrating Cells in the Forebrain

The source and destination of these tangentially migrating cells, however, remained a mystery until experiments by Anderson *et al*. suggested that neurons migrated from the GE to the cortex where they gave rise preferentially to GABAergic interneurons (Anderson *et al*., 1997; Tamamaki *et al*., 1997). This conclusion is based mainly upon the observation that there are virtually no neocortical GABAergic neurons in *Dlx1/2* double knockout mice, two homeobox transcription factors expressed in the ventricular and subventricular zones of the GE (Anderson *et al*., 1997). The GE is located in the ventral part of the telencephalon and is producing neurons of the basal ganglia (Fentress *et al*., 1981; Qiu *et al*., 1995). This ventral structure can be divided into three subregions using neuroanatomical and molecular criteria: the medial, the lateral, and the caudal parts (Corbin *et al*., 2000). Several transcription factors are differentially expressed in these three regions (Table 2).

Recent *in utero* homotopic transplantation experiments performed in mice have revealed that these distinct regions give rise to specific neuronal populations displaying strikingly different patterns of cell migration (Fig. 3): the *medial* GE gives rise to the majority of GABAergic interneurons of the cortex and hippocampus (Lavdas *et al*., 1999; Anderson *et al*., 2001; Wichterle *et al*., 2001; Polleux *et al*., 2002) whereas precursors in the *lateral* GE generates projecting medium spiny neurons of the striatum, nucleus accumbens and olfactory tubercle and to the granule and periglomerular cells in the olfactory bulb (Wichterle *et al*., 2001). The pattern of migration of neurons originating in the caudal GE is less well characterized but it has recently been shown that precursors in this region give rise to interneurons found in layer 5 of the neocortex, various regions of the limbic system and also neurons of the striatum (Nery *et al*., 2002).

TABLE 2. Transcription Factors Expression in Different Subregions of the Ganglionic Eminence

	Mash1	*Dlx1/Dlx2*	*Nkx2.1*	*Lhx6*	*Gsh2*
MGE	+	+	+	+	−
LGE	+	+	−	−	+
CGE	+	+	?	?	?

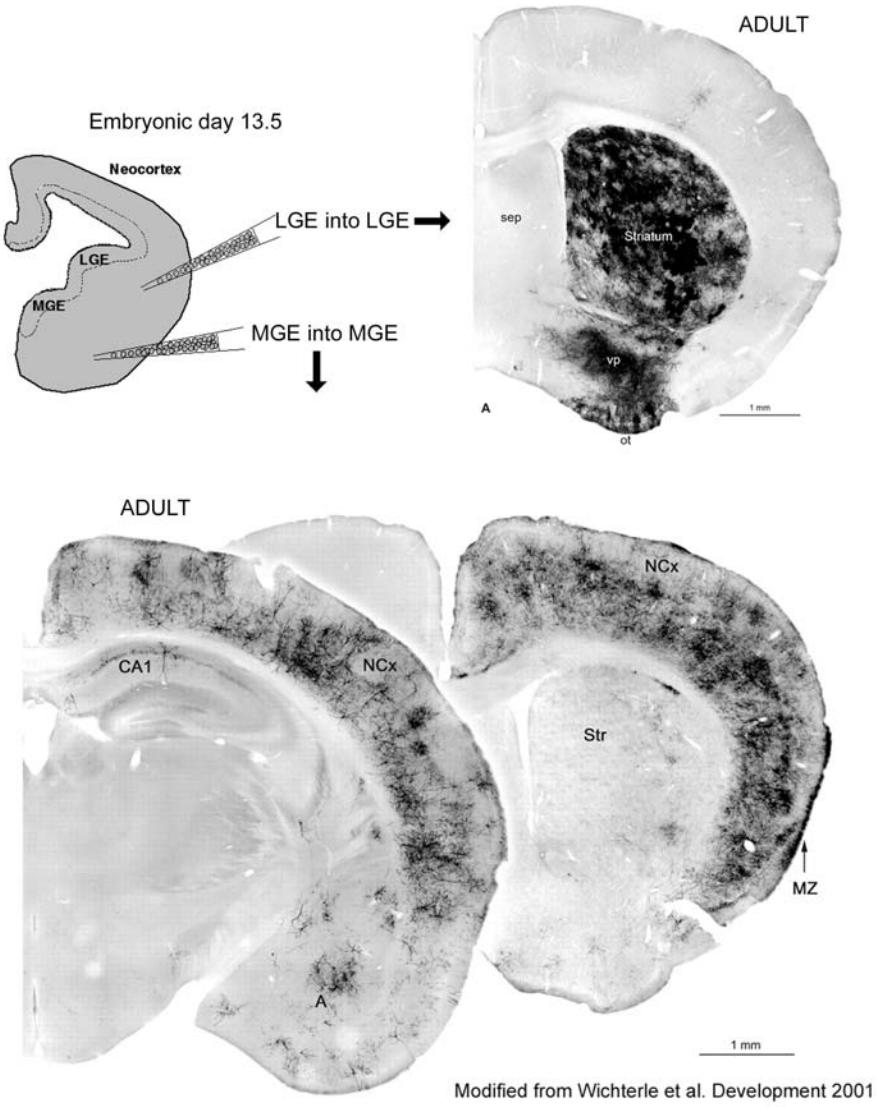

FIGURE 3. Generation and migration of cortical interneurons from the medial ganglionic eminence. Disssociated neurons (tagged with alkaline phosphatase) isolated from LGE or MGE were transplanted homotopically into LGE or MGE, respectively, at early stages of neuronal migration in cortex. Location and differentiation of transplanted neurons were analyzed in adult brains. Strikingly, MGE cells all migrated into cerebral cortex to become cortical interneurons, whereas LGE cells populated the striatum. LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence. Modified with permission from Wichterle *et al*., 2001.

Cellular and Molecular Substrates for Tangential Migration of Cortical Interneurons

Tangentially migrating interneurons display a characteristic unipolar morphology during translocation with a long leading process dragging behind their nucleus (Fig. 2) (Anderson *et al*., 1997; Tamamaki *et al*., 1997; Polleux *et al*., 2002). Interneurons are migrating tangentially through the intermediate zone or the marginal zone, two axon-rich layers located, respectively, deep and superficial, relative to the CP, where all neurons accumulate in a layer-specific manner to undergo their terminal differentiation (O'Leary and Nakagawa, 2002).

During migration to the cortex, tangential migrating interneurons are not using radial glial cells processes as a scaffold during translocation and these cells do not appear to fasciculate along a specific cellular scaffold (Polleux *et al*., 2002) although it has been proposed that they interact with corticofugal axons (Denaxa *et al*., 2001). *In vitro*, the neural cell-adhesion molecule TAG-1 (also called contactin-2) expressed by corticofugal axons has been shown to play a role in the control of interneuron migration.

Extracellular Cues Regulating Tangential Migration in the Forebrain

The extracellular cues controlling the tangential migration of interneurons from the GE to the cortex can be classified in three categories: (1) extracellular cues regulating their motility (motogenic cues), (2) directional cues guiding their migration

toward the appropriate territories, and (3) stop-signals abolishing their motility and therefore dictating where interneurons should terminally differentiate.

Cues Controlling the Motility of Tangentially Migrating Interneurons

Several factors expressed along the migrating pathway of cortical interneurons have recently been shown to be potent stimulators of interneurons motility. Both the hepatocyte growth factor (HGF, also called scatter factor) and the neurotrophin NT4/5 are expressed in the cortex during mouse embryogenesis and are potent stimulators of interneurons migration (Behar *et al*., 1997; Brunstrom *et al*., 1997; Powell *et al*., 2001; Polleux *et al*., 2002). Neurons migrating tangentially from the MGE to the cortex express c-Met and trkB, the high-affinity receptors for HGF and NT4, respectively. Furthermore, mice mutant for urokinase-type plasminogen activator receptor (u-PAR), a key component of HGF activation, exhibit reduced interneuron migration to the frontal and parietal cortex (Powell *et al*., 2001). This decreased number of interneurons in the cortex of u-PAR knockout mice has important behavioral consequences on the establishment of the normal cortical circuitry characterized by an imbalanced level of excitation and inhibition which leads to epilepsia (Powell *et al*., 2003). Mice presenting a targeted deletion of the tyrosine kinase receptor trkB, the high-affinity receptor of NT4, also present a significant reduction of the number of interneurons migrating from the MGE to the cortex (Polleux *et al*., 2002). The motogen activity resulting from the activitation of these tyrosine kinase receptors (c-Met and trkB) is likely to be mediated through their ability to activate phosphoinositide 3-(PI3-)kinase (Polleux *et al*., 2002), a key regulator of cytoskeleton reorganization and cell motility in nonneuronal cell types (Iijima *et al*., 2002).

Guidance Cues (Sema 3A and Sema 3F; Slits)

Several axon guidance cues have been shown to play a role in directing interneuron migration from the GE to the cortex. The diffusible chemorepulsive Sema3A and Sema3F are expressed in the postmitotic mantle region of the developing striatum and migrating interneurons from the MGE express Neuropilin 1 (*Npn1*) and Neuropilin 2 (*Npn2*) (Marin *et al*., 2001; Tamamaki *et al*., 2003), Sema3A and -3F respective receptors (Chen *et al*., 1997; Kolodkin *et al*., 1997; Giger *et al*., 1998). *In vitro* experiments demonstrate that MGE-derived interneurons are repulsed by Sema3A and Sema3F in a cooperative manner. Furthermore, the *in vivo* analysis of mice presenting targeted deletion of *Npn1* and *Npn2* demonstrate that they are required for the selective avoidance of the striatum by cortical interneurons and therefore for the directed migration to the cortex (Marin *et al*., 2001; Tamamaki *et al*., 2003).

Slit1 and Slit2, another short-range chemorepulsive cue for axons expressed in the ventricular zone of the GE as well as in the medial part of GE, has been shown to repulse MGE-derived interneurons *in vitro* (Zhu *et al*., 1999). However, Slit 1/2 double knockout mice do not show any defect of guided migration toward the cortex but nevertheless show a defect in the position of specific interneuronal population within the basal telencephalon, close to the midline (Marin *et al*., 2003). The cortex exerts a chemoattractive activity on migrating interneurons but these cortex-derived cues remains to be identified.

Finally, membrane-bound cell-adhesion molecules, cadherins, delineate sharp territories of expression restricted to the dorsal telencephalon (*R*-Cadherin) and the LGE (Cadherin-6) in E10–11 developing mouse embryos. Evidence using both electroporation-mediated ectopic expression of cadherins or the *in vivo* analysis of Cadherin-6 knockout mice demonstrate its role in the appropriate sorting of striatal and cortical neuronal populations (Inoue *et al*., 2001).

Stop-Signals

Once migrating interneurons have reached the CP, they are targeting specific layers according to their birthdate just as radially migrating neurons do (Fairen *et al*., 1986). So far, few molecules have been characterized for their capacity to stop the motility of tangentially migrating interneurons and even less is known about the putative cues that coordinate the layer-specific targeting of these two populations of neurons. Interestingly, several studies have shown that tangentially migrating neurons are expressing functional calcium-permeable AMPA receptors (but not NMDA receptors) which could be activated by glutamate released from corticofugal axons (Metin *et al*., 2000) and/or GABA released from tangentially migrating interneurons themselves (Poluch and Konig, 2002). Both GABA and glutamate have been shown to control the motility of migrating neurons in the developing cortex (Behar *et al*., 1996, 1998, 1999, 2000) and AMPA receptor activation leads to neurite retraction and is sufficient to stop migration of cortical interneurons in embryonic slice cultures (Poluch *et al*., 2001). Because the neurotransmitter glutamate is expressed at high levels in the CP (Behar *et al*., 1999), it could trigger an AMPA-receptor-dependent calcium influx that could act as a stop-signal for tangentially migrating interneurons in their final cortical environment. Further work will be necessary to validate this model meanwhile the identity of the cues leading to the coordinated, layer-specific accumulation of interneurons and excitatory glutamaergic neurons remains mysterious and the center of a lot of attention.

Differences between the Pattern of Tangential Migration in Rodents and Humans

There might be important differences between the pattern of tangential migration of GE-derived interneurons between rodent and human brain. Recent work demonstrate that a contingent of GE-derived interneurons migrate medially from the ventral telencephalon to the diencephalon in the human developing brain but not in nonhuman primate or in mouse embryos (Letinic and Rakic, 2001). Moreover, in the human brain retroviral lineage studies performed *in vitro* suggest that a substantial proportion of cortical

GABAergic neurons are generated in the dorsal telencephalon (Letinic *et al*., 2002) in contrast with what is observed in the embryonic mouse telencephalon (Anderson *et al*., 1997a). In the human embryonic brain, dividing precursors located in the dorsal telencephalon are expressing *Mash1* and *Dlx1/2* and have been shown to be competent to generate GABAergic interneurons in the cortical neuroepithelium of human-primates (Letinic *et al*., 2002) but not in rodents (Fode *et al*., 2000). This suggests that modifications in the expression pattern of transcription factors in the forebrain could underlie species-specific programs for the generation of neocortical local circuit neurons (Letinic *et al*., 2002).

Other Structures Displaying Nonradial Migration

Many other regions of the developing central nervous system are characterized by nonradial neuronal migration, including the RMS of olfactory interneurons and the tangential migration of granule cells in the cerebellum.

The Rostral Migratory Stream (RMS)

Precursors of the two populations of olfactory interneurons (periglomerular and granule cells) are not produced within the olfactory bulb but are generated by precursors located in the LGE during embryonic development (Altman, 1969; Lois and Alvarez-Buylla, 1993, 1994; Lois *et al*., 1996; Dellovade *et al*., 1998; Sussel *et al*., 1999; Corbin *et al*., 2000; Wichterle *et al*., 2001). This migration is unique because it continues throughout adulthood in rodents providing a constant number of GABAergic neurons to the olfactory bulb. In the adult brain, olfactory interneurons are generated from the subependymal layer lining the lateral ventricles, a proliferative epithelium deriving from the subventricular zone of the embryonic GE (Doetsch and Alvarez-Buylla, 1996; Doetsch *et al*., 1997, 1999a, b).

The interneurons migrating in the adult RMS are also unique with regard to their neurophilic rather than gliophilic mode of migration, requiring interactions between migrating interneurons (Lois and Alvarez-Buylla, 1994; Lois *et al*., 1996). When explanted *in vitro*, these interneurons form chains by migrating along each other. This so-called *chain migration* is dependent of the expression of specific cell-adhesion molecules of the immunoglobulin superfamily such as the polysialylated form of neural cell-adhesion molecule (PSA-NCAM; reviewed in Marin *et al*., 2003).

Cerebellar Granule Cell Migration

Another population of interneurons migrates nonradially in the cerebellum: the granule cells migrating from the external granule layer (EGL) to the internal granular layer (IGL) during early postnatal stages of rodent development (reviewed in Hatten, 1999). The rate of migration of cerebellar granule neurons also is modulated through the control of intracellular calcium levels by activation of NMDA-, AMPA-, and somatostatin receptors (Komuro and Rakic, 1992, 1993, 1996; Yacubova and Komuro, 2002). Activation of somatostatin receptors increases the rate of granule cell migration near their site of birth in the EGL, but decreases their rate of migration near their final destination in the IGL. Correspondingly, the size and frequency of spontaneous Ca2+ fluctuations is enhanced by somatostatin in the early phase of migration, whereas spike-like Ca2+ transients are eliminated by somatostatin in the late phase (Yacubova and Komuro, 2002).

This mode of migration is characterized by a dynamic switch between tangential and radial mode of migration: after translocation in the superficial EGL, granule interneurons make a sharp 90° turn to migrate along the radial processes of Bergmann glia spanning the molecular layer, to reach the deep IGL where they will undergo terminal differentiation (Komuro and Rakic, 1995). This switch from tangential to radial mode of translocation is not unique to cerebellar granule cells but is also observed for cortical interneurons (Polleux *et al*., 2002) and is likely to reflect a basic property of migrating interneurons.

REFERENCES

Altman, J., 1969, Autoradiographic and histological studies of postnatal neurogenesis. 3. Dating the time of production and onset of differentiation of cerebellar microneurons in rats, *J. Comp. Neurol.* 136:269–293.

Anderson, S.A., Eisenstat, D.D., Shi, L., and Rubenstein, J.L., 1997, Interneuron migration from basal forebrain to neocortex: Dependence on Dlx genes, *Science* 278:474–476.

Anderson, S.A., Marin, O., Horn, C., Jennings, K., and Rubenstein J.L., 2001, Distinct cortical migrations from the medial and lateral ganglionic eminences, *Development* 128:353–363.

Anton, E.S., Cameron, R.S., and Rakic, P., 1996, Role of neuron–glial junctional domain proteins in the maintenance and termination of neuronal migration across the embryonic cerebral wall, *J. Neurosci.* 16:2283–2293.

Anton, E.S., Kreidberg, J.A., and Rakic, P., 1999, Distinct functions of alpha3 and alpha(v) integrin receptors in neuronal migration and laminar organization of the cerebral cortex, *Neuron* 22:277–289.

Anton, E.S., Marchionni, M.A., Lee, K.F., and Rakic, P., 1997, Role of GGF/neuregulin signaling in interactions between migrating neurons and radial glia in the developing cerebral cortex, *Development* 124: 3501–3510.

Antonicek, H., Persohn, E., and Schachner, M., 1987, Biochemical and functional characterization of a novel neuron–glia adhesion molecule that is involved in neuronal migration, *J. Cell. Biol.* 104:1587–1595.

Bader, B.L., Rayburn, H., Crowley, D., and Hynes, R.O., 1998, Extensive vasculogenesis, angiogenesis, and organogenesis precede lethality in mice lacking all alpha v integrins, *Cell* 95:507–519.

Behar, T.N., Schaffner, A.E., Scott, C.A., O'Connell, C., and Barker, J.L., 1998, Differential response of cortical plate and ventricular zone cells to GABA as a migration stimulus, *J. Neurosci.* 18:6378–6387.

Behar, T.N., Schaffner, A.E., Scott, C.A., Greene, C.L., and Barker, J.L., 2000, GABA receptor antagonists modulate postmitotic cell migration in slice cultures of embryonic rat cortex, *Cereb. Cortex* 10: 899–909.

Behar, T.N., Smith, S.V., Kennedy, R.T., McKenzie, J.M., Maric, I., and Barker, J.L., 2001, GABA(B) receptors mediate motility signals for migrating embryonic cortical cells, *Cereb. Cortex* 11:744–753.

Behar, T.N., Li, Y.X., Tran, H.T., Ma, W., Dunlap, V., Scott, C. *et al*., 1996, GABA stimulates chemotaxis and chemokinesis of embryonic

cortical neurons via calcium-dependent mechanisms, *J. Neurosci.* 16: 1808–1818.

Behar, T.N., Scott, C.A., Greene, C.L., Wen, X., Smith, S.V., Maric, D. *et al*., 1999, Glutamate acting at NMDA receptors stimulates embryonic cortical neuronal migration, *J. Neurosci.* 19:4449–4461.

Behar, T.N., Dugich-Djordjevic, M.M., Li, Y.X., Ma, W., Somogyi, R., Wen, X. *et al*., 1997, Neurotrophins stimulate chemotaxis of embryonic cortical neurons, *Eur. J. Neurosci.* 9:2561–2570.

Blystone, S.D., Slater, S.E., Williams, M.P., Crow, M.T., and Brown, E.J., 1999, A molecular mechanism of integrin crosstalk: Alphavbeta3 suppression of calcium/calmodulin-dependent protein kinase II regulates alpha5beta1 function, *J. Cell. Biol.* 145:889–897.

Bodary, S.C. and McLean, J.W., 1990, The integrin beta 1 subunit associates with the vitronectin receptor alpha v subunit to form a novel vitronectin receptor in a human embryonic kidney cell line, *J. Biol. Chem.* 265:5938–5941.

Borg, J.P., Ooi, J., Levy, E., and Margolis, B., 1996, The phosphotyrosine interaction domains of X11 and FE65 bind to distinct sites on the YENPTY motif of amyloid precursor protein, *Mol. Cell. Biol* 16: 6229–6241.

Brunstrom, J.E., Gray-Swain, M.R., Osborne, P.A., and Pearlman, A.L., 1997, Neuronal heterotopias in the developing cerebral cortex produced by neurotrophin-4, *Neuron* 18:505–517.

Cahana, A., Escamez, T., Nowakowski, R.S., Hayes, N.L., Giacobini, M., von Holst, A. *et al*., 2001, Targeted mutagenesis of Lis1 disrupts cortical development and LIS1 homodimerization, *Proc. Natl. Acad. Sci. USA*. 98:6429–6434.

Cameron, R.S. and Rakic, P., 1994, Identification of membrane proteins that comprise the plasmalemmal junction between migrating neurons and radial glial cells, *J. Neurosci.* 14:3139–3155.

Caspi, M., Atlas, R., Kantor, A., Sapir, T., and Reiner, O., 2000, Interaction between LIS1 and doublecortin, two lissencephaly gene products, *Hum. Mol. Genet.* 9:2205–2213.

Caviness, V.S., 1976, Patterns of cell and fiber ditribution in the neocortex of the reeler mutant mouse, *J. Comp. Neurol.* 170:435–448.

Caviness, V.S., Jr., So, D.K., and Sidman, R.L., 1972, The hybrid reeler mouse, *J. Heredity* 63:241–246.

Caviness, V.S., Jr. and Sidman, R.L., 1973, Time of origin or corresponding cell classes in the cerebral cortex of normal and *reeler* mutant mice: An autoradiographic analysis, *J. Comp. Neurol.* 148:141–151.

Chae, T., Kwon, Y.T., Bronson, R., Dikkes, P., Li, Ew., and Tsai, L.H., 1997, Mice lacking p35, a neuronal specific activator of Cdk5, display cortical lamination defects, seizures, and adult lethality, *Neuron* 18: 29–42.

Chazal, G., Durbec, P., Jankovski, A., Rougon, G., and Cremer, H., 2000, Consequences of neural cell adhesion molecule deficiency on cell migration in the rostral migratory stream of the mouse, *J. Neurosci.* 20:1446–1457.

Chen, H., Chedotal, A., He, Z., Goodman, C.S., and Tessier-Lavigne, M., 1997, Neuropilin-2, a novel member of the neuropilin family, is a high affinity receptor for the semaphorins Sema E and Sema IV but not Sema III, *Neuron* 19:547–559.

Chen, W.J., Goldstein, J.L., and Brown, M.S., 1990, NPXY, a sequence often found in cytoplasmic tails, is required for coated pit-mediated internalization of the low density lipoprotein receptor, *J. Biol. Chem.* 265: 3116–3123.

Cheresh, D.A., Smith, J.W., Cooper, H.M., and Quaranta, V., 1989, A novel vitronectin receptor integrin (alpha v beta x) is responsible for distinct adhesive properties of carcinoma cells, *Cell* 57:59–69.

Chuong, C.M., Crossin, K.L., and Edelman, G.M., 1987, Sequential expression and differential function of multiple adhesion molecules during the formation of cerebellar cortical layers, *J. Cell. Biol.* 104:331–342.

Colognato, H. and Yurchenco, P.D., 2000, Form and function: The laminin family of heterotrimers, *Dev. Dyn.* 218:213–234.

Corbin, J.G., Gaiano, N., Machold, R.P., Langston, A., and Fishell, G., 2000, The Gsh2 homeodomain gene controls multiple aspects of telencephalic development, *Development* 127:5007–5020.

Cousin, B., Leloup, C., Penicaud, L., and Price, J., 1997, Developmental changes in integrin beta-subunits in rat cerebral cortex, *Neurosci. Lett.* 234:161–165.

D'Arcangelo, G., Miao, G.G., Chen, S.C., Soares, H.D., Morgan, J.I., and Curran, T., 1995, A protein related to extracellular matrix proteins deleted in the mouse mutant *reeler*, *Nature* 374:719–723.

D'Arcangelo, G., Homayouni, R., Keshvara, L., Rice, D.S., Sheldon, M., and Curran, T., 1999, Reelin is a ligand for lipoprotein receptors, *Neuron* 24:471–479.

De Arcangelis, A., Mark, M., Kreidberg, J., Sorokin, L., and Georges-Labouesse, E., 1999, Synergistic activities of alpha3 and alpha6 integrins are required during apical ectodermal ridge formation and organogenesis in the mouse, *Development* 126: 3957–3968.

de Carlos, J.A., Lopez-Mascaraque, L., and Valverde, F., 1996, Dynamics of cell migration from the lateral ganglionic eminence in the rat, *J. Neurosci.* 16:6146–6156.

Dellovade, T.L., Pfaff, D.W., and Schwanzel-Fukuda, M., 1998, Olfactory bulb development is altered in small-eye (Sey) mice, *J. Comp. Neurol.* 402:402–418.

Denaxa, M., Chan, C.H., Schachner, M., Parnavelas, J.G., and Karagogeos, D., 2001, The adhesion molecule TAG-1 mediates the migration of cortical interneurons from the ganglionic eminence along the corticofugal fiber system, *Development* 128:4635–4644.

des Portes, V., Francis, F., Pinard, J.M., Desguerre, I., Moutard, M.L., Snoeck, I. *et al*., 1998, Doublecortin is the major gene causing X-linked subcortical laminar heterotopia (SCLH), *Hum. Mol. Genet.* 7: 1063–1070.

Doetsch, F. and Alvarez-Buylla, A., 1996, Network of tangential pathways for neuronal migration in adult mammalian brain, *Proc. Natl. Acad. Sci. USA* 93:14895–14900.

Doetsch, F., Garcia-Verdugo, J.M., and Alvarez-Buylla, A., 1997, Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain, *J. Neurosci.* 17: 5046–5061.

Doetsch, F., Garcia-Verdugo, J.M., and Alvarez-Buylla, A., 1999a, Regeneration of a germinal layer in the adult mammalian brain, *Proc. Natl. Acad. Sci. USA* 96:11619–11624.

Doetsch, F., Caille, I., Lim, D.A., Garcia-Verdugo, J.M., and Alvarez-Buylla, A., 1999b, Subventricular zone astrocytes are neural stem cells in the adult mammalian brain, *Cell* 97:703–716.

Edmondson, J.C., Liem, R.K., Kuster, J.E., and Hatten, M.E., 1988, Astrotactin: A novel neuronal cell surface antigen that mediates neuron–astroglial interactions in cerebellar microcultures, *J. Cell Biol.* 106:505–517.

Efimov, V.P. and Morris, N.R., 2000, The LIS1-related NUDF protein of *Aspergillus nidulans* interacts with the coiled-coil domain of the NUDE/RO11 protein, *J. Cell. Biol.* 150:681–688.

Eksioglu, Y.Z., Scheffer, I.E., Cardenas, P., Knoll, J., DiMario, F., Ramsby, G. *et al*., 1996, Periventricular heterotopia: An X-linked dominant epilepsy locus causing aberrant cerebral cortical development, *Neuron* 16:77–87.

Fairen, A., Cobas, A., and Fonseca, M., 1986, Times of generation of glutamic acid decarboxylase immunoreactive neurons in mouse somatosensory cortex, *J. Comp. Neurol.* 251:67–83.

Falconer, M.M., Echeverri, C.J., and Brown, D.L., 1992, Differential sorting of beta tubulin isotypes into colchicine-stable microtubules during neuronal and muscle differentiation of embryonal carcinoma cells, *Cell Motil. Cytoskeleton* 21:313–325.

Fassler, R. and Meyer, M., 1995, Consequences of lack of beta 1 integrin gene expression in mice, *Genes Dev.* 9:1896–1908.

Faulkner, N.E., Dujardin, D.L., Tai, C.Y., Vaughan, K.T., O'Connell, C.B., Wang, Y. *et al*., 2000, A role for the lissencephaly gene LIS1 in mitosis and cytoplasmic dynein function, *Nat. Cell. Biol.* 2:784–791.

Feng, Y. and Walsh, C.A., 2001, Protein-protein interactions, cytoskeletal regulation and neuronal migration *Nat. Rev. Neurosci.* 2:408–416.

Feng, Y., Olson, E.C., Stukenberg, P.T., Flanagan, L.A., Kirschner, M.W., and Walsh, C.A., 2000, LIS1 regulates CNS lamination by interacting with mNudE, a central component of the centrosome, *Neuron* 28: 665–679.

Fentress, J.C., Stanfield, B.B., and Cowan, W.M., 1981, Observation on the development of the striatum in mice and rats, *Anat. Embryol. (Berl)* 163:275–298.

Fishell, G., Mason, C.A., and Hatten, M.E., 1993a, Dispersion of neural progenitors within the germinal zones of the forebrain, *Nature* 362: 636–638.

Fishell, G. and Kriegstein, A.R., 2003, Neurons from radial glia: The consequences of asymmetric inheritance, *Curr. Opin. Neurobiol.* 13:34–41.

Fishman, R.B. and Hatten, M.E., 1993, Multiple receptor systems promote CNS neural migration, *J. Neurosci.* 13:3485–3495.

Fode, C., Ma, Q., Casarosa, S., Ang, S.L., Anderson, D.J., and Guillemot, F., 2000, A role for neural determination genes in specifying the dorsoventral identity of telencephalic neurons, *Genes. Dev.* 14: 67–80.

Fox, J.W., Lamperti, E.D., Eksioglu, Y.Z., Hong, S.E., Feng, Y., Graham, D.A. *et al*., 1998, Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia, *Neuron* 21: 1315–1325.

Francis, F., Koulakoff, A., Boucher, D., Chafey, P., Schaar, B., Vinet, M.C. *et al*., 1999, Doublecortin is a developmentally regulated, microtubule-associated protein expressed in migrating and differentiating neurons, *Neuron* 23:247–256.

Franco, B., Guioli, S., Pragliola, A., Incerti, B., Bardoni, B., Tonlorenzi, R. *et al*., 1991, A gene deleted in Kallmann's syndrome shares homology with neural cell adhesion and axonal path-finding molecules, *Nature* 353:529–536.

Galileo, D.S., Majors, J., Horwitz, A.F., and Sanes, J.R., 1992, Retrovirally introduced antisense integrin RNA inhibits neuroblast migration in vivo, *Neuron* 9:1117–1131.

Georges-Labouesse, E., Mark, M., Messaddeq, N., and Gansmuller, A., 1998, Essential role of alpha 6 integrins in cortical and retinal lamination, *Curr. Biol.* 8:983–986.

Georges-Labouesse, E., Messaddeq, N., Yehia, G., Cadalbert, L., Dierich, A., and Le Meur, M., 1996, Absence of integrin alpha 6 leads to epidermolysis bullosa and neonatal death in mice, *Nat. Genet.* 13:370–373.

Gertler, F.B., Hill, K.K., Clark, M.J., and Hoffmann, F.M., 1993, Dosage-sensitive modifiers of *Drosophila* abl tyrosine kinase function: Prospero, a regulator of axonal outgrowth, and disabled, a novel tyrosine kinase substrate, *Genes Dev.* 7:441–453.

Giger, R.J., Urquhart, E.R., Gillespie, S.K., Levengood, D.V., Ginty, D.D., and Kolodkin, A.L., 1998, Neuropilin-2 is a receptor for semaphorin IV: Insight into the structural basis of receptor function and specificity, *Neuron* 21:1079–1092.

Gilmore, E.C., Ohshima, T., Goffinet, A.M., Kulkarni, A.B., and Herrup, K., 1998, Cyclin-dependent kinase 5-deficient mice demonstrate novel developmental arrest in cerebral cortex, *J. Neurosci.* 18: 6370–6377.

Gleeson, J.G., Lin, P.T., Flanagan, L.A., and Walsh, C.A., 1999, Doublecortin is a microtubule-associated protein and is expressed widely by migrating neurons, *Neuron* 23:257–271.

Gleeson, J.G., Allen, K.M., Fox, J.W., Lamperti, E.D., Berkovic, S., Scheffer, I. *et al*., 1998, Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein, *Cell* 92:63–72.

Gonzalez, J.L., Russo, C.J., Goldowitz, D., Sweet, H.O., Davisson, M.T., and Walsh, C.A., 1997, Birthdate and cell marker analysis of scrambler: A novel mutation affecting cortical development with a *reeler*-like phenotype, *J. Neurosci.* 17:9204–9211.

Graus-Porta, D., Blaess, S., Senften, M., Littlewood-Evans, A., Damsky, C., Huang, Z. *et al*., 2001, Beta1-class integrins regulate the development of laminae and folia in the cerebral and cerebellar cortex, *Neuron* 31: 367–379.

Gray, G.E., Leber, S.M., and Sanes, J.R., 1990, Migratory patterns of clonally related cells in the developing central nervous system, *Experientia* 46: 929–940.

Gregory, W.A., Edmondson, J.C., Hatten, M.E., and Mason, C.A., 1988, Cytology and neuron–glial apposition of migrating cerebellar granule cells in vitro, *J. Neurosci.* 8:1728–1738.

Grumet, M., 1992, Structure, expression, and function of Ng-CAM, a member of the immunoglobulin superfamily involved in neuron-neuron and neuron–glia adhesion, *J. Neurosci. Res.* 31:1–13.

Grumet, M., Hoffman, S., Crossin, K.L., and Edelman, G.M., 1985, Cytotactin, an extracellular matrix protein of neural and non-neural tissues that mediates glia–neuron interaction, *Proc. Natl. Acad. Sci. USA* 82:8075–8079.

Hack, I., Bancila, M., Loulier, K., Carroll, P., and Cremer, H., 2002, Reelin is a detachment signal in tangential chain-migration during postnatal neurogenesis, *Nat. Neurosci.* 5:939–945.

Hagg, T., Portera-Cailliau, C., Jucker, M., and Engvall, E., 1997, Laminins of the adult mammalian CNS; laminin-alpha2 (merosin M-) chain immunoreactivity is associated with neuronal processes, *Brain. Res.* 764:17–27.

Halfter, W., Dong, S., Yip, Y.P., Willem, M., and Mayer, U., 2002, A critical function of the pial basement membrane in cortical histogenesis, *J. Neurosci.* 22:6029–6040.

Hatten, M.E., 1990, Riding the glial monorail: A common mechanism for glial-guided neuronal migration in different regions of the developing mammalian brain, *Trends Neurosci.* 13:179–184.

Hatten, M.E., 1993, The role of migration in central nervous system neuronal development, *Curr. Opin. Neurobiol.* 3:38–44.

Hatten, M.E., 1999, Central nervous system neuronal migration, *Annu. Rev. Neurosci.* 22:511–539.

Hatten, M.E. and Mason, C.A., 1990, Mechanisms of glial-guided neuronal migration in vitro and in vivo, *Experientia* 46:907–916.

Hattori, M., Adachi, H., Tsujimoto, M., Arai, H., and Inoue, K., 1994, Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor acetylhydrolase [corrected], *Nature* 370:216–218.

Hiesberger, T., Trommsdorff, M., Howell, B.W., Goffinet, A., Mumby, M.C., Cooper, J.A. *et al*., 1999, Direct binding of Reelin to VLDL receptor and ApoE receptor 2 induces tyrosine phosphorylation of disabled-1 and modulates tau phosphorylation, *Neuron* 24:481–489.

Hirotsune, S., Fleck, M.W., Gambello, M.J., Bix, G.J., Chen, A., Clark, G.D. *et al*., 1998, Graded reduction of Pafah1b1 (Lis1) activity results in neuronal migration defects and early embryonic lethality, *Nat. Genet.* 19:333–339.

Hirotsune, S., Takahara, T., Sasaki, N., Hirose, K., Yoshiki, A., Ohashi, T. *et al*., 1995, The *reeler* gene encodes a protein with an EGF-like motif expressed by pioneer neurons, *Nat. Genet.* 10:77–83.

Hirsch, E., Gullberg, D., Balzac, F., Altruda, F., Silengo, L., and Tarone, G., 1994, Alpha v integrin subunit is predominantly located in nervous tissue and skeletal muscle during mouse development, *Dev. Dyn.* 201:108–120.

Hodivala-Dilke, K.M., DiPersio, C.M., Kreidberg, J.A., and Hynes, R.O., 1998, Novel roles for alpha3beta1 integrin as a regulator of cytoskeletal assembly and as a trans-dominant inhibitor of integrin receptor function in mouse keratinocytes, *J. Cell. Biol.* 142:1357–1369.

Hong, S.E., Shugart, Y.Y., Huang, D.T., Shahwan, S.A., Grant, P.E., Hourihane, J.O. *et al*., 2000, Autosomal recessive lissencephaly with

cerebellar hypoplasia is associated with human RELN mutations, *Nat. Genet.* 26:93–96.

Horesh, D., Sapir, T., Francis, F., Wolf, S.G., Caspi, M., Elbaum, M. *et al*., 1999, Doublecortin, a stabilizer of microtubules, *Hum. Mol. Genet.* 8: 1599–1610.

Howell, B.W., Herrick, T.M., and Cooper, J.A., 1999a, Reelin-induced tryosine phosphorylation of disabled 1 during neuronal positioning, *Genes Dev.* 13:643–648.

Howell, B.W., Hawkes, R., Soriano, P., and Cooper, J.A., 1997, Neuronal position in the developing brain is regulated by mouse disabled-1, *Nature* 389:733–737.

Howell, B.W., Lanier, L.M., Frank, R., Gertler, F.B., and Cooper, J.A., 1999b, The disabled 1 phosphotyrosine-binding domain binds to the internalization signals of transmembrane glycoproteins and to phospholipids, *Mol. Cell. Biol.* 19:5179–5188.

Hu, H., 2000, Polysialic acid regulates chain formation by migrating olfactory interneuron precursors, *J. Neurosci. Res.* 61:480–492.

Iijima, M., Huang, Y.E., and Devreotes, P., 2002, Temporal and spatial regulation of chemotaxis, *Dev. Cell.* 3:469–478.

Inoue, T., Tanaka, T., Takeichi, M., Chisaka, O., Nakamura, S., and Osumi, N., 2001, Role of cadherins in maintaining the compartment boundary between the cortex and striatum during development, *Development* 128:561–569.

Jacques, T.S., Relvas, J.B., Nishimura, S., Pytela, R., Edwards, G.M., Streuli, C.H. *et al*., 1998, Neural precursor cell chain migration and division are regulated through different beta1 integrins, *Development* 125: 3167–3177.

Jankovski, A. and Sotelo, C., 1996, Subventricular zone–olfactory bulb migratory pathway in the adult mouse: Cellular composition and specificity as determined by heterochronic and heterotopic transplantation, *J. Comp. Neurol.* 371:376–396.

Kavanaugh, W.M. and Williams, L.T., 1994, An alternative to SH2 domains for binding tyrosine-phosphorylated proteins, *Science* 266: 1862–1865.

Kirkpatrick, L.L. and Brady, S.T., 1994, Modulation of the axonal microtubule cytoskeleton by myelinating Schwann cells, *J. Neurosci.* 14: 7440–7450.

Kirschenbaum, B., Doetsch, F., Lois, C., and Alvarez-Buylla, A., 1999, Adult subventricular zone neuronal precursors continue to proliferate and migrate in the absence of the olfactory bulb, *J. Neurosci.* 19: 2171–2180.

Kitagawa, M., Umezu, M., Aoki, J., Koizumi, H., Arai, H., and Inoue, K., 2000, Direct association of LIS1, the lissencephaly gene product, with a mammalian homologue of a fungal nuclear distribution protein, rNUDE, *FEBS Lett.* 479:57–62.

Kleinman, H.K., McGarvey, M.L., Liotta, L.A., Robey, P.G., Tryggvason, K., and Martin, G.R., 1982, Isolation and characterization of type IV procollagen, laminin, and heparan sulfate proteoglycan from the EHS sarcoma, *Biochemistry* 21:6188–6193.

Ko, J., Humbert, S., Bronson, R.T., Takahashi, S., Kulkarni, A.B., Li, E. *et al*., 2001, p35 and p39 are essential for cyclin-dependent kinase 5 function during neurodevelopment, *J. Neurosci.* 21:6758–6771.

Kolodkin, A.L., Levengood, D.V., Rowe, E.G., Tai, Y.T., Giger, R.J., and Ginty, D.D., 1997, Neuropilin is a semaphorin III receptor, *Cell* 90: 753–762.

Komuro, H. and Rakic, P., 1992, Selective role of N-type calcium channels in neuronal migration, *Science* 257:806–809.

Komuro, H. and Rakic, P., 1993, Modulation of neuronal migration by NMDA receptors, *Science* 260:95–97.

Komuro, H. and Rakic, P., 1995, Dynamics of granule cell migration: A confocal microscopic study in acute cerebellar slice preparations, *J. Neurosci.* 15:1110–1120.

Komuro, H. and Rakic, P., 1996, Intracellular Ca2+ fluctuations modulate the rate of neuronal migration, *Neuron* 17:275–285.

Kornack, D.R. and Rakic, P., 2001, The generation, migration, and differentiation of olfactory neurons in the adult primate brain, *Proc. Natl. Acad. Sci. USA* 98:4752–4757.

Kreidberg, J.A., Donovan, M.J., Goldstein, S.L., Rennke, H., Shepherd, K., Jones, R.C. *et al*., 1996, Alpha 3 beta 1 integrin has a crucial role in kidney and lung organogenesis, *Development* 122:3537–3547.

Kwon, Y.T. and Tsai, L.H., 1998, A novel disruption of cortical development in p35(−/−) mice distinct from *reeler, J. Comp. Neurol.* 395:510–522.

Kwon, Y.T., Gupta, A., Zhou, Y., Nikolic, M., and Tsai, L.H., 2000, Regulation of N-cadherin-mediated adhesion by the p35-Cdk5 kinase, *Curr. Biol.* 10:363–372.

Lambert de Rouvroit, C. and Goffinet, A.M., 1998, The *reeler* mouse as a model of brain development, *Adv. Anat. Embryol. Cell Biol.* 150:1–106.

Lavdas, A.A., Grigoriou, M., Pachnis, V., and Parnavelas, J.G., 1999, The medial ganglionic eminence gives rise to a population of early neurons in the developing cerebral cortex, *J. Neurosci.* 19:7881–7888.

Law, D.A., DeGuzman, F.R., Heiser, P., Ministri-Madrid, K., Killeen, N., and Phillips, D.R., 1999, Integrin cytoplasmic tyrosine motif is required for outside-in alphaIIbbeta3 signalling and platelet function, *Nature* 401:808–811.

Lei, Y. and Warrior, R., 2000, The Drosophila Lissencephaly1 (DLis1) gene is required for nuclear migration, *Dev. Biol.* 226:57–72.

Letinic, K. and Rakic, P., 2001, Telencephalic origin of human thalamic GABAergic neurons, *Nat. Neurosci.* 4:931–936.

Letinic, K., Zoncu, R., and Rakic, P., 2002, Origin of GABAergic neurons in the human neocortex, *Nature* 417:645–649.

Lindner, J., Rathjen, F.G., and Schachner, M., 1983, L1 mono- and polyclonal antibodies modify cell migration in early postnatal mouse cerebellum, *Nature* 305:427–430.

Liu, Z., Steward, R., and Luo, L., 2000, Drosophila Lis1 is required for neuroblast proliferation, dendritic elaboration and axonal transport, *Nat. Cell. Biol.* 2:776–783.

Lois, C. and Alvarez-Buylla, A., 1993, Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia, *Proc. Natl. Acad. Sci. USA* 90:2074–2077.

Lois, C. and Alvarez-Buylla, A., 1994, Long-distance neuronal migration in the adult mammalian brain, *Science* 264:1145–1148.

Lois, C., Garcia-Verdugo, J.M., and Alvarez-Buylla, A., 1996, Chain migration of neuronal precursors, *Science* 271:978–981.

Loo, D.T., Kanner, S.B., and Aruffo, A., 1998, Filamin binds to the cytoplasmic domain of the beta1-integrin. Identification of amino acids responsible for this interaction, *J. Biol. Chem.* 273:23304–23312.

Margolis, B., 1996, The PI/PTB domain: A new protein interaction domain involved in growth factor receptor signaling, *J. Lab. Clin. Med.* 128: 235–241.

Maricich, S.M., Gilmore, E.C., and Herrup, K., 2001, The role of tangential migration in the establishment of mammalian cortex, *Neuron* 31:175–178.

Marin, O., Yaron, A., Bagri, A., Tessier-Lavigne, M., and Rubenstein, J.L., 2001, Sorting of striatal and cortical interneurons regulated by semaphorin–neuropilin interactions, *Science* 293:872–875.

Marin, O., Plump, A.S., Flames, N., Sanchez-Camacho, C., Tessier-Lavigne, M., and Rubenstein, J.L., 2003, Directional guidance of interneuron migration to the cerebral cortex relies on subcortical Slit1/2-independent repulsion and cortical attraction, *Development* 130: 1889–1901.

McEvilly, R.J., de Diaz, M.O., Schonemann, M.D., Hooshmand, F., and Rosenfeld, M.G., 2002, Transcriptional regulation of cortical neuron migration by POU domain factors, *Science* 295:1528–1532.

Mechtersheimer, G., Barth, T., Hartschuh, W., Lehnert, T., and Moller, P., 1994, In situ expression of beta 1, beta 3 and beta 4 integrin subunits in non-neoplastic endothelium and vascular tumours, *Virchows Arch.* 425:375–384.

Metin, C., Denizot, J.P., and Ropert, N., 2000, Intermediate zone cells express calcium-permeable AMPA receptors and establish close contact with growing axons, *J. Neurosci.* 20:696–708.

Miner, J.H., Cunningham, J., and Sanes, J.R., 1998, Roles for laminin in embryogenesis: Exencephaly, syndactyly, and placentopathy in mice lacking the laminin alpha5 chain, *J. Cell. Biol.* 143:1713–1723.

Misson, J.P., Austin, C.P., Takahashi, T., Cepko, C.L., and Caviness, V.S., Jr., 1991, The alignment of migrating neural cells in relation to the murine neopallial radial glial fiber system, *Cereb. Cortex* 1: 221–229.

Miyagoe-Suzuki, Y., Nakagawa, M., and Takeda, S., 2000, Merosin and congenital muscular dystrophy, *Microsc. Res. Tech* 48:181–191. [pii].

Montgomery, A.M., Becker, J.C., Siu, C.H., Lemmon, V.P., Cheresh, D.A., Pancook, J.D. *et al*., 1996, Human neural cell adhesion molecule L1 and rat homologue NILE are ligands for integrin alpha v beta 3, *J. Cell Biol.* 132:475–485.

Moro, F., Carrozzo, R., Veggiotti, P., Tortorella, G., Toniolo, D., Volzone, A., and Guerrini, R., 2002, Familial periventricular heterotopia: Missense and distal truncating mutations of the FLN1 gene, *Neurology* 58: 916–921.

Moskowitz, P.F. and Oblinger, M.M., 1995, Transcriptional and post-transcriptional mechanisms regulating neurofilament and tubulin gene expression during normal development of the rat brain, *Brain. Res. Mol. Brain. Res.* 30:211–222.

Moyle, M., Napier, M.A., and McLean, J.W., 1991, Cloning and expression of a divergent integrin subunit beta 8, *J. Biol. Chem.* 266: 19650–19658.

Nadarajah, B. and Parnavelas, J.G., 2002, Modes of neuronal migration in the developing cerebral cortex, *Nat. Rev. Neurosci.* 3:423–432.

Nadarajah, B., Alifragis, P., Wong, R.O., and Parnavelas, J.G., 2002, Ventricle-directed migration in the developing cerebral cortex, *Nat. Neurosci.* 5:218–224.

Nadarajah, B., Brunstrom, J.E., Grutzendler, J., Wong, R.O., and Pearlman, A.L., 2001, Two modes of radial migration in early development of the cerebral cortex, *Nat. Neurosci.* 4:143–150.

Nagano, T., Yoneda, T., Hatanaka, Y., Kubota, C., Murakami, F., and Sato, M., 2002, Filamin A-interacting protein (FILIP) regulates cortical cell migration out of the ventricular zone, *Nat. Cell. Biol.* 4:495–501.

Nery, S., Fishell, G., and Corbin, J.G., 2002, The caudal ganglionic eminence is a source of distinct cortical and subcortical cell populations, *Nat. Neurosci.* 5:1279–1287.

Niethammer, M., Smith, D.S., Ayala, R., Peng, J., Ko, J., and Lee, M.S. *et al*., 2000, NUDEL is a novel Cdk5 substrate that associates with LIS1 and cytoplasmic dynein, *Neuron* 28:697–711.

Nikolic, M., Chou, M.M., Lu, W., Mayer, B.J., and Tsai, L.H., 1998, The p35/Cdk5 kinase is a neuron-specific Rac effector that inhibits Pak1 activity, *Nature* 395:194–198.

O'Leary, D.D. and Nakagawa, Y., 2002, Patterning centers, regulatory genes and extrinsic mechanisms controlling arealization of the neocortex, *Curr. Opin. Neurobiol.* 12:14–25.

O'Rourke, N.A., Chenn, A., and McConnell, S.K., 1997, Postmitotic neurons migrate tangentially in the cortical ventricular zone, *Development* 124:997–1005.

O'Rourke, N.A., Dailey, M.E., Smith, S.J., and McConnell, S.K., 1992a, Diverse migratory pathways in the developing cerebral cortex, *Science* 258:299–302.

O'Rourke, N.A., Sullivan, D.P., Kaznowski, C.E., Jacobs, A.A., and McConnell, S.K., 1995, Tangential migration of neurons in the developing cerebral cortex, *Development* 121:2165–2176.

Ogawa, M., Miyata, T., Nakajima, K., and Mikoshiba, K., 1997, [The action of reelin in the layering of cortical neurons in cerebrum], *Tanpakushitsu Kakusan Koso* 42:577–583.

Ogawa, M., Miyata, T., Nakajima, K., Yagyu, K., Seike, M., Ikenaka, K. *et al*., 1995, The *reeler* gene-associated antigen on Cajal–Retzius neurons is a crucial molecule for laminar organization of cortical neurons, *Neuron* 14:899–912.

Ohshima, T., Ward, J.M., Huh, C.G., Longenecker, G., Veeranna, Pant, H.C. *et al*., 1996, Targeted disruption of the cyclin-dependent kinase 5 gene results in abnormal corticogenesis, neuronal pathology and perinatal death, *Proc. Natl. Acad. Sci. USA* 93:11173–11178.

Ohta, Y., Suzuki, N., Nakamura, S., Hartwig, J.H., and Stossel, T.P., 1999, The small GTPase RalA targets filamin to induce filopodia, *Proc. Natl. Acad. Sci. USA* 96:2122–2128.

Olson, E.C. and Walsh, C.A., 2002, Smooth, rough and upside-down neocortical development, *Curr. Opinion. Gen. Dev.* 12:320–327.

Parnavelas, J.G., 2000, The origin and migration of cortical neurones: New vistas, *Trends. Neurosci.* 23:126–131.

Parnavelas, J.G., Barfield, J.A., Franke, E., and Luskin, M.B., 1991, Separate progenitor cells give rise to pyramidal and nonpyramidal neurons in the rat telencephalon, *Cereb. Cortex* 1:463–468.

Pencea, V., Bingaman, K.D., Freedman, L.J., and Luskin, M.B., 2001, Neurogenesis in the subventricular zone and rostral migratory stream of the neonatal and adult primate forebrain, *Exp. Neurol.* 172:1–16.

Peretto, P., Merighi, A., Fasolo, A., and Bonfanti, L., 1997, Glial tubes in the rostral migratory stream of the adult rat, *Brain. Res. Bull.* 42:9–21.

Pleasure, S.J., Anderson, S., Hevner, R., Bagri, A., Marin, O., Lowenstein, D.H. *et al*., 2000, Cell migration from the ganglionic eminences is required for the development of hippocampal GABAergic interneurons, *Neuron* 28:727–740.

Polleux, F., Whitford, K.L., Dijkhuizen, P.A., Vitalis, T., and Ghosh, A., 2002, Control of cortical interneuron migration by neurotrophins and PI3-kinase signaling, *Development* 129:3147–3160.

Poluch, S. and Konig, N., 2002, AMPA receptor activation induces GABA release from neurons migrating tangentially in the intermediate zone of embryonic rat neocortex, *Eur. J. Neurosci.* 16:350–354.

Poluch, S., Drian, M.J., Durand, M., Astier, C., Benyamin, Y., and Konig, N., 2001, AMPA receptor activation leads to neurite retraction in tangentially migrating neurons in the intermediate zone of the embryonic rat neocortex, *J. Neurosci. Res.* 63:35–44.

Powell, E.M., Mars, W.M., and Levitt, P., 2001, Hepatocyte growth factor/scatter factor is a motogen for interneurons migrating from the ventral to dorsal telencephalon, *Neuron* 30:79–89.

Powell, E.M., Campbell, D.B., Stanwood, G.D., Davis, C., Noebels, J.L., and Levitt, P., 2003, Genetic disruption of cortical interneuron development causes region- and GABA cell type-specific deficits, epilepsy, and behavioral dysfunction, *J. Neurosci.* 23:622–631.

Qiu, M., Bulfone, A., Martinez, S., Meneses, J.J., Shimamura, K., Pedersen, R.A. *et al*., 1995, Null mutation of Dlx-2 results in abnormal morphogenesis of proximal first and second branchial arch derivatives and abnormal differentiation in the forebrain, *Genes Dev.* 9: 2523–2538.

Quattrocchi, C.C., Wannenes, F., Persico, A.M., Ciafre, S.A., D'Arcangelo, G., Farace, M.G. *et al*., 2002, Reelin is a serine protease of the extracellular matrix, *J. Biol. Chem.* 277:303–309.

Rakic, P., 1990. Principles of neural cell migration, *Experientia* 46:882–891.

Rakic, P., 1971a, Guidance of neurons migrating to the fetal monkey neocortex, *Brain. Res.* 33:471–476.

Rakic, P., 1971b, Neuron–glia relationship during granule cell migration in developing cerebellar cortex. A Golgi and electronmicroscopic study in Macacus Rhesus, *J. Comp. Neurol.* 141:283–312.

Rakic, P., 1971c, Neuron–glia relationship during granule cell migration in developing cerebellar cortex. A Golgi and electron microscopic study in Macacus Rhesus, *J. Comp. Neurol.* 141:283–312.

Rakic, P., 1972a, Mode of cell migration to the superficial layers of fetal monkey neocortex, *J. Comp. Neurol.* 145:61–83.

Rakic, P., 1972b, Extrinsic cytological determinants of basket and stellate cell dendritic pattern in the cerebellar molecular layer, *J. Comp. Neurol.* 146:335–354.

Rakic, P., 1972c, Mode of cell migration to the superficial layers of fetal monkey neocortex, *J. Comp. Neurol.* 145:61–83.

Rakic, P., 1988, Specification of cerebral cortical areas, *Science* 241:170–176.

Rakic, P., 1990, Principles of neural cell migration, *Experientia* 46:882–891.

Rakic, P. and Komuro, H., 1995, The role of receptor/channel activity in neuronal cell migration, *J. Neurobiol.* 26:299–315.

Rakic, P. and Caviness, V.S., Jr., 1995, Cortical development: View from neurological mutants two decades later, *Neuron* 14:1101–1104.

Rakic, P., Cameron, R.S., and Komuro, H., 1994, Recognition, adhesion, transmembrane signaling and cell motility in guided neuronal migration, *Curr. Opin. Neurobiol.* 4:63–69.

Rakic, P., Knyihar-Csillik, E., and Csillik, B., 1996, Polarity of microtubule assemblies during neuronal cell migration, *Proc. Natl. Acad. Sci. USA* 93:9218–9222.

Rakic, P., 2003, Elusive radial glial cells: Historical and evolutionary perspective, *Glia* 43:19–32.

Redies, C. and Takeichi, M., 1993, Expression of N-cadherin mRNA during development of the mouse brain, *Dev. Dyn.* 197:26–39.

Reiner, O., Carrozzo, R., Shen, Y., Wehnert, M., Faustinella, F. *et al*., 1993, Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats, *Nature* 364:717–721.

Rice, D.S., Sheldon, M., D'Arcangelo, G., Nakajima, K., Goldowitz, D., and Curran, T., 1998, Disabled-1 acts downstream of Reelin in a signaling pathway that controls laminar organization in the mammalian brain, *Development* 125:3719–3729.

Ringstedt, T., Linnarsson, S., Wagner, J., Lendahl, U., Kokaia, Z., Arenas, E. *et al*., 1998, BDNF regulates reelin expression and Cajal–Retzius cell development in the cerebral cortex, *Neuron* 21:305–315.

Rio, C., Rieff, H.I., Qi, P., Khurana, T.S., and Corfas, G., 1997, Neuregulin and erbB receptors play a critical role in neuronal migration, *Neuron* 19:39–50.

Rivas, R.J. and Hatten, M.E., 1995, Motility and cytoskeletal organization of migrating cerebellar granule neurons, *J. Neurosci.* 15:981–989.

Rousselot, P., Lois, C., and Alvarez-Buylla, A., 1995, Embryonic (PSA) N-CAM reveals chains of migrating neuroblasts between the lateral ventricle and the olfactory bulb of adult mice, *J. Comp. Neurol.* 351: 51–61.

Rutishauser, U. and Jessell, T.M., 1988, Cell adhesion molecules in vertebrate neural development, *Physiol. Rev.* 68:819–857.

Sanes, J.R., 1989, Extracellular matrix molecules that influence neural development, *Annu. Rev. Neurosci.* 12:491–516.

Sapir, T., Elbaum, M., and Reiner, O., 1997, Reduction of microtubule catastrophe events by LIS1, platelet-activating factor acetylhydrolase subunit, *Embo. J.* 16:6977–6984.

Sarkisian, M.R., Frenkel, M., Li, W., Oborski, J.A., and LoTurco, J.J., 2001, Altered interneuron development in the cerebral cortex of the flathead mutant, *Cereb. Cortex* 11:734–743.

Sasaki, S., Shionoya, A., Ishida, M., Gambello, M.J., Yingling, J., Wynshaw-Boris, A. *et al*., 2000, A LIS1/NUDEL/cytoplasmic dynein heavy chain complex in the developing and adult nervous system, *Neuron* 28:681–696.

Sharma, C.P., Ezzell, R.M., and Arnaout, M.A., 1995, Direct interaction of filamin (ABP-280) with the beta 2-integrin subunit CD18, *J. Immunol.* 154:3461–3470.

Sheen, V.L., Dixon, P.H., Fox, J.W., Hong, S.E., Kinton, L., Sisodiya, S.M. *et al*., 2001, Mutations in the X-linked filamin 1 gene cause periventricular nodular heterotopia in males as well as in females, *Hum. Mol. Genet.* 10:1775–1783.

Sheldon, M., Rice, D.S., D'Arcangelo, G., Yoneshima, H., Nakajima, K., Mikoshiba, K. *et al*., 1997, Scrambler and yotari disrupt the disabled gene and produce a *reeler*-like phenotype in mice, *Nature* 389: 730–733.

Shimamura, K. and Takeichi, M., 1992, Local and transient expression of E-cadherin involved in mouse embryonic brain morphogenesis, *Development* 116:1011–1019.

Sidman, R.L. and Rakic, P., 1973, Neuronal migration, with special reference to developing human brain: A review, *Brain Res.* 62:1–35.

Simon, K.O., Nutt, E.M., Abraham, D.G., Rodan, G.A., and Duong, L.T., 1997, The alphavbeta3 integrin regulates alpha5beta1-mediated cell migration toward fibronectin, *J. Biol. Chem.* 272:29380–29389.

Smith, D.S., Niethammer, M., Ayala, R., Zhou, Y., Gambello, M.J., Wynshaw-Boris, A. *et al*., 2000, Regulation of cytoplasmic dynein behaviour and microtubule organization by mammalian Lis1, *Nat. Cell. Biol.* 2: 767–775.

Stephens, L.E., Sutherland, A.E., Klimanskaya, I.V., Andrieux, A., Meneses, J., Pedersen, R.A. *et al*., 1995, Deletion of beta 1 integrins in mice results in inner cell mass failure and peri-implantation lethality, *Genes. Dev.* 9:1883–1895.

Stipp, C.S., Litwack, E.D., and Lander, A.D., 1994, Cerebroglycan: An integral membrane heparan sulfate proteoglycan that is unique to the developing nervous system and expressed specifically during neuronal differentiation, *J. Cell. Biol.* 124:149–160.

Stitt, T.N. and Hatten, M.E., 1990, Antibodies that recognize astrotactin block granule neuron binding to astroglia, *Neuron* 5:639–649.

Stossel, T.P., Condeelis, J., Cooley, L., Hartwig, J.H., Noegel, A., Schleicher, M. *et al*., 2001, Filamins as integrators of cell mechanics and signalling, *Nat. Rev. Mol. Cell. Biol.* 2:138–145.

Sunada, Y., Edgar, T.S., Lotz, B.P., Rust, R.S., and Campbell, K.P., 1995, Merosin-negative congenital muscular dystrophy associated with extensive brain abnormalities, *Neurology* 45:2084–2089.

Sussel, L., Marin, O., Kimura, S., and Rubenstein, J.L., 1999, Loss of Nkx2.1 homeobox gene function results in a ventral to dorsal molecular respecification within the basal telencephalon: Evidence for a transformation of the pallidum into the striatum, *Development* 126: 3359–3370.

Sweet, H.O., Bronson, R.T., Johnson, K.R., Cook, S.A., and Davisson, M.T., 1996, Scrambler, a new neurological mutation of the mouse with abnormalities of neuronal migration, *Mamm. Genome* 7:798–802.

Takeichi, M., 1991, Cadherin cell adhesion receptors as a morphogenetic regulator, *Science* 251:1451–1455.

Tamamaki, N., Fujimori, K.E., and Takauji, R., 1997, Origin and route of tangentially migrating neurons in the developing neocortical intermediate zone, *J. Neurosci.* 17:8313–8323.

Tamamaki, N., Fujimori, K., Nojyo, Y., Kaneko, T., and Takauji, R., 2003. Evidence that Sema3A and Sema3F regulate the migration of GABAergic neurons in the developing neocortex, *J. Comp. Neurol.* 455:238–248.

Tan, S.-S. and Breen, S., 1993, Radial mosaicism and tangential cell dispersion both contribute to mouse neocortical development, *Nature* 362: 638–639.

Tan, S.-S., Faulkner-Jones, B., Breen, S.J., Walsh, M., Bertram, J.F., and Reese, B.E., 1995, Cell dispersion patterns in different cortical regions studied with an X-inactivated transgenic marker, *Development* 121:1029–1039.

Taylor, K.R., Holzer, A.K., Bazan, J.F., Walsh, C.A., and Gleeson, J.G., 2000, Patient mutations in doublecortin define a repeated tubulin-binding domain, *J. Biol. Chem.* 275:34442–34450.

Tian, M., Hagg, T., Denisova, N., Knusel, B., Engvall, E., and Jucker, M., 1997, Laminin-alpha2 chain-like antigens in CNS dendritic spines, *Brain Res.* 764:28–38.

Tomasiewicz, H., Ono, K., Yee, D., Thompson, C., Goridis, C., Rutishauser, U. and Magnuson, T., 1993, Genetic deletion of a neural cell adhesion molecule variant (N-CAM-180) produces distinct defects in the central nervous system, *Neuron* 11:1163–1174.

Trommsdorff, M., Borg, J.P., Margolis, B., and Herz, J., 1998, Interaction of cytosolic adaptor proteins with neuronal apolipoprotein E receptors and the amyloid precursor protein, *J. Biol. Chem.* 273: 33556–33560.

Trommsdorff, M., Gotthardt, M., Hiesberger, T., Shelton, J., Stockinger, W., Nimpf, J. *et al*., 1999, *Reeler*/Disabled-like disruption of neuronal

migration in knockout mice lacking the VLDL receptor and ApoE receptor 2, *Cell* 97:689–701.

Walsh, C. and Cepko, C.L., 1992, Widespread dispersion of neuronal clones across functional regions of the cerebral cortex, *Science* 255: 434–440.

Ware, M.L., Fox, J.W., Gonzalez, J.L., Davis, N.M., Lambert de Rouvroit, C., Russo, C.J. *et al*., 1997 Aberrant splicing of a mouse disabled homolog, mdab1, in the scrambler mouse, *Neuron* 19:239–249.

Wichterle, H., Garcia-Verdugo, J.M., and Alvarez-Buylla, A., 1997, Direct evidence for homotypic, glia-independent neuronal migration, *Neuron* 18:779–791.

Wichterle, H., Turnbull, D.H., Nery, S., Fishell, G., and Alvarez-Buylla, A., 2001, In utero fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian basal forebrain, *Development* 128:3759–3771.

Yacubova, E. and Komuro, H., 2002, Stage-specific control of neuronal migration by somatostatin, *Nature* 415:77–81.

Yang, J.T., Rayburn, H., and Hynes, R.O., 1993, Embryonic mesodermal defects in alpha 5 integrin-deficient mice, *Development* 119: 1093–1105.

Yang, J.T., Rayburn, H., and Hynes, R.O., 1995, Cell adhesion events mediated by alpha 4 integrins are essential in placental and cardiac development, *Development* 121:549–560.

Yoneshima, H., Nagata, E., Matsumoto, M., Yamada, M., Nakajima, K., Miyata, T. *et al*., 1997, A novel neurological mutant mouse, yotari, which exhibits *reeler*-like phenotype but expresses CR-50 antigen/reelin, *Neurosci. Res.* 29:217–223.

Zhang, Z. and Galileo, D.S., 1998, Retroviral transfer of antisense integrin alpha6 or alpha8 sequences results in laminar redistribution or clonal cell death in developing brain, *J. Neurosci.* 18:6928–6938.

Zhu, Y., Li, H., Zhou, L., Wu, J.Y., and Rao, Y., 1999, Cellular and molecular guidance of GABAergic neuronal migration from an extracortical origin to the neocortex, *Neuron* 23:473–485.