Annu. Rev. Neurosci. 2003. 26:441–83
doi: 10.1146/annurev.neuro.26.041002.131058

First published online as a Review in Advance on February 26, 2003

CELL MIGRATION IN THE FOREBRAIN

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Key Words radial, tangential, interneuron, pyramidal neuron, telencephalon

■ **Abstract** The forebrain comprises an intricate set of structures that are required for some of the most complex and evolved functions of the mammalian brain. As a reflection of its complexity, cell migration in the forebrain is extremely elaborated, with widespread dispersion of cells across multiple functionally distinct areas. Two general modes of migration are distinguished in the forebrain: radial migration, which establishes the general cytoarchitectonical framework of the different forebrain subdivisions; and tangential migration, which increases the cellular complexity of forebrain circuits by allowing the dispersion of multiple neuronal types. Here, we review the cellular and molecular mechanisms underlying each of these types of migrations and discuss how emerging concepts in neuronal migration are reshaping our understanding of forebrain development in normal and pathological situations.

INTRODUCTION

Cell migration plays an essential role in tissue formation during development. In multicellular organisms, elaborate patterns of cell movement are required during morphogenesis to generate complex structures. The forebrain is undoubtedly one of the most intricate regions of the mammalian brain, and its extraordinary degree of organization reflects the complexity of the migratory movements required to generate it. Defects in neuronal migration during development of the forebrain lead to mental retardation, epilepsy, and severe learning disabilities. Abnormal cell migration also occurs in other diseases affecting the forebrain; in cancer, for example, it underlies invasion and metastasis. Understanding how cell migration occurs in the forebrain is therefore essential to discerning the mechanisms underlying its normal and pathological development.

The forebrain comprises a complex set of structures that derive from the most anterior region of the neural tube, the prosencephalon (Figure 1) (Marín & Rubenstein

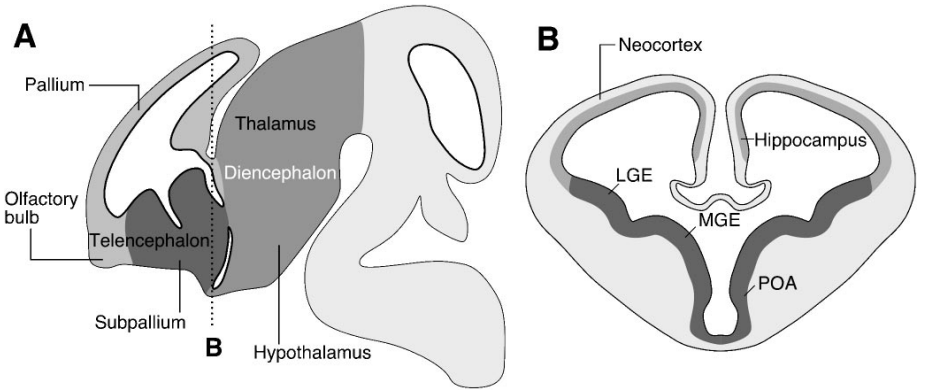

Figure 1 Anatomical organization of the developing forebrain. (*A*) Schema of a sagittal section through the brain of an E12.5 mouse showing the main subdivisions of the forebrain, the diencephalon and the telencephalon. In the telencephalon, the pallium is depicted in lighter gray than the subpallium. (*B*) Schema of a transversal section through the telencephalon of an E12.5 mouse, indicating some of its main subdivisions. LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; POA, anterior preoptic area.

2002). The prosencephalon consists of the diencephalon and telencephalic vesicles, which evaginate from the dorsal aspect of the rostral diencephalon. The telencephalon has two major regions: the pallium (roof) and the subpallium (base). The pallium gives rise to the cerebral cortex and hippocampus, whereas the subpallium consists of three primary subdivisions: the striatal, pallidal, and telencephalic stalk domains, all of which extend medially into the septum. Finally, the olfactory bulbs develop as bilateral evaginations from a region of the prosencephalic neural plate intercalated between the septal and the cortical anlagen (Cobos et al. 2001b, Rubenstein et al. 1998).

Patterning and regional specification of the forebrain precede cell migration. As in other regions of the central nervous system (CNS), specification of cell types in the forebrain requires the creation of distinct antero-posterior and dorsoventral progenitor domains by the coordinated activity of several morphogenetic centers (Marín & Rubenstein 2002, Wilson & Rubenstein 2000). The induction of specific transcription factors in different progenitor domains acts as an intermediary between morphogenetic cues and the acquisition of a specific cell phenotype. Through a mechanism that involves mutually repressive interactions, these transcription factors establish boundaries between different progenitor zones, which leads to the consolidation of progenitor domain identity. Once cells are specified, they are set to migrate to their final position in the mantle of the forebrain.

As in other CNS regions, two general types of migration have been identified in the forebrain on the basis of its orientation: radial migration, in which cells migrate from the progenitor zone toward the surface of the brain following the

radial disposition of the neural tube; and tangential migration, in which cells migrate orthogonal to the direction of radial migration. Below we describe examples of both types of cell migration in the forebrain. Differences and similarities between these two general types of migration modes are discussed at the end of this review.

RADIAL MIGRATION

Early studies on the development of different regions of the brain and spinal cord led to the suggestion that the radial movement of newborn cells is a general trend during the formation of the CNS in vertebrates (Ramón y Cajal 1891). The notion of radial organization in the CNS is founded on the principle that there is a point-to-point relationship between the ventricular zone (VZ) of the neural tube and the pial surface. During development, the radial glial scaffold provides the physical link between these two structures (the glial coordinate system of Nieuwenhuys; see Nieuwenhuys et al. 1998), acting as guides on which neuroblasts migrate to reach their destination (Rakic 1972a).

Radial glial cells arise throughout the neural tube during early development of the VZ. Each radial glial cell has its soma in the VZ and elaborates a process that spans the wall of the neural tube and reaches the pial surface (Bergman glial cells are one exception to this principle), where it is anchored to the basal membrane (Gadisseux et al. 1989, Kölliker 1890, Magini 1888, Ramón y Cajal 1911, Retzius 1892, Schmechel & Rakic 1979). After neuronal production ceases, radial glial cells retract their ventricular and pial attachments and differentiate into astrocytes (Gaiano et al. 2000, Levitt et al. 1981, Pixley & de Vellis 1984, Ramón y Cajal 1911, Schmechel & Rakic 1979, Voigt 1989). Despite their name, radial glial cells do not simply function as static supportive elements. Instead, radial glial cells are dynamic components of the developing cortex, which undergo mitosis to produce new neurons (Heins et al. 2002; Malatesta et al. 2000; Miyata et al. 2001; Noctor et al. 2001, 2002). Thus, radial glial cells represent an intermediate stage in the stem-cell lineage of the CNS (Alvarez-Buylla et al. 1990, 2001; Gray & Sanes 1992; Halliday & Cepko 1992; Zerlin et al. 1995).

The suggestion that young neurons use the radial glial scaffold to migrate to their final destination derives from the analysis of the alignment of postmitotic neurons with radial glial fibers during the development of cerebellar and cerebral cortices (Rakic 1971a,b, 1972b, 1974). These pioneer observations have been extensively supported by many in vitro (Anton et al. 1996, Edmondson & Hatten 1987, Mason et al. 1988, O'Rourke et al. 1992) and in vivo studies (De Carlos et al. 1996, Gadisseux et al. 1990, Gregory et al. 1988, Misson et al. 1991, Miyata et al. 2001, Noctor et al. 2001), leading to the view that most neuronal precursors in the brain migrate along radial glial fibers. In favor of this notion, molecular abnormalities affecting the development of radial glial cells lead to abnormal neuronal migration (Table 1) (Anton et al. 1997, Caric et al. 1997, Feng et al. 1994, Götz et al. 1998, Halfter et al. 2002, Rio et al. 1997, Ross & Walsh 2001).

TABLE 1 Factors affecting radial glial cell development

Gene	Function	Effect on radial glial cell development
Pax6[a]	Transcription factor	Promotes neurogenesis and differentiation of cortical radial glial cells
Notch1[b]	Receptor	Notch1 signaling promotes radial glia identity
Nrg1[c]	Growth factor	Identified as glial growth factor (GGF), neuregulin promotes the elongation and maintenance of radial glial cells, in part through the brain lipid-binding protein (BLBP)
ErbB2[c]	Nrg1 receptor	Same as *Nrg1*
ErbB4[c]	Nrg1 receptor	Same as *Nrg1*
Blbp[d]	Nrg1 signaling	Brain lipid-binding protein induces differentiation of radial glial cells
Itga3[e]	Cell adhesion receptor	Integrin $\alpha 3$ prevents premature differentiation of radial glial cells into astrocytes
Itga6[f]	Cell adhesion receptor	Integrin $\alpha 6$ is required for pial basal lamina formation, which is essential for normal radial glial cell development
Itgb1[g]	Cell adhesion receptor	Integrin $\beta 1$ is required for pial basal lamina formation, which is essential for normal radial glial cell development
Lamc1[h]	ECM structural constituent	Laminin $\gamma 1$ is required for pial basal lamina formation, which is essential for normal radial glial cell development
Reelin[i]	ECM secreted protein	Radial glia scaffold forms abnormally in the hippocampus of mice deficient in Reelin
Dab1[i]	Cytoplasmic adapter protein	Radial glial scaffold forms abnormally in the hippocampus of mice deficient in Dab1

[a]Caric et al. 1997, Götz et al. 1998, Heins et al. 2002

[b]Gaiano et al. 2000

[c]Anton et al. 1997, Rio et al. 1997

[d]Feng et al. 1994

[e]Anton et al. 1999

[f]Georges-Labouesse et al. 1998

[g]Graus-Porta et al. 2001

[h]Halfter et al. 2002

[i]Hunter-Schaedle 1997, Forster et al. 2002

In the forebrain, radial migration has been preferentially studied during the development of the cerebral cortex, and thus most of our current knowledge of the mechanisms that control radial migration derives from the analysis of this structure. Although it seems likely that similar mechanisms mediate radial migration in other regions of the forebrain, it should be kept in mind that different mechanisms might govern radial migration in those structures that develop in the absence of lamination (i.e., the formation of cortical layers), such as the striatum.

Modes of Radial Migration in the Cerebral Cortex

Radial migration of neurons generated in cortical progenitor zones follows a series of highly coordinated stages and is thought to involve at least two different modes of cell movement. The first cohort of neurons that migrate out of the cortical VZ constitutes the preplate (reviewed in Allendoerfer & Shatz 1994), originally described in Golgi-stained preparations as the primordial plexiform layer (Marín-Padilla 1971). The second wave of neuronal migration forms the cortical plate, which splits the preplate into two layers, the marginal zone and the subplate. Cajal-Retzius cells, which are born at the time the preplate is formed, remain near the pial surface in the marginal zone, whereas the rest of the primordial cells constitute the subplate. The development of the cerebral cortex progresses with successive waves of migration, which position neurons within different layers in the cortical plate (future cortical layers 2–6). Consequently, the marginal zone and subplate contain the earliest-generated neurons of the cortex (Chun et al. 1987, Kostovic & Rakic 1980, Luskin & Shatz 1985), whereas the cortical plate contains progressively older neurons. It is interesting that radial migration mechanisms seem to differ for cells destined to each one of these structures—the preplate and the cortical plate.

The conventional view of neuronal migration during the development of the cerebral cortex is primarily based on observations of the migratory behavior of neurons destined to the cortical plate, where it is well established that migrating neuroblasts use the processes of radial glial cells to reach their final position (Edmondson & Hatten 1987, Noctor et al. 2001, Rakic 1972b, Rakic 1974). Cells that adopt glial-guided locomotion have a short leading process that is not attached to the pial surface and display a saltatory pattern of locomotion, that is, short and rapid forward movements followed by relatively long stationary phases (Nadarajah et al. 2001).

A second type of radial migration has been described for cortical cells migrating out of the VZ at early stages of corticogenesis. This type of radial migration, named somal translocation (the perikaryal translocation of Morest; see Morest 1970), appears to be largely independent of radial glial cells (Nadarajah & Parnavelas 2002). Cells undergoing somal translocation typically have a long process that terminates at the pial surface and a short trailing process (Brittis et al. 1995, Miyata et al. 2001, Morest 1970, Nadarajah et al. 2001). Time-lapse experiments have shown that translocating cells first extend a process to the pial surface as they leave the VZ, and then they lose their ventricular attachments while maintaining their pial connections (Nadarajah et al. 2001). Thus, the migratory behavior of translocating cells is distinct from those undergoing glial-guided locomotion because their movement is relatively continuous and the leading process becomes progressively shorter. It should be noted, however, that glial-guided cells appear to use somal translocation on the last stage of their migration, once they have made contact with the pial surface of the cortex (Nadarajah et al. 2001).

The existence of two distinct modes of radial migration suggests that these different migratory behaviors may have evolved independently during evolution

of the cortex. If this is the case, it seems conceivable that the molecular mechanisms underlying somal translocation and glial-guided locomotion are also different. In agreement with this hypothesis, mutations that affect the cascade of signaling mechanisms that regulate the glial-guided migration do not severely affect the formation of the preplate (which appears to rely on somal translocation) (Gilmore & Herrup 2001, Nadarajah et al. 2001), whereas alteration of the pial basement membrane (which is required for anchoring the processes of translocating neurons and radial glia) affects both the development of the preplate and cortical plate (Graus-Porta et al. 2001, Halfter et al. 2002).

MOLECULAR MECHANISMS OF GLIAL-GUIDED MIGRATION IN THE CEREBRAL CORTEX

Our current understanding of the mechanisms controlling radial migration derives primarily from the study of glial-guided locomotion in the cerebral cortex, although analysis of other regions of the forebrain is providing new insights about this process (Bagri et al. 2002, Hamasaki et al. 2001b). The migration of young neurons to the cortical plate from the cortical VZ involves at least four consecutive but partially overlapping processes: first, initiation of movement; second, attachment to the radial glial fiber; third, locomotion, which involves nucleokinesis; and fourth, detachment of the radial glial fiber and acquisition of appropriate laminar position (Figure 2).

Modulation of Radial Movement by Motogenic Factors

Brain derived neurotrophic factor (BDNF) and NT4, members of the neurotrophin family, have been shown to promote the migration of cortical neurons. TrkB, the high-affinity receptor of BDNF and NT4, is expressed in migrating neurons in the cortical plate (Behar et al. 1997). Both BDNF and NT4 stimulate the motility of embryonic cortical cells in vitro through a Ca^{2+}-dependent mechanism that involves autophosphorylation of TrkB (Behar et al. 1997). Consistent with this observation, misexpression of TrkB ligands in the developing brain has dramatic effects on cortical neuronal migration. Thus, infusion of NT4 or BDNF into the lateral ventricle or application of these proteins on slices of the developing cortex produces neuronal heterotopias, which appear to be the result of increased neuronal migration (Brunstrom et al. 1997). Similarly, overexpression of BDNF in the ventricular zone of developing embryos results in alterations of the cortex (Ringstedt et al. 1998).

Neurotransmitters also play a role in modulating the migration of cortical projection neurons. For example, γ-aminobutyric acid (GABA) is expressed in the developing cortex in a pattern suitable to influence migrating cortical neurons (Soriano et al. 1989, Van Eden et al. 1989). In vitro, GABA induces dissociated embryonic cortical neurons to migrate, and pharmacological experiments suggest that this effect is mediated through multiple GABA receptors (Behar et al.

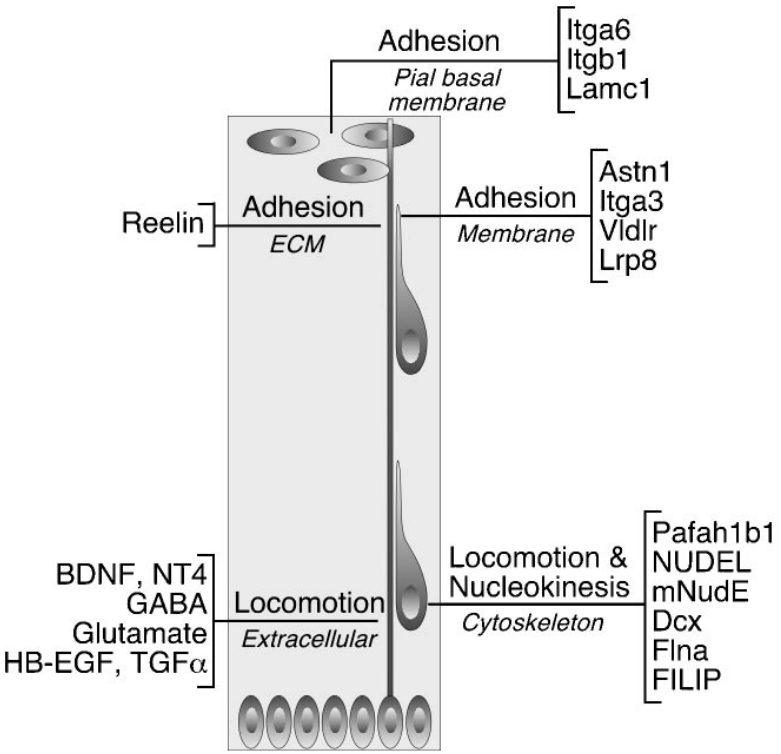

Figure 2 Mechanisms regulating radial migration in the cerebral cortex. Shown is a schematic representation of radially migrating neurons in the developing cortex, where the ventricular zone is to the bottom and the marginal zone is to the top. Molecules involved in radial migration are indicated in relation to their function (e.g., locomotion) and location (e.g., extracellular).

1996, Behar et al. 2001). It is interesting that $GABA_{A/C}$ receptors are involved in the movement of cells from the proliferative zones of the cortex to the intermediate zone, whereas $GABA_B$ receptors appear to influence migration from the intermediate zone to the cortical plate (Behar et al. 2000). Another example of a receptor whose activity modulates the movement of radial migrating cells is the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor. Thus, blockade of NMDA receptors decreases cell migration, whereas enhancement of NMDA receptor activity or inhibition of extracellular glutamate uptake increases the rate of cell movement (Behar et al. 1999, Komuro & Rakic 1993). Regardless of which receptor is involved, modulation of radial migration by neurotransmitters ultimately depends on fluctuations in the concentration of cytosolic Ca^{2+} (Behar et al. 2000, 1999; Gressens et al. 2000; Horgan & Copenhaver 1998; Komuro & Rakic 1993).

Signaling through the epidermal growth factor receptor (EGFR) is also implicated in the modulation of radial movement in the telencephalon. EGFR and its ligands, including heparin-binding EGF (HB-EGF) and TGFα, are expressed in the developing cortex (Kornblum et al. 1997, Nakagawa et al. 1998). Mice lacking EGFR display an accumulation of neuronal precursors in telencephalic proliferative zones, suggesting a defect in their migration (Threadgill et al. 1995). In line with this observation, expression of high levels of EGFR in the embryonic cortex enhances radial migration (Burrows et al. 1997). The ability of cortical cells to migrate in response to EGFR ligands depends on both their distribution and the levels of EGFR expression, since only cells expressing high levels of EGFR appear to increase radial migration in response to EGFR ligands (Caric et al. 2001).

Neuronal-Glial Interactions

Several molecules have been implicated in regulating the interaction of migrating cells with the radial glia (Table 1). The first of these factors to be identified was Astrotactin (*Astn1*), a glycoprotein expressed by migrating neurons both in the cerebellum and in the cerebral cortex (Edmondson et al. 1988). Antibodies against Astrotactin block the adhesion of granule cells to cerebellar glia and reduce their rate of migration (Fishell & Hatten 1991, Stitt & Hatten 1990), whereas ectopic expression of Astrotactin in 3T3 cells promotes their adhesion to glia (Zheng et al. 1996). Accordingly, mice lacking *Astn1* display slowed radial migration (Adams et al. 2002). The identification of a second member of the Astrotactin family (*Astn2*), whose expression is largely overlapping with that of *Astn1* (M.E. Hatten, personal communication), suggests that *Astn1* and *Astn2* may cooperate in neuron-glia adhesive interactions critical for radial migration.

Integrins, cell-surface glycoproteins that mediate cell-cell and cell–extracellular matrix (ECM) interactions (Hemler 1999), appear also to be implicated in the association between migrating neurons and radial glia (Figure 2). Function-blocking antibodies against α3 integrin reduce the rate of migration and cause neuronal detachment from radial glial fibers in vitro (Anton et al. 1999, Dulabon et al. 2000). Moreover, radial migration is altered in the cerebral cortex of α3 integrin mutant mice (Anton et al. 1999). Thus, although large numbers of neurons reach their normal position in the cortex, some cells arrest their migration prematurely and fail to migrate to their appropriate layer. As a result, cortical layers are less precisely defined than in normal mice. Blocking antibodies against αv integrin also perturb the interaction between neurons and radial glial cells in vitro (Anton et al. 1999), but genetic evidence is necessary to verify the involvement of this integrin in the development of the cortex in vivo.

Integrins are expressed as cell-surface heterodimers consisting of α and β subunits. Because β1 integrin is the only subunit known to bind to α3 integrin (Hemler 1999), blocking β1 integrin function should produce similar alterations to those observed when the activity of α3 integrin is perturbed. Accordingly, blocking antibodies against β1 integrin perturbs neuron-glia interactions in vitro (Anton et al. 1999). Moreover, analysis of mice in which the β1 integrin gene was selectively

inactivated in the precursors of neurons and glia by Cre/Lox-mediated recombination also revealed that β1 integrin is essential for cortical development (Graus-Porta et al. 2001). However, the defects observed in the cortex of β1 integrin mutants appear to be largely secondary to the abnormal development of the basement membrane and the marginal zone and not directly due to a defect in neuron-glia interactions. Thus, cortical lamination was not severely perturbed in β1 integrin mutants, although the width of layers II/III in the mutants was increased compared to control mice (Graus-Porta et al. 2001)—a feature that could be reminiscent of the phenotype described in α3 integrin mutants (Anton et al. 1999). The differences observed between α3 integrin and β1 integrin mutant mice are most likely due to the fact that β1 integrin binds other α subunits, such as α6 integrin. Consistent with this notion, a phenotype similar—although less severe—to that described in β1 integrin mutant mice is found in mice mutant for the α6 integrin gene (Georges-Labouesse et al. 1998).

Locomotion During Radial Migration

A critical aspect during radial migration concerns the dynamic adaptation of the microtubule network. Time-lapse experiments have shown that two processes involving the microtubule cytoskeleton are essential for neuronal migration: the extension of a leading process and the translocation of the nucleus (Edmondson & Hatten 1987, Komuro & Rakic 1996, Nadarajah et al. 2001, Rakic et al. 1996, Rivas & Hatten 1995). These observations indicate that proteins controlling the cellular machinery responsible for these processes are likely to play a major role in neuronal migration.

Several genes have been identified that regulate events related to the microtubule cytoskeleton during radial migration. One of these genes is *Lis1* (the noncatalytic β1 subunit of the platelet-activating factor acetylhydrolase, *Pafah1b1*), which encodes for a protein involved in multiple protein-protein interactions (Feng & Walsh 2001, Gupta et al. 2002). Mutations in human *Lis1* cause a severe form of lissencephaly named Miller-Dieker syndrome (Hattori et al. 1994, Reiner et al. 1993), which appears to reduce neuronal number and the rate of migration. Accordingly, neuronal migration is delayed in the cortex of mice with one inactive allele of *Lis1*, and mice with further reduction of LIS1 activity display severe cortical disorganization (Hirotsune et al. 1998). Moreover, analysis of mice expressing a truncated *Lis1* allele demonstrates that cortical neurons migrate slowly in the absence of normal LIS1 (Cahana et al. 2001).

The function of LIS1 in neuronal migration is still unclear. NudF, a LIS1 homolog in *Aspergillus nidulans*, and *Drosophila* dLis1 are both required for nuclear migration (Lei & Warrior 2000, Xiang et al. 1995). In all organisms studied, LIS1 binds tubulin and other proteins that interact with the microtubule network (Sapir et al. 1997). In the brain, one of these proteins is cytoplasmic dynein (Faulkner et al. 2000, Smith et al. 2000), a microtubule-based motor protein involved in the intracellular transport of organelles and in retrograde axonal transport. Overexpression of LIS1 leads to the aggregation of dynein and dynactin, as well as transport of

microtubule fragments to the cell periphery (Smith et al. 2000). Consistent with these findings, dynactin fails to aggregate, and microtubules are largely concentrated near the nucleus in fibroblasts derived from *Lis1* heterozygous mice (Sasaki et al. 2000, Smith et al. 2000). Moreover, LIS1-deficient neurons in *Drosophila* display axonal transport abnormalities (Liu et al. 2000). Thus, LIS1 appears to control microtubule dynamics in migrating cells through its association with tubulin and dynein/dynactin.

Two additional proteins interact directly with LIS1 in mammals: NUDEL and mNudE, homologs of the *A. nidulans* protein NudF (Efimov & Morris 2000, Kitagawa et al. 2000, Niethammer et al. 2000, Sasaki et al. 2000). NUDEL and mNudE colocalize with LIS1, although they appear to interact with LIS1 at different developmental stages (Efimov & Morris 2000, Kitagawa et al. 2000, Niethammer et al. 2000, Sasaki et al. 2000). In addition, mNudE associates with specific proteins in the centrosome—the major microtubule-organizing center of animal cells—and with the light chain of dynein, whereas NUDEL interacts primarily with the heavy chain of dynein (Feng et al. 2000). Overexpression experiments suggest that NUDEL controls the localization of dynein (Niethammer et al. 2000, Sasaki et al. 2000), whereas mNudE affects the microtubule network at the centrosome (Feng et al. 2000). Because the centrosome plays a prominent role in cell division, it is possible that LIS-mNudE-dynein interactions also contribute to mitosis and cell-cycle progression (Faulkner et al. 2000, Liu et al. 2000).

Doublecortin (*Dcx*) is another gene whose mutation in humans leads to X-linked lissencephaly (des Portes et al. 1998, Gleeson et al. 1998). Mutations in *Dcx* cause lissencephaly in males, whereas affected female patients have a double cortex syndrome, also known as subcortical band heterotopia. The latter condition probably reflects a mosaic state owing to the random inactivation of normal and mutant X chromosomes. Multiple lines of evidence suggest that DCX is a microtubule-associated protein (MAP) that functions in the stabilization of the microtubule network (Francis et al. 1999, Gleeson et al. 1999a, Horesh et al. 1999). DCX is expressed in migrating and differentiating neurons, where it interacts with polymerized microtubules. Recombinant DCX stimulates the polymerization of tubulin in vitro, and overexpression of DCX in heterologous cells leads to the formation of abnormally thick bundles of microtubules that are resistant to depolymerization (Gleeson et al. 1999a). Structural analysis also supports the idea that DCX is a MAP. DCX contains two repeats that form a β-grasp superfold, a structural motif found in Ras-related GTP-binding proteins. These repeats bind to tubulin and drive microtubule polymerization and stabilization (Taylor et al. 2000). Moreover, missense point mutations within these repeats are found in lissencephalic patients, which suggests that their integrity is essential for DCX function (Gleeson et al. 1999b).

An engineered loss-of-function mutation in the *Dcx* locus in mice causes a disrupted cytoarchitecture in the hippocampus but exhibits roughly normal lamination in the neocortex (Corbo et al. 2002). *Lis1* mutant mice also display a rather subtle phenotype in the neocortex but show prominent hippocampal defects (Fleck et al.

2000). LIS1 and DCX appear to be coexpressed, interact, and function in the same protein complex in the developing brain (Caspi et al. 2000). Thus, although their functions are likely to be distinct, these proteins may coordinate similar processes during neuronal migration, such as the translocation of the nucleus and other soma contents during cell movement.

The roles of LIS1 and DCX in the developing cortex illustrate the prominent influence that microtubule dynamics have on neuronal migration. The actin cytoskeleton also regulates the motility of migrating neurons, as demonstrated by the prominent migration defects observed in humans with mutations in the gene encoding the actin-binding protein Filamin α (FLNA), also known as Filamin 1 (Fox et al. 1998, Moro et al. 2002, Sheen et al. 2001). Mutations in *FlnA* cause periventricular heterotopia, a migration disorder in which many neurons destined for the cortical plate fail to migrate and instead accumulate close to the progenitor zones of the cerebral cortex (Eksioglu et al. 1996). FLNA crosslinks F-actin into orthogonal arrays, increasing the viscosity of the F-actin network and enhancing cell motility (Stossel et al. 2001). FLNA is expressed in migratory neurons as they leave the VZ (Fox et al. 1998), which suggests that its expression overlaps with the mechanism that signals the start of the migration of cortical neurons. Conversely, molecules expressed in the VZ prevent premature migration toward the cortical plate. One of these molecules is the Filamin A interacting protein (FILIP), a protein that negatively regulates the function of FLNA (Nagano et al. 2002). FILIP is expressed in VZ cells and induces the degradation of FLNA, preventing premature migration of cortical neurons. Thus, the coordinated function of FLNA and FILIP regulates the initiation of radial migration in the cortex.

Layer Formation

Once migrating neurons have reached their destination, they have to detach from the radial glia processes and halt their migration. Birthdating studies have shown that layers in the cortical plate (future cortical layers 2–6) are established according to an inside-outside pattern, where the deeper layers contain cells that become postmitotic earlier than the cells in more superficial layers (Angevine & Sidman 1961, Rakic 1974). Thus, neurons born simultaneously (in terms of cell-cycle sequence rather than time of neurogenesis *per se*) (Takahashi et al. 1999) migrate and stop migrating roughly at the same time, so they all occupy the same cortical layer. Although it has been shown that the laminar identity of cortical neurons is determined early in the cell cycle (McConnell & Kaznowski 1991, Frantz & McConnell 1996), the nature of the factors that control the migration of cortical neurons to their appropriate layer is poorly understood.

Analysis of mutations in mice and humans has revealed that the interaction between migrating neurons and Cajal-Retzius cells is essential for this process (Table 2). As noted earlier, Cajal-Retzius cells remain in the marginal zone of the cortex after the first wave of neurons destined to the cortical plate (the future layer 6) split the preplate into the marginal zone and the subplate. During the

TABLE 2 Genetics of radial migration in the cortex

Gene	Name and function	Description of mutation
Astn1[a]	Astrotactin1; neuron-glia adhesion molecule	Decreased neuron–radial glia binding, slowed radial migration
Itga3[b]	α3 Integrin; cell adhesion receptor, interacts with Reelin	Abnormal laminar position of cortical projection neurons, which tend to occupy deeper positions than normal
Itga6[c]	α6 Integrin; cell adhesion receptor	Abnormal laminin deposition, cortical layer perturbation without layer inversion
Itgb1[d]	β1 Integrin; cell adhesion receptor, interacts with Reelin	Abnormal basement membrane remodeling, cortical layer perturbation without layer inversion
Lamc1[e]	γ1 Laminin; ECM structural constituent	Abnormal basement membrane, cortical layer perturbation without layer inversion
Pafah1b1[f]	Platelet-activating factor acetylhydrolase, isoform 1b, beta1 subunit; interacts with tubulin, dynein, NUDEL, mNudE	Also known as *Lis1*, its mutation causes lissencephaly in humans. Decreased rate of migration and cortical disorganization in mice
Dcx[g]	Doublecortin; microtubule-associated protein	Lissencephaly in humans. Disrupted hippocampal cytoarchitecture but normal neocortical lamination in mice
Flna[h]	Filamin alpha, actin-binding protein	Also known as Filamin 1, its mutation causes periventricular heterotopia in humans
Reln[i]	Reelin, ECM secreted protein	Lissencephaly in humans. Inverted cortical layering, including the subplate, in *reeler*
Vldlr[j]	Very-low-density lipoprotein receptor, Reelin receptor	Same as *reeler* when mutated simultaneously with *Lrp8*
Lrp8[j]	Low-density lipoprotein receptor-related protein 8, Reelin receptor	Same as *reeler* when mutated simultaneously with *Vldlr*. Also known as ApoE receptor 2
Dab1[k]	Disabled homolog 1; interacts with Vldlr, Lrp8	Same as *reeler*. Mutated in *scrambler* and *yotari*
Cdk5[l]	Cyclin-dependent kinase 5; phosphorylate Dab1 and NUDEL	Inverted cortical layering, without affecting the subplate
Cdk5r1[m]	Cyclin-dependent kinase 5, regulatory subunit 1 (p35)	Same as *Cdk5* when mutated simultaneously with *Cdk5r2*
Cdk5r2[m]	Cyclin-dependent kinase 5, regulatory subunit 2 (p39)	Same as *Cdk5* when mutated simultaneously with *Cdk5r1*

[a]Adams et al. 2002

[b]Anton et al. 1997

[c]Georges-Labouesse et al. 1998

[d]Graus-Porta et al. 2001

[e]Halfter et al. 2002

[f]Reiner et al. 1993, Hattori et al. 1994, Hirotsune et al. 1998, Cahana et al. 2001

[g]des Portes et al. 1998, Gleeson et al. 1998, Corbo et al. 2002

[h]Fox et al. 1998, Sheen et al. 2001, Moro et al. 2002

[i]D'Arcangelo et al. 1995, Hirotsune et al. 1995, Ogawa et al. 1995, Hong et al. 2000

[j]Trommsdorff et al. 1999

[k]Howell et al. 1997, Sheldon et al. 1997, Ware et al. 1997

[l]Ohshima et al. 1996, Gilmore et al. 1998

[m]Chae et al. 1997, Kwon & Tsai 1998, Ko et al. 2001

subsequent days, cohorts of migrating neurons pass over previous neurons until they reach the proximity of the marginal zone, where they detach from the radial glia. These observations suggest that the interaction between migrating neurons and some cells in the marginal zone—the Cajal-Retzius cells—has a prominent influence in the laminar organization of the cortex. Cajal-Retzius cells express Reelin, a large secreted protein that associates with the ECM and, when mutated, causes the disruption in neuronal migration observed in *reeler* mutant mice (D'Arcangelo et al. 1995, Hirotsune et al. 1995, Ogawa et al. 1995) and lissencephaly with cerebellar hypoplasia in humans (Hong et al. 2000). In *reeler* mice, the first wave of migrating cells destined to form the cortical plate fails to split the preplate. Subsequently, new waves of migrating neurons are unable to pass the previous ones and accumulate in progressively deeper positions, creating a cortex in which layers 2–6 are roughly inverted (Caviness 1982, Hoffarth et al. 1995, Ogawa et al. 1995, Rice & Curran 2001, Sheppard & Pearlman 1997). Of note, many neurons are correctly positioned in *reeler* (Caviness 1982), which suggests that normal positioning can occur in the absence of Reelin and that the layer inversion reported in the *reeler* cortex is an oversimplification of the actual phenotype.

Reelin is a high-affinity ligand for two members of the LDL family of lipoprotein receptors, the very-low-density lipoprotein receptor (VLDLR) and the low-density lipoprotein receptor-related protein 8 (LRP8, also known as ApoER2), which are expressed by migrating cortical cells (D'Arcangelo et al. 1999, Hiesberger et al. 1999). Signaling through VLDLR/LRP8 mediates Reelin internalization and tyrosine phosphorylation of the mouse homolog of the *Drosophila* protein Disabled, DAB1 (D'Arcangelo et al. 1999; Hiesberger et al. 1999; Howell et al. 1999, 2000). DAB1 is a cytoplasmic adapter protein that interacts with the cytoplasmic tails of VLDLR and LRP8 (Trommsdorff et al. 1998, 1999) and is linked to events related to the reorganization of microtubules and microfilaments in the cytoskeleton. Remarkably, mice lacking both the *Vldlr* and *Lrp8* genes (Trommsdorff et al. 1999), mice with a targeted disruption of the *Dab1* gene (Howell et al. 1997), and naturally occurring mutants affecting the *Dab1* gene—*scrambler* and *yotari*—(Gonzalez et al. 1997, Rice et al. 1998, Sheldon et al. 1997, Sweet et al. 1996, Ware et al. 1997, Yoneshima et al. 1997) have lamination defects that are indistinguishable from those found in *reeler* mice. This suggests that Reelin, VLDLR, LRP8, and DAB1 work in the same genetic pathway controlling neuronal position during radial migration.

A second signaling pathway controls neuronal positioning during development of the cortex. This second pathway involves the cyclin-dependent kinase 5 (Cdk5) and its activating subunits, p35 and p39. Mice deficient in *Cdk5*, *p35*, or both *p35* and *p39* exhibit lamination defects that are similar but not identical to those observed in mice with defects in Reelin signaling (Chae et al. 1997, Gilmore et al. 1998, Ko et al. 2001, Kwon & Tsai 1998, Ohshima et al. 1996). Moreover, mice lacking the class III POU domain transcription factors *Brn1* and *Brn2*, which cell-autonomously regulate the expression of p35 and p39 in migrating cortical

neurons, also exhibit a cortical inversion (McEvilly et al. 2002). Mutations in the Cdk5 signaling pathway do not prevent normal splitting of the preplate into the marginal zone and subplate but still cause an inversion of cortical lamination in a manner evocative of that observed in *reeler* mutants. These findings suggest that the splitting of the preplate and the acquisition of normal cortical lamination are partially independent processes, with the initial invasion of the preplate depending primarily on Reelin. Consistent with this view, subplate neurons separate from Cajal-Retzius cells in *reeler* mice in which Reelin is ectopically expressed in the VZ (Magdaleno et al. 2002). Expression of Reelin in the VZ, however, is not able to rescue the lamination defects observed in the cortex of *reeler* mice, which suggests that expression of Reelin in the marginal zone of the cortex is indispensable for normal cortical lamination.

How does Reelin influence the laminar positioning of migrating cells in the cerebral cortex? It has been suggested that Reelin inhibits neuronal migration and thus acts as a stop signal for radially migrating neurons (Dulabon et al. 2000, Frotscher 1997, Sheppard & Pearlman 1997). This is primarily based on the observation that exposure to full-length recombinant Reelin reduces the rate of radial migration (Dulabon et al. 2000). Contrary to this hypothesis, ectopic expression of Reelin in the VZ of the cortex does not prevent radial migration (Magdaleno et al. 2002). Moreover, if Reelin works merely as a stop signal for radially migrating cells, one would not expect cells to accumulate at progressively more distant positions from the marginal zone in *reeler* mutants.

A second hypothesis to explain the effects of Reelin on radial migration is that Reelin—and probably other factors produced by Cajal-Retzius cells—could directly regulate the identity and function of radial glia, and thus defects in the glial scaffold would underlie the alteration of cortical lamination (Super et al. 2000). This is consistent with the observation that localized expression of Reelin in the marginal zone seems to be crucial for its function in cortical lamination (Magdaleno et al. 2002), that a normal radial glial scaffold fails to form in the dentate gyrus of the hippocampus in *reeler*, *scrambler*, and $\beta 1$ integrin mutant mice (Forster et al. 2002, Hunter-Schaedle 1997), and that loss of Cajal-Retzius cells or $\alpha 3$ integrin promotes premature differentiation of radial glial cells into cortical astrocytes (Anton et al. 1999, Super et al. 2000).

A third possibility is that Reelin promotes detachment of migrating neurons from the processes of radial glial cells. Because successive waves of neurons born from the same radial progenitor cell ordinarily use the same radial process to reach the cortical plate (Noctor et al. 2001, Rakic 1988), the lack of detachment of early-born neurons from the radial glial process may constitute a physical barrier for the migration of subsequent cohorts of neurons toward the marginal zone. Accordingly, there is a persistent apposition of migrating neurons with radial glial fibers in *reeler* mice (Pinto-Lord et al. 1982). Moreover, Reelin appears to modify the adhesive interactions between neuronal precursors migrating toward the olfactory bulb, inducing the shift from chain migration to individual radial migration necessary for the dispersion of newly generated neurons in the olfactory

bulb (Hack et al. 2002). Thus, changes in the adhesive interactions between neurons and radial glial cells may play a prominent role in the establishment of distinct layers in the developing cerebral cortex.

The influence of Reelin on the adhesive properties of radially migrating neurons may be the result of its interaction with other proteins. For example, it has been shown that Reelin binds to $\alpha 3\beta 1$ integrin receptors, which are expressed in radially migrating neurons (Dulabon et al. 2000). Cells lacking $\alpha 3$ integrin are no longer sensitive to radial detachment induced by Reelin (Dulabon et al. 2000), which suggests that the interaction between Reelin and $\alpha 3\beta 1$ integrin receptors is responsible for the separation of migrating neurons from radial glial fibers and, consequently, the establishment of laminar organization in the cortex. Unlike the *Vldld/ApoER2* double mutants, however, loss of $\alpha 3$ or $\beta 1$ integrins does not cause an inversion of cortical lamination (Anton et al. 1999, Graus-Porta et al. 2001), indicating that $\alpha 3\beta 1$ integrin receptors are not responsible in vivo for the establishment of cortical layers. Reelin also binds to members of the cadherin-related neuronal receptor (CNR) family, which are expressed in cortical-plate neurons that are adjacent to the marginal zone (Senzaki et al. 1999), although the functional significance of this interaction is still unknown.

Is there a nexus between the Reelin and Cdk5 signaling pathways? The defects observed in mutants comprising proteins involved in each of these pathways are remarkably similar, which suggests that Reelin and Cdk5 signaling overlap to some degree. Cdk5 is a serine/threonine kinase that phosphorylates proteins that maintain cytoskeletal structures and promote cell motility. It is interesting that Cdk5 and Reelin signaling can phosphorylate Dab1 independently of each other (Keshvara et al. 2002). Although it is unknown how Dab1 tyrosine phosphorylation translates into the activation of signaling cascades and cytoskeleton rearrangements, these observations suggest that there is cross talk between the two signaling pathways that control cell positioning in the cerebral cortex. In addition, a recent series of experiments demonstrated that NUDEL is likely to be a physiological substrate of Cdk5 (Niethammer et al. 2000, Sasaki et al. 2000), which indicates that some of the defects observed in Cdk5 mutants may be caused by abnormal motility of radially migrating neurons.

TANGENTIAL MIGRATION IN THE FOREBRAIN

The radial glial scaffold provides the primary guidance system for CNS-migrating neurons. Nevertheless, it has long been recognized that cells disperse in the forebrain in patterns that do not coincide with the plane of the glial fiber system (Altman 1969, Austin & Cepko 1990, Morest 1970, O'Rourke et al. 1992, Price & Thurlow 1988, Rakic & Sidman 1969, Shoukimas & Hinds 1978, Stensaas 1967, Walsh & Cepko 1992). Tangential migration, as the nonradial migration of cells in the CNS is generally designated, comprises distinct types of cell movement that diverge primarily in the type of substrate used by migrating cells. In some cases, groups

of neurons migrate using each other to promote their migration, as in the case of olfactory bulb interneuron precursors. In other cases, tangentially migrating neurons follow growing axons to reach their destination. Finally, some tangentially migrating neurons may not follow specific cellular substrates and instead disperse in a rather individual manner, such as the cells migrating from the subpallium to the pallium. Regardless of their mode of migration, cells moving tangentially do not seem to respect regional forebrain boundaries. Thus, cells move across different subdivisions of the forebrain (Heffron & Golden 2000, Letinic & Rakic 2001) or even traverse long axonal pathways (Spassky et al. 2002, Wray 2001). In addition, tangentially migrating cells respond to some of the same molecules that control the guidance of growing axons (Tessier-Lavigne & Goodman 1996).

In the following sections, we review the cellular and molecular mechanisms controlling tangential migration in the forebrain. We describe three different types of tangential migration, which illustrate the different substrates used by tangentially migrating cells: first, the rostral migratory stream; second, the migration of Gonadotropin-releasing hormone (GnRH) neurons; and third, the migration of interneurons and oligodendrocytes from the subpallium to the cortex.

MECHANISMS OF MIGRATION IN THE ROSTRAL MIGRATORY STREAM

In mammals, precursors of olfactory interneurons (periglomerular and granule cells) are not intrinsically generated in the olfactory bulb but instead are born in the subpallium and reach their destination through tangential migration (Altman 1969, Lois & Alvarez-Buylla 1994, Luskin 1993). The precise origin of olfactory interneurons in the embryonic subpallium is still a matter of debate, although both experimental embryology (Wichterle et al. 2001) and genetic experiments (Corbin et al. 2000, Dellovade et al. 1998, Marín & Rubenstein 2001, Sussel et al. 1999, Yun et al. 2001) suggest that most precursors of olfactory interneurons are generated in the dorsal region of the lateral ganglionic eminence (LGE).

The migration of olfactory interneuron precursors continues through adulthood, providing a constant supply of new GABAergic local circuit neurons to the olfactory bulb (Lois & Alvarez-Buylla 1994). The origin of olfactory interneuron precursors in the postnatal telencephalon is the subventricular zone (SVZ) (Altman 1969, Lois & Alvarez-Buylla 1994, Luskin et al. 1988), a mitotically active region that surrounds most of the ependymal wall of the lateral ventricles and is thought to develop at least in part from residual progenitor cells derived from the LGE. Consistent with this idea, LGE-derived cells transplanted into the adult SVZ give rise to neurons that migrate rostrally to the olfactory bulb (Wichterle et al. 1999). Migration of olfactory interneurons in the adult occurs along a highly restricted route termed the rostral migratory stream (RMS) (Kornack & Rakic 2001, Lois & Alvarez-Buylla 1994, Pencea et al. 2001, Thomas et al. 1996), which is readily apparent at early postnatal stages (Luskin 1993, Pencea et al. 2001). In contrast to

the migration of olfactory interneuron precursors during embryonic stages, which spread through a large extracellular space as they move toward the olfactory bulb (Kishi et al. 1990), migrating neuronal precursors in the adult SVZ are organized as a network of chains that coalesce to form the RMS (Doetsch & Alvarez-Buylla 1996, Doetsch et al. 1997, Lois et al. 1996, Rousselot et al. 1995). Thus, the cellular and molecular mechanisms underlying the migration of olfactory interneuron precursors may differ in adults and embryos.

Neonatal and adult olfactory interneuron precursors move in close association to each other, which suggests that neurophilic interactions are important for this type of cellular translocation, called chain migration. Chains of interneuron precursors are ensheathed by astrocytes in vivo (Jankovski & Sotelo 1996, Lois et al. 1996, Peretto et al. 1997, Thomas et al. 1996), although experiments in vitro suggest that chain migration is largely independent of the assistance of astrocytes or other cell types (Wichterle et al. 1997). In contrast, embryonic olfactory interneuron precursors seem to migrate less closely associated, and chains do not form in vitro from embryonic cells obtained from the LGE (J.E. Long and J.L.R. Rubenstein, unpublished results). It is interesting that chain migration of early postnatal olfactory interneuron precursors in vitro depends on the extracellular substrate used (Kleinman et al. 1982, Wichterle et al. 1997). This observation suggests that the change in the migratory behavior of olfactory interneuron precursors—individual versus chain migration—may be a consequence of a modification in the extracellular composition of the RMS or in the adhesive properties of migrating cells that occurs perinatally.

The polysialylated form of the neural cell adhesion molecule (PSA-N-CAM), a member of the immunoglobulin superfamily that mediates homo- and heterophilic cell-cell interactions, is one of the factors that appears to play a role in this process. Mutation of N-CAM in mice results in a small olfactory bulb and the accumulation of olfactory interneuron precursors in the SVZ (Chazal et al. 2000, Cremer et al. 1994, Tomasiewicz et al. 1993). These defects are thought to be caused by the specific loss of the polysialylated form of N-CAM because enzymatic removal of the polysialic acid (PSA) moiety associated with N-CAM mimics the defects observed in N-CAM mutant mice (Ono et al. 1994). PSA-deficient cells migrate normally when transplanted into a wild-type RMS, which suggests that loss of PSA-N-CAM does not impair the migratory ability of olfactory interneuron precursors (Hu et al. 1996). PSA-N-CAM may instead facilitate olfactory precursors to use neighboring cells as their substrate to increase their migratory speed in the highly restrictive conditions of the adult RMS (Chazal et al. 2000). Accordingly, PSA-N-CAM is weakly expressed in the embryonic and neonatal RMS, when few chains are formed, but its expression is strong at later postnatal stages, when chain migration is the predominant form of cellular translocation in the RMS (Hu 2000, Murase & Horwitz 2002, Pencea et al. 2001, Rousselot et al. 1995). Moreover, enzymatic removal of polysialic acid (PSA) results in the dispersion of chains into single cells both in vitro and in vivo (Hu 2000). Finally, interneuron migration within the olfactory bulb, where the cells disperse individually, is not affected

by loss of PSA (Hu et al. 1996, Ono et al. 1994), which reinforces the notion that PSA-N-CAM is required for the cellular interactions necessary during chain migration.

Several additional adhesion molecules have been identified in the migratory route of olfactory interneuron precursors. The pattern of expression of these molecules is highly dynamic, suggesting that differences in the interaction between migrating cells and the ECM may also determine the differential behavior of olfactory migrating cells at different stages (Murase & Horwitz 2002). For example, Tenascin-C, a ligand for $\alpha v\beta 3$ and $\alpha v\beta 6$ integrins (Yokosaki et al. 1996), is strongly expressed in the astrocytes that form the tubes through which olfactory precursors migrate in the adult RMS (Jankovski & Sotelo 1996), and αv-, $\beta 3$-, and $\beta 6$-integrin subunits are also present in the postnatal RMS. During embryonic stages, on the other hand, $\alpha 1$ and $\beta 1$ integrins and $\alpha 5$ and $\gamma 1$ laminins are found in the route of olfactory interneuron precursors (Murase & Horwitz 2002), which suggests that migrating cells use $\alpha 1\beta 1$ integrins to migrate along a laminin substrate. Although blocking experiments in vitro suggest that specific integrin subunits are required for the migration of olfactory interneuron precursors (Jacques et al. 1998, Murase & Horwitz 2002), the lack of abnormalities in the olfactory bulb of mice with individual mutations for some of these molecules precludes a more definitive assessment about the function of these proteins in the migration of olfactory precursors.

In addition to ECM molecules, proteins that mediate cell-cell contact also modulate chain migration. For example, members of the Eph family of tyrosine kinases and their membrane-associated ephrin ligands are expressed in cells of the RMS. Ephrin-B2 and ephrin-B3 are expressed in astrocytes that encase the chains of migrating precursors, whereas EphA4, EphB2, and EphB3 receptors are expressed in yet unidentified cells within the RMS (Conover et al. 2000). Partial disruption of Eph/ephrin interactions through the infusion of clustered EphB2 or ephrin-B2 ectodomains (i.e., lacking their signaling components) into the lateral ventricle of adult mice disrupts migration of neuroblasts in the RMS (Conover et al. 2000). This result suggests that signaling from both EphB receptors and ephrin-B ligands is required to maintain the stability of migrating chains, maybe in a similar manner as PSA-N-CAM contributes to the maintainance chain migration. However, because Eph/ephrin signaling can modulate proliferation in the SVZ (Conover et al. 2000), it is possible that disruption of neuroblast chain migration in the RMS may be a secondary defect.

Migration of interneuron precursors from the subpallial telencephalon to the olfactory bulb is a highly directional process (Hu & Rutishauser 1996, Lois & Alvarez-Buylla 1994). Migrating cells are bipolar, with a short trailing process and a leading process tipped by large growth cones oriented toward the olfactory bulb (Kishi 1987, Murase & Horwitz 2002). Time-lapse experiments show a highly uniform direction of migration in the RMS, with relatively few cells displaying transitory retrograde migration (Murase & Horwitz 2002). Moreover, when the network of chains of the adult SVZ is eliminated by a transient antimitotic treatment,

the SVZ network is able to rapidly regenerate and restore the normal direction of migration (Doetsch et al. 1999), which suggests that signals in this region regulate this process.

Because the cellular mechanisms of migration may be different for embryonic and adult neuroblasts, it is conceivable that different molecules regulate the migration of olfactory interneurons through development and in the adult RMS. In the embryonic brain, it has been proposed that chemorepulsive factors present in the septum may direct migration of immature interneurons toward the olfactory bulb (Hu & Rutishauser 1996). Slit1 and Slit2, two secreted proteins that interact with Robo receptors (Brose et al. 1999, Li et al. 1999), are thought to be responsible for this activity (Hu 1999, Wu et al. 1999). Both Slits are expressed in the embryonic and adult septum (Itoh et al. 1998, Yuan et al. 1999). Moreover, in vitro experiments have shown that Slits repel migrating cells derived from the embryonic subpallium or the postnatal SVZ (Hu 1999, Wu et al. 1999), which suggests that these proteins may contribute to setting the direction of the olfactory neuroblasts migration. The olfactory bulbs of *Slit1* and *Slit2* double mutants are smaller than normal at birth, though they contain GABAergic interneurons (O. Marín, A.S. Plump, M. Tessier-Lavigne, J.L.R. Rubenstein, unpublished results). The precise contribution of these proteins to the migration of olfactory neuroblasts in vivo remains to be elucidated.

In addition to the existence of a repulsive activity that may guide interneuron neuroblasts to the olfactory bulb during embryonic stages, it has been suggested that an attractive activity present in the olfactory bulb may contribute to setting the direction of this migration. Netrin1 is expressed in mitral cells of the olfactory bulb during embryonic stages and early postnatal development, whereas the Netrin1 receptors DCC (for deleted in colorectal cancer) and Neogenin (a DCC-related protein) are expressed in migrating cells from E15 to P5 (Murase & Horwitz 2002). Moreover, anti-DCC antibodies altered the direction of the leading process of migrating neuroblasts in slice cultures, which suggests that this receptor may be implicated in establishing directionality in this migration (Murase & Horwitz 2002).

However, several lines of evidence argue against the hypothesis that an olfactory bulb attractant is responsible for setting the direction of migration in the adult RMS. First, Netrin1 expression in the olfactory bulb is greatly reduced by P4 (Murase & Horwitz 2002). Second, Netrin1 does not affect migration from postnatal SVZ explants in vitro (Mason et al. 2001). Furthermore, the RMS persists and directional migration of SVZ precursors continues after elimination of the olfactory bulb (Jankovski et al. 1998, Kirschenbaum et al. 1999). Accordingly, it has been suggested that the directionality of neuroblast migration in the adult RMS is not achieved by direct attraction from the olfactory bulb but rather by the combination of Slit-mediated repulsion in the SVZ and motogenic activity present in the RMS (Mason et al. 2001). In support of this hypothesis, it has been recently found that postnatal RMS astrocytes stimulate the migration of SVZ cells through the release of a protein activity called MIA (for migration-inducing activity)

(Mason et al. 2001). Astrocytes are present throughout the entire RMS (Jankovski & Sotelo 1996, Lois et al. 1996, Peretto et al. 1997, Thomas et al. 1996), which suggests that this activity may act as a motogenic factor within the adult RMS.

AXONOPHILIC MIGRATION IN THE FOREBRAIN: LHRH NEURONS

The migration of neurons expressing Gonadotropin-releasing hormone (GnRH, also known as luteinizing hormone–releasing hormone, LHRH) constitutes the best-characterized example of axonophilic migration in the forebrain (Wray 2001). GnRH neurons are derived from the nasal placode (Schwanzel-Fukuda & Pfaff 1989, Wray et al. 1989), but they eventually reside in the postnatal preoptic area and hypothalamus, where they control the release of gonadotropic hormones from the anterior pituitary gland and facilitate reproductive behavior (Fink 1988). To reach the forebrain, GnRH neurons migrate along the nasal septum, cross the cribiform plate under the olfactory bulb, and proceed into the forebrain following vomeronasal (VMN) axons. Thus, the migration of GnRH neurons is axonophilic in nature.

GnRH neurons migrate toward the brain following the VMN nerves in the nose. These axons express peripherin, PSA-N-CAM, DCC, and TAG1, an axonal surface glycoprotein (Schwanzel-Fukuda et al. 1992; Schwarting et al. 2001; Wray et al. 1994; Yoshida et al. 1995, 1999). Once the axons of the VMN nerve enter the brain, they split into two branches, one that grows into the olfactory bulb and another that extends toward the lamina terminalis. The vast majority of GnRH neurons migrate selectively along the latter pathway, which retains expression of TAG1 and DCC.

Several factors have been suggested to influence the migration of GnRH neurons before they enter the brain. For example, $GABA_A$ receptor agonists inhibit the migration of GnRH neurons in vitro without altering the VMN axons or the number of GnRH cells (Bless et al. 2000, Fueshko et al. 1998). In addition, the enzymatic removal of PSA from N-CAM during embryonic development or the application of antibodies against N-CAM inhibits the migration of a large number of GnRH neurons in vitro (Schwanzel-Fukuda et al. 1994, Yoshida et al. 1999). However, migration of GnRH neurons is normal in N-CAM mutant mice (Yoshida et al. 1999), which suggests that N-CAM is not essential for the axonophilic migration of GnRH neurons. Recently, a novel factor termed NELF (for nasal embryonic LHRH factor) has been identified in a differential screen comparing a migrating with a nonmigrating GnRH cell (Kramer & Wray 2000). It is interesting that NELF is expressed on both GnRH and VMN axons prior to their entrance in the forebrain, but it is downregulated from GnRH neurons as they migrate toward the hypothalamus. The role of NELF in the migration of GnRH remains to be determined.

Experimental embryological manipulations have demonstrated that GnRH neurons follow VMN axons even when they extend into ectopic locations of the brain (Gao et al. 2000). Accordingly, the trajectory of the caudal branch of the VMN

and the route followed by GnRH neurons in the forebrain are similarly altered in DCC-mutant mice despite the fact that GnRH neurons do not express the Netrin1 receptor DCC after they enter the forebrain (Deiner & Sretavan 1999, Schwarting et al. 2001). These observations reinforce the notion that migration of GnRH neurons is largely dependent on their interactions with axons.

Kallman syndrome (KS) represents a clinical expression of the dependence of GnRH neuron migration on the development of the VMN nerve. KS is characterized by anosmia, hypogonadism, and occasionally mental retardation. The hypogonadism in KS appears to be caused by the defect in the migration of the GnRH-secreting neurons from the olfactory placode to the preoptic and hypothalamic areas, which is likely secondary to failure of VMN axons to penetrate the olfactory bulb (Schwanzel-Fukuda & Pfaff 1989). The mutation responsible for one form of KS has been mapped to a gene designated *Kal1* (Franco et al. 1991), which encodes an ECM protein termed Anosmin-1. Recently, it has been shown that Anosmin-1 promotes axonal branch formation from olfactory bulb output neurons (Soussi-Yanicostas et al. 2002), although its role in the guidance VMN axon has not been studied.

CONTROL OF CELL MIGRATION FROM THE SUBPALLIUM TO THE PALLIUM

The embryonic subpallium is the origin of a large number of cells that migrate tangentially toward the developing cerebral cortex and hippocampus (Anderson et al. 1997, Corbin et al. 2001, De Carlos et al. 1996, Lavdas et al. 1999, Letinic et al. 2002, Marín & Rubenstein 2001, Pleasure et al. 2000, Sussel et al. 1999, Tamamaki et al. 1997, Wichterle et al. 1999). Cells tangentially migrating into the cortex give rise primarily to GABAergic interneurons (Anderson et al. 2002, Cobos et al. 2001a, Stühmer et al. 2002, Wichterle et al. 2001), although the subpallium also appears to generate cortical oligodendrocytes during embryogenesis (Olivier et al. 2001, Spassky et al. 1998). Cells tangentially migrating to the cortex have multiple origins within the subpallium (Anderson et al. 2001, Jiménez et al. 2002, Nery et al. 2002), although most GABAergic interneurons seem to derive from the medial ganglionic eminence (MGE) (Table 3) (Lavdas et al. 1999, Sussel et al. 1999, Wichterle et al. 1999, Wichterle et al. 2001), and the origin of oligodendrocytes appears to be largely restricted to the entopeduncular area (AEP) (Olivier et al. 2001, Spassky et al. 1998). The MGE is the source of interneurons for other forebrain structures, such as the striatum (Marín et al. 2000).

Interneurons migrating toward the cortex follow very restricted routes. During the early stages of their migration, interneurons fated to the cortex avoid entering the developing striatum and thereby invade the cortex either superficial or deep to the striatal mantle (Marín et al. 2001). Superficially migrating neurons initially avoid the cortical plate and migrate through the marginal zone of the cortex or through the subplate (Lavdas et al. 1999). On the other hand, deeply migrating interneurons migrate at first through the lower intermediate zone (DeDiego et al.

TABLE 3 Factors affecting development of cortical interneurons

Gene	Function in telencephalon	Effect on interneuron production or migration
Titf1[a] *(Nkx2-1)*	Transcription factor; cell specification of MGE, AEP, and POa	Mutation of *Nkx2-1* causes reduction of cortical interneurons (~50%) and complete loss of striatal interneurons at birth
Pax6[b]	Transcription factors specification and differentiation in pallium and LGE	Prevents excessive migration. Its loss causes increased migration from the subpallium to the cortex
Dlx1/2[c]	Transcription factor; cell differentiation in LGE, MGE, AEP, and POa	Simultaneous mutation of *Dlx1* and *Dlx2* causes severe loss of cortical (75%–100%), striatal, and olfactory interneurons at birth
Ascl1[d] *(Mash1)*	Transcription factor; cell differentiation in LGE, MGE, AEP, and POa	Mutation of *Mash1* causes reduction of cortical (~50%) and striatal interneurons at birth
Emx1/2[e]	Transcription factors; neurogenesis in pallium	Mutation of *Emx1* and *Emx2* causes reduced interneuron migration from the subpallium
Cit[f]	Citron kinase; cytokinesis	Its mutation in *flathead* rats causes a severe reduction of cortical interneurons (~70%)
Cntn2[g] *(Tag1)*	Cell adhesion molecule; expressed in cortical axons	Antibodies against Contactin2 (TAG1) reduce interneuron migration to the cortex in vitro
Hgf[h]	Growth factor; motogenic	Promotes scattering of interneurons. Antibodies against HGF reduce interneuron migration to the cortex in vitro
u-PAR[h]	Urokinase-type plasminogen activator receptor; HGF activation	Mice lacking u-PAR have reduced numbers of calbindin interneurons in the cortex, most prominently in frontal and parietal cortex
BDNF, NT4[i]	Growth factor; motogenic, differentiation	Cause ectopic accumulation of interneurons in the cortex; stimulate MGE migration in vitro; affect differentiation of GABA cells
TrkB[i]	BDNF/NT4 receptor; motogenic, differentiation	Its mutation causes reduction of calbindin interneurons in the embryonic cortex (~50%)
Slit1/2[j]	Guidance molecules	Repel cells from the embryonic LGE in vitro. Their simultaneous mutation does not perturb interneuron migration to the cortex
Sema3A/3F[k]	Guidance molecules	Repel MGE-derived cells migrating to the cortex in vitro
Nrp1[k]	Neuropilin1; Sema3A receptor	A dominant negative form of Nrp1 reduces interneuron migration to the cortex and increases migration to the striatum in vitro
Nrp2[k]	Neuropilin2; Sema3F receptor	Its mutation causes increased number of interneurons in the striatum

[a]Sussel et al. 1999, Marín et al. 2000

[b]Chapouton et al. 1999, Stoykova et al. 2000, Yun et al. 2001

[c]Anderson et al. 1997, Pleasure et al. 2000

[d]Casarosa et al. 1999, Marín et al. 2000

[e]Shinozaki et al. 2002

[f]Sarkisian et al. 2001, 2002

[g]Denaxa et al. 2001

[h]Powell et al. 2001

[i]Jones et al. 1994, Brunstrom et al. 1997, Polleux et al. 2002

[j]Zhu et al. 1999, Marín et al. 2003

[k]Marín et al. 2001, Tamamaki et al. 2003

1994, Denaxa et al. 2001, Lavdas et al. 1999), but as development proceeds they seem to occupy a deeper position within the developing cortex, largely overlapping the SVZ (Del Rio et al. 1992, Marín & Rubenstein 2001, Wichterle et al. 2001). Of note, whereas interneurons migrating through the marginal zone and subplate travel individually, cells invading the cortical SVZ migrate as a rather compact cluster. Thus, perhaps this deep migration contributes cells to the developing SVZ of the cortex in a manner similar to how the RMS supplies cells to the SVZ of the olfactory bulb (Anderson et al. 2001, Marín & Rubenstein 2001, Wichterle et al. 2001).

Three different types of factors influence the tangential migration of interneurons from the subpallium and pallium: first, factors that stimulate the movement of interneurons; second, structural elements that constitute the substrate for their migration; and third, cues that direct interneurons toward their target through the appropriate pathways (Figure 3).

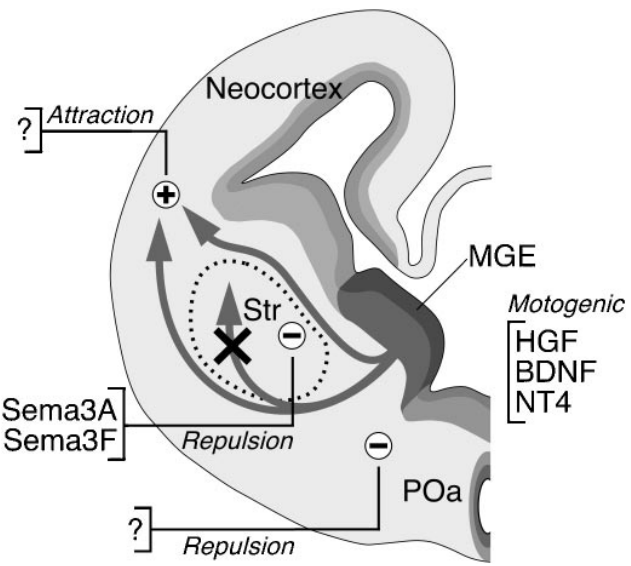

Figure 3 Mechanisms regulating interneuron migration from the subpallium to the cerebral cortex. Schematic drawing of a transversal section through the telencephalon in which the midline is to the right and dorsal is to the top. (*i*) Several motogenic factors, including HGF, BDNF, and NT4 promote the migration of neurons from the medial ganglionic eminence (MGE). (*ii*) An unidentified repulsive activity (*minus sign*) present in the preoptic area (POa) prevents ventral migration of interneurons, directing them toward the cortex. (*iii*) Expression of Sema3A and Sema3F in the mantle of the developing striatum (Str) prevents cortical interneurons, which express neuropilin receptors, from entering this structure. (*iv*) An unidentified attractive activity (*plus sign*) guides interneurons toward the cortex and probably contributes to their medial spreading.

Motogenic Factors for Tangentially Migrating Interneurons

Cells tangentially migrating from the MGE to the cortex have an outstanding migratory capability (Wichterle et al. 1999), which suggests that they are highly responsive to scatter factors in the telencephalon. One of these molecules is hepatocyte growth factor (HGF), which is expressed in the telencephalon at the time of interneuron migration to the cortex (Powell et al. 2001). In slice cultures, HGF increases the number of cells migrating away from the subpallium, whereas antibodies against HGF inhibit cell movement. Moreover, mice lacking the urokinase-type plasminogen activator receptor (u-PAR, one of the enzymes that cleaves the inactive pro-form of HGF to the biologically active protein) have fewer cortical calbindin interneurons at birth than normal (Powell et al. 2001). Similar to radially migrating neurons in the embryonic cortex (Behar et al. 2000), tangential migration of GABAergic interneurons is also strongly stimulated in vitro by BDNF and NT4 and attenuated by tyrosine kinase inhibitors (Polleux et al. 2002). In addition, it has been reported that TrkB mutant mice have a significant decrease in the number of calbindin interneurons migrating tangentially in the embryonic cortex, leading to the suggestion that TrkB signaling is indeed essential for normal interneuron migration to the cortex (Polleux et al. 2002). However, because BDNF induces the expression of calbindin and neuropeptides in telencephalic GABAergic cells, and loss of BDNF results in the downregulation of these molecules in cortical interneurons (Arenas et al. 1996, Fiumelli et al. 2000, Jones et al. 1994), it is unclear whether the reduction of calbindin in the embryonic cortex of TrkB mutant mice actually reflects a decrease in the number of migrating interneurons or just a mere reduction in the expression of calbindin by these cells.

What is the Substratum Used by Tangentially Migrating Interneurons?

Presently, the substratum that interneurons use in their migration toward the cortex is unknown. Tangential migration appears to be independent of interactions with radial glial cells, unless migrating cells glide across one glial palisade to the next as they move perpendicular to the radial glial processes. On the other hand, some tangentially migrating cells in the intermediate zone of the cortex appear to be closely associated with corticofugal axons (Denaxa et al. 2001, Métin et al. 2000, Métin & Godement 1996, O'Rourke et al. 1995), which has led to the suggestion that interneurons may use axons as a substratum for migration. Accordingly, antibodies against TAG-1, which is expressed on corticofugal axons, reduce the number of interneurons reaching the cortex in slice cultures (Denaxa et al. 2001). However, analysis of *Tag1*-mutant mice has not revealed major alterations in the tangential migration of interneurons to the embryonic cortex (Denaxa et al. 2002). Moreover, the fact that a large number of cells migrating from the subpallium to the pallium are concentrated in the axon-sparse lower intermediate zone or in the SVZ, avoiding the axon-rich upper intermediate zone, suggests that tangentially migrating cells preferentially use substrates other than axons.

Directional Guidance of Migrating Interneurons

Guidance of tangentially migrating interneurons involves the coordination of multiple guidance cues (Figure 3), similar to growing axons steering through different terrains in search of their target. The general direction of interneuron migration—ventral to dorsal—appears to be established by the simultaneous activity of chemorepulsive and chemoattractive factors produced by the preoptic area (POa) and the cortex, respectively (Marín et al. 2003, Wichterle et al. 2003). A repulsive activity in the POa prevents interneurons from migrating in a ventral direction and is largely responsible for their dorsal orientation toward the cortex. The molecule(s) responsible for the chemorepulsive activity present in the POa has not been identified yet. Previous studies have suggested that repulsion of interneurons from the subpallium toward the cortex is mediated by Slits (Zhu et al. 1999), large ECM molecules that possess chemorepulsive activity for growing axons and migrating cells in a variety of systems (Brose & Tessier-Lavigne 2000). However, the chemorepulsive activity found in the POa is still present in mice with targeted mutations in both *Slit1* and *Slit2*, the two Slit members expressed in the subpallium (Marín et al. 2003). Moreover, migration of interneurons to the cortex is normal in *Slit1*/*Slit2* mutants (Marín et al. 2003), which suggests that Slits do not play a major role in this tangential migration. Netrin1 has been implicated in repelling striatal neurons from the LGE (Hamasaki et al. 2001b); however, mice simultaneously lacking *Slit1*, *Slit2*, and *Netrin1* have normal numbers of interneurons at birth (Marín et al. 2003), which indicates that none of these molecules is essential for the tangential migration of interneurons to the cortex.

The existence of a diffusible cortical attractive activity (CAA) for tangentially migrating interneurons has been recently revealed by two independent approaches (Marín et al. 2003, Wichterle et al. 2003). Thus, MGE-derived cells preferentially migrate toward cortical cells in matrigel matrix experiments (Marín et al. 2003, Wichterle et al. 2003). In slice cultures, the addition of an ectopic cortex deviates the migration of MGE-derived cells from their normal route, attracting the cells in a distance-dependent manner (Marín et al. 2003). Moreover, genetic disruption of the embryonic cortex in *Emx1* and *Emx2* double mutants reduces tangential migration of interneurons from the subpallium (Shinozaki et al. 2002), which supports the notion that factors present in the embryonic cortex directly affect the migration of interneurons from the subpallium. Of note, migration of interneurons from the MGE to the level of the subpallial/pallial boundary is largely independent of the cortex (Marín et al. 2003), indicating that the role of the CAA may be to guide interneurons once they reach the pallium. In line with this observation, the direction of migration from lateral toward medial regions of the cortex is preserved in the absence of the subpallium (O. Marín and J.L.R. Rubenstein, unpublished observations), and the CAA appears to be present in a high-medial to low-lateral gradient in the cortex (Marín et al. 2003), which suggests that it may contribute to the proper dispersion of interneurons through different cortical areas. The molecular nature of the CAA remains to be determined.

In addition to controlling the ventral to dorsal direction of migration, guidance cues are also required to distribute interneurons to different telencephalic structures. For example, sorting of interneurons destined for the cerebral cortex or the striatum appears to be mediated by Neuropilin/Semaphorin interactions (Marín et al. 2001). Neuropilins are transmembrane receptors that mediate the repulsive actions of class 3 semaphorins on axons (Raper 2000). In the subpallium, Neuropilin1 and Neuropilin2 are expressed by interneurons that migrate to the cortex but not by interneurons that invade the developing striatum. Expression of neuropilins allows migrating cortical interneurons to respond to a chemorepulsive activity in the striatal mantle, of which the class 3 semaphorins (Sema3A and Sema3F) are components (Figure 3). Loss of Neuropilin1 or Neuropilin2 function increases the number of interneurons migrating to the striatum and decreases the number reaching the embryonic cortex (Marín et al. 2001). Expression of Sema3A and Sema3F may also influence the distribution of GABAergic interneurons in the embryonic cortex (Tamamaki et al. 2002).

The guidance of neurons tangentially migrating to the cortex may also be influenced by neuronal activity in a similar manner to the way in which growth cone turning responses to guidance cues are modulated by electrical activity in a Ca^{2+}-dependent manner (Ming et al. 2001). Thus, glutamate released from corticofugal axons could lead to receptor activation in tangentially migrating cells and thereby modulate their response to guidance cues. Tangentially migrating cells display intracellular calcium changes in response to agonists of NMDA, AMPA/Kainate, and $GABA_A$ receptors (Métin et al. 2000, Soria & Valdeolmillos 2002), and stimulation of AMPA receptors in slice cultures induces neurite retraction and GABA release in tangentially migrating cells (Poluch et al. 2001, Poluch & Konig 2002). Additional experiments are required to clarify the functional significance of the endogenous activation of these receptors on tangential migration.

Once they reach the pallium, interneurons invade the cortical plate and distribute into different cortical layers. It has been shown that cortical interneurons, like projection neurons, are generally born in an inside-out order with respect to their location within the cortical layers and roughly contemporaneously with pyramidal neurons that occupy the same layer (Fairén et al. 1986, Miller 1985, Peduzzi 1988). It is interesting that molecules that influence migration of projection neurons, such as Cdk5, do not seem to influence the tangential migration of interneurons from the subpallium to the cortex or their subsequent movement into the cortical plate (Gilmore & Herrup 2001). It is not known, however, whether the laminar distribution of GABAergic cells is affected in mutants with defects in cortical lamination. Inroads to solve this question are being made with the analysis of the distribution of small subpopulations of GABAergic interneurons in the cortex of *reeler* mice. Thus, the laminar position of a subpopulation of GABAergic interneurons that express the neuropeptide somatostatin is altered in *reeler* mutants (A. Renfro, O. Marín, J.L.R. Rubenstein, J.W. Swann, and G. D'Arcangelo, unpublished results), which suggests that subpopulations of interneurons either respond to Reelin to find their appropriate cortical layer or they are able to follow specific

subpopulations of pyramidal neurons—those that are born roughly at the same time—independently of their laminar position within the cortex. Cortical interneurons appear to seek the VZ of the cortex before moving radially to take up their positions in the cortical plate (Nadarajah et al. 2002), which indicates that positional information present in the VZ may instruct interneurons to find their appropriate lamina.

COMMON THEMES IN RADIAL AND TANGENTIAL MIGRATIONS

How Different are the Cellular Interactions in Radial and Tangential Migrations?

The large majority of migrating cells in the forebrain use cellular substrates for their migration. Thus, despite the difference in the orientation of the migration, all types of radial and tangential migrations share an obvious common feature: contact to other cells. In some cases, neurons use the processes of other cells to guide their migration, such as the radially migrating cortical projection neurons or the tangentially migrating GnRH neurons. It has always been considered that migration along radial fibers was fundamentally different from migration along axons because of the distinct nature of radial glial cells and neurons. The recent findings suggesting that radial glial cells are indeed neuronal progenitors in the cerebral cortex (Heins et al. 2002; Malatesta et al. 2000; Miyata et al. 2001; Noctor et al. 2001, 2002) have opened the door for a new interpretation of the cellular interactions occurring during migration in the forebrain. Thus, the interactions between cortical neurons and radial glial cells, GnRH neurons and vomeronasal axons, or among olfactory interneurons during chain migration may be more similar than we previously thought. In line with this observation, a recent study has suggested that Reelin may have a general role as a detachment factor in neuronal migration, either acting on the interaction between radial processes and migrating neurons or on the interaction between apposing cells in chain migration (Hack et al. 2002). Similarly, early radial translocation and tangential migration of interneurons both appear to be largely independent of contact with other cell types, which suggests that these two migrations, distinct in their orientation, may also share common mechanisms.

Do Neurons Switch Between Different Migration Modes?

Tangentially migrating cells are able to disperse in a radial fashion. For example, once interneurons derived from the MGE have reached the cortex, they turn radially into the cortical plate to seek their appropriate cortical layer. Similarly, newly generated olfactory interneurons migrate radially after they reach the olfactory bulb through the RMS. Are tangentially migrating cells able to undergo glial-guided radial migration? It has been shown that interneurons migrating radially into the

cortical plate commonly make contact with radial glial cells, but the orientation of their leading process is not always aligned with the processes of radial glial cells (Polleux et al. 2002). This would suggest that interneurons do not require radial glial cells for their migration into the cortical plate. On the contrary, migration of granule cells in the cerebellum seems to be largely dependent on their interaction with glial processes, even though they reach the cerebellar primordia by tangential migration (Hatten 1999). Thus, it seems conceivable that tangentially migrating cells change their repertoire of adhesive molecules once they switch into a radial mode of migration.

COORDINATION OF RADIAL AND TANGENTIAL MIGRATIONS AND THE FORMATION OF COMPLEX NEURONAL CIRCUITS

It is now clear that most structures in the forebrain, including the cortex, hippocampus, olfactory bulb, striatum, and hypothalamus, arise from the integration of neurons arriving via radial and tangential migrations. Radially migrating neurons are born in the VZ, which gives rise to most of the cells found in each structure. In contrast, tangentially migrating neurons typically arise from distant progenitor zones, in some cases very far away from the place where these neurons finally reside. What is the advantage of producing different cell types in diverse locations of the forebrain? One explanation for this phenomenon is that patterning and migratory processes have been intimately linked during development of the CNS. For example, the generation of certain populations of telencephalic neurons with distinct neurotransmitter phenotypes appears to be linked to specific progenitor cells that are located in different dorsoventral subdivisions of the telencephalon. Thus, glutamatergic neurons appear to be produced exclusively from progenitor cells in the pallium, whereas most GABAergic neurons may be generated in the subpallium, and cholinergic neurons may derive solely from the most ventral region of the subpallium (Marín et al. 2000, Wilson & Rubenstein 2000). As a result, tangential migration in the CNS might be a mechanism selected through evolution to increase the cellular complexity of specific circuits, such as the cerebral cortex. An additional implication of this hypothesis is that tangential migration would also occur from the pallium to the subpallium when cell types specified in dorsal regions of the telencephalon are required in ventral structures, and recent studies suggest that this can be the case (Hamasaki et al. 2001a, Striedter et al. 1998, Tomioka et al. 2000).

The discovery that the development of complex structures in the forebrain, such as the cerebral cortex, requires radial and tangential migrations has important clinical implications. Because the majority of the neurons in the cortex are projection neurons, disruption of the migration of these neurons typically results in severe malformation of the cortex (Ross & Walsh 2001). In contrast, defects in the migration or final arrangement of cortical interneurons may lead to more subtle morphological defects that nevertheless may cause severe impairment of cortical

function. The cortex of mice defective in u-PAR, for example, has a prominent reduction in the number of calbindin interneurons without compromising the overall morphology of the cortex (Powell et al. 2001). Of note, u-PAR-defective mice live, but suffer from severe physiological alterations in cortical activity (Powell et al. 2003). Moreover, mice with a targeted mutation of the aristaless-related homeobox gene (*Arx*) have abnormal migration and differentiation of GABAergic cortical interneurons (Kitamura et al. 2002). This observation may explain some of the clinical features of several syndromes in humans, including the X-linked lissencephaly with abnormal genitalia syndrome, the X-linked infantile spasm syndrome, and a less severe epileptic syndrome, all of which appear to arise from different types of mutations in *Arx* (Bienvenu et al. 2002, Kitamura et al. 2002, Stromme et al. 2002). Thus, it seems conceivable to foresee that the identification of new genes affecting tangential migration in the forebrain will contribute to our understanding of other complex neurological diseases.

ACKNOWLEDGMENTS

Research on neuronal migration in our laboratories is supported by a grant from MCYT BMC2002-03337 to O.M., and by Nina Ireland and grants from NIDA R01DA12462, NIMH RO1MH49428-01, RO1MH51561-01A1, and K02MH01046-01 to J.L.R.R.

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