

## CENTRAL NERVOUS SYSTEM NEURONAL MIGRATION

Mary E. Hatten

The Rockefeller University, 1230 York Avenue, New York, New York 10021-6399;  
e-mail: hatten@rockvax.rockefeller.edu

KEY WORDS: neurogenesis, neuronal layers, cortex, cerebellum

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### ABSTRACT

Widespread cell migrations are the hallmark of vertebrate brain development. In the early embryo, morphogenetic movements of precursor cells establish the rhombomeres of the hindbrain, the external germinal layer of the cerebellum, and the regional boundaries of the forebrain. In midgestation, after primary neurogenesis in compact ventricular zones has commenced, individual postmitotic cells undergo directed migrations along the glial fiber system. Radial migrations establish the neuronal layers. Three molecules have been shown to function in glial guided migration—astrotactin, glial growth factor, and erbB. In the postnatal period, a wave of secondary neurogenesis produces huge numbers of interneurons destined for the cerebellar cortex, the hippocampal formation, and the olfactory bulb. Molecular analysis of the genes that mark stages of secondary neurogenesis show similar expression patterns of a number of genes. Thus these three regions may have genetic pathways in common. Finally, we consider emerging studies on neurological mutant mice, such as *reeler*, and human brain malformations. Positional cloning and identification of mutated genes has led to new insights on laminar patterning in brain.

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### INTRODUCTION

During development of the central nervous system (CNS), far-ranging cell migrations deploy young neurons toward the surface of the developing brain. The sheer number of migrating neurons, billions in the vertebrate forebrain, and the distances traversed, up to centimeters in primates, are remarkable. In vertebrates, neurons settle into six neuronal laminae within the forebrain, and in those laminae they interact with ingrown axons to form the neuronal circuitry

of brain. As specific classes of cells come to reside in specific layers, migration also reflects a program of neuronal fate. This program of neurogenesis occurs in an inside-out manner, with the earliest-generated neurons positioned in the deepest layers and later-generated neurons occupying the superficial layers. Molecular genetic studies indicate that CNS migrations fall within a three-step program of development that includes establishment of cell identity, directed migration, and assembly into compact neuronal layers.

### ESTABLISHMENT OF BRAIN REGIONS

Although classical accounts of brain development used microscopy and [<sup>3</sup>H] thymidine labeling to document neurogenesis, migration, and synaptogenesis, recent molecular genetic studies placed CNS development within a program of embryology. In this model, genes involved in neural induction set forth the program of CNS development (Harland 1997, Hemmati-Brivanlou 1994). The initial step in this process is the establishment of the anterior-posterior (AP) axis and the subdivision of the brain vesicles (Rubenstein et al 1998). A program of transcription factor expression marks domains that will become the forebrain (Rubenstein et al 1998), midbrain and cerebellum (Joyner 1996), hindbrain (Guthrie 1996), and spinal cord (Jessell & Lee 1999). The onset of axial patterns within the nervous system is closely linked to the onset of neural induction. Thus, as the expression of specific transcription factors commences within different territories of the emerging CNS, subsets of neurons begin to acquire a dorsal or ventral identity. The dorsalization of cells occurs via locally acting peptide growth factors, which induce cells toward dorsal cell fates, and sonic hedgehog inducing cells toward ventral fates (Doniach 1995, Roelink et al 1994, Jessell & Lumsden 1997). By virtue of their location in the dorsal or ventral aspect of the neuraxis, cells become specified toward cortical and subcortical fates.

The establishment of the dorso-ventral (DV) axis is concurrent with the expression of transcription factors that mark specific cell types within the dorsal and ventral areas. As discussed in detail below, this program of gene expression is in progress at early embryonic periods (E8.5-E13), the time of neurogenesis of cells within these brain regions. This is important to the migrations that will commence in the next stage of development because cells in the dorsal regions form laminar structures and those in ventral regions form nonlaminar structures (thalamus and lateral geniculate nucleus are exceptions to this generalization). A two-step program thus underlies patterning in the forebrain, hippocampal formation, cerebellar cortex, and olfactory bulb, the regions of laminar architecture.

In the following sections, we first consider the concerted actions of local positional cues, which set forth programs of cell specification and control the movement of the young neuron along the radial glial fiber system. Next, the

formation of the basic embryonic layers of cortex is reviewed, with focus on the mechanisms of cell migration and the formation of neuronal layers. Finally, the migration of neurons is reviewed, from the secondary germinal matrices—the subventricular zone of cortex, the lateral ganglionic eminence, and the external germinal layer (EGL) of the cerebellum—to the laminar framework set forth by early patterns of cell specification, lamination, and migration. The latter migrations direct large numbers of interneurons into cortical regions at late stages of development, when primary input/output neurons have established rudimentary cell layers.

### CELL MOVEMENTS IN EARLY EMBRYOGENESIS

At early phases of development, before young neurons leave the ventricular zone, cells move in the neuroepithelium. In the hindbrain, proliferating precursor cells move from one rhombomere into the other (Jessell & Lumsden 1997; Lumsden 1990, 1996; Lumsden & Keynes 1989). Once the cells become postmitotic, they are restricted to a specific rhombomere (Fraser et al 1990). In the emerging cerebellar anlage, cells within the EGL undergo a morphogenetic movement from the dorsal ridge where they originate across the roof of the anlage. When granule cells exit the cell cycle, in the perinatal period, they turn to radial migration along the glial fibers. At early stages of murine (E10–E16) and ferret (E33–35) cortical development, precursor cells within the ventricular zones move tangentially (Fishell et al 1993), often dispersing across regional boundaries (Walsh & Cepko 1994, Reid et al 1997). As small movements within proliferative zones of cortex disperse the neurons across wide areas of cortex, these studies are especially noteworthy.

### RADIAL MIGRATION: THE PREDOMINANT PATHWAY

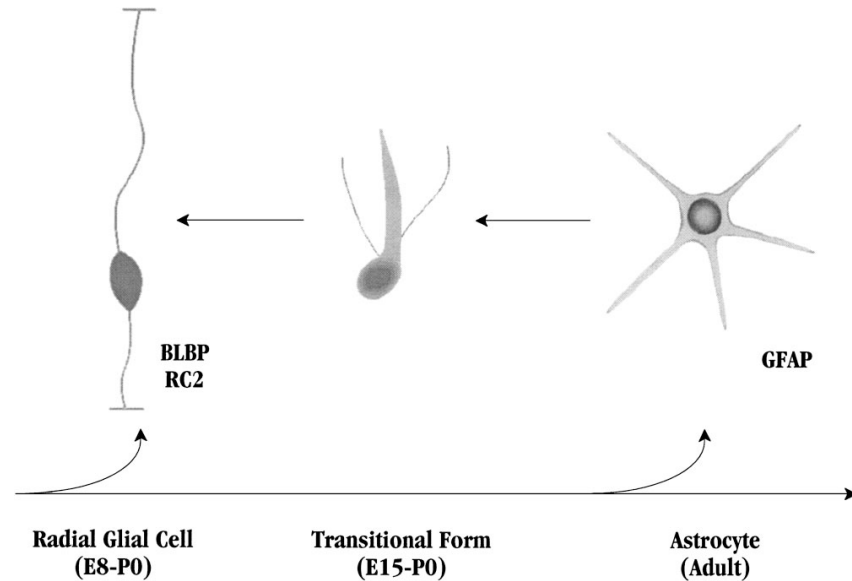
Over the past century, studies on developing cortical regions of brain have provided evidence for a radial pathway of development (Ramon y Cajal 1955, 1995). This pathway follows from the radial disposition of the germinative zones of the neural tube, which are organized into a pseudo-stratified epithelium. The alignment of postmitotic neurons with a system of radial glial fibers during periods of cortical formation led to the general hypothesis that radial glia provide a scaffold for directed migrations in brain (Rakic 1971, 1972, 1978; Sidman & Rakic 1973). Support for this model has been widespread, with *in vitro* (Edmondson & Hatten 1987, Fishell & Hatten 1991, Hatten 1993) and *in vivo* studies (Gao & Hatten 1994a,b; Anton et al 1996) demonstrating that 80–90% of the billions of neuronal precursors in mammalian cortex migrate along glial fibers.

### FORMATION OF THE RADIAL GLIAL SCAFFOLD

The question of glial differentiation is inevitably linked to that of neuronal migration. During development, glial cells assume forms and functions that subserve those of the developing neurons. Early on, glial cells elaborate processes that span the wall of the developing neural tube (Kolliker 1890, Ramon y Cajal 1995, Retzius 1894). These radial glial cells provide the primary pathway for directed migrations (Rakic 1972). Experiments on radial glial cells purified from embryonic cortex and identified by their expression of the antigen markers BLBP and RC2 show that diffusible signals from the young neurons induce the extension of processes by this class of glia (Hunter & Hatten 1995). Among these are RF60, a neuronal protein that is abundant in the mid-gestational period when migration is robust, decreasing in later periods when migration wanes, and undetectable in the adult, after the program of migration has established the neuronal laminae (Hunter & Hatten 1995). The neuronal growth factor GGF (glial growth factor), or neuregulin, is another inducer of the radial glial phenotype. GGF induces the expression of the brain lipid protein BLBP (Anton et al 1997). BLBP has been shown (Feng et al 1994, Xu et al 1996) to be a fundamental protein of the radial glial cell and an important marker of this early phase of glial cell development so critical for cell migration.

After the epoch of cell migration, glial cells transform into stellate astrocytes. Schmechel & Rakic (1979a,b) first demonstrated this transformation *in vivo*; later critical studies (see Culican et al 1990) demonstrated intermediate glial forms during the transformation from a radial to a stellate phenotype (Figure 1). The latter have long been recognized by their abundant expression of the glial intermediate filament GFAP (Hatten & Liem 1981), the major component of stellate glial cell processes. One radial glial phenotype, the Bergmann glial cell of the cerebellar cortex, expresses both GFAP and BLBP during neuronal migration (Feng et al 1994). The Bergman cell is unique in this respect and in the fact that it projects radially aligned processes across half the span of the emerging cerebellar cortex. This glial cell specializes in supporting the migration of granule cells, from the displaced germinal zone where they proliferate on the roof of the cerebellar anlage, to the depth of the cerebellar anlage.

The expression of BLBP by Bergmann glial cells supports a role for BLBP in signaling events needed for expression of cell properties that support migration (Feng et al 1994). As seen for radial glial cells, Bergmann glial cell process extension is strictly dependent on interactions with neurons (Feng & Heintz 1995). Video microscopy of this event shows that neuronal contact stimulates Bergmann glial process extension, and that antibodies against the neuronal protein astrotactin block process formation (Mason et al 1988, Edmondson et al 1988). The latter is presumably the result of a failure of the neurons to establish

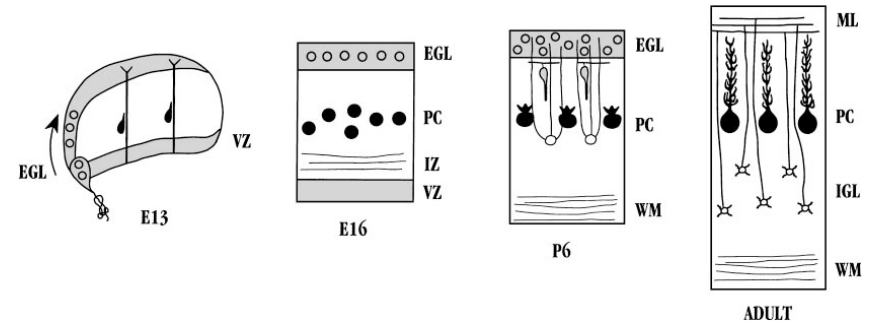


**Figure 1** Scheme of astroglial cell differentiation. In the embryonic period, radial glial cells form a dense network of glial fibers. These cells can be recognized in cell culture by the expression of the cell markers BLBP and RC2. As the period of neuronal migration closes, the radial glia transform into astrocytes. Transitional forms are evident in vivo. In addition to this “forward” differentiation, adult glial cells can be induced to revert to the embryonic, radial phenotype by the addition of the neuronal factor RC60 (see text for details).

a close apposition with the glia, an apposition where cell surface receptors and diffusible factors produced by the neuron act to induce and maintain glial processes. Thus, the glial scaffold is induced by factors produced by young neurons. Once migration across the scaffold is completed, the radial glial cells disappear and cells are locked in position by the formation of specific axon-target interactions (Baird et al 1992).

## DEVELOPMENT OF THE CEREBELLAR CORTEX, A MODEL FOR CORTICAL LAMINATION

Development of the cerebellar system involves generation of the deep nuclei of the cerebellum and the overlying cortex (Figure 2). By [<sup>3</sup>H]thymidine labeling, neurons of the deep nuclei are generated first (Altman & Bayer 1985b),



**Figure 2** Program of development in the cerebellar cortex. At early developmental period (left), both of the principal neuron classes are specified. While Purkinje cells become postmitotic (filled circles) and migrate through the wall of the cerebellar anlage, precursors of the granule cell (unfilled circles) sweep across the roof in a morphogenetic movement. In the perinatal period, granule cells become postmitotic and migrate inward, along the Bergmann glia, to assume a position deep to the Purkinje cell. In the adult (right), the pattern of connections of the granule neuron and the Purkinje cell (coronal plane) are established. Granule cells extend parallel fibers, which form synaptic connections with the dendrites of the Purkinje cells. EGL, External germinal layer; VZ, ventricular zone; WM, white matter; IZ, intermediate zone; IGL, internal granule layer.

followed by precursors of the Purkinje cell (Altman & Bayer 1985c). Purkinje cells migrate along the radial glial fibers out beyond the mantle of postmitotic precursors. Thereafter, the Purkinje cells settle into a broad zone where they remain until the early postnatal period. In the murine cerebellum, Purkinje cell precursors are generated between embryonic days 11–13. Thus, neurogenesis of the principal output neuron of the cerebellar cortex, the Purkinje cell, occurs within the early phases of cerebellar development. The migration of these cells along the radial glial system to form a rudimentary zone overlying the germinal zone provides a scaffold for the formation of the other neuronal layer of the cerebellar cortex, the internal granule cell layer (Altman & Bayer 1985b).

Classical studies of *reeler* mutant mice show a failure of layer formation in developing cerebral cortex and cerebellum (Caviness & Sidman 1973, Caviness 1982, Caviness & Rakic 1978). In these regions, cortical neurons disperse among the layers and their dendritic arbors project in all directions. Molecular cloning of the *reeler* gene (D’Arcangelo et al 1995) suggests that the Reelin protein may function in the formation of the cortical laminae. In the cerebellum, the gene is proposed to act on the Purkinje cell. Reelin is a large extracellular protein secreted by cells in the marginal zone of the cerebellar anlage and of the cortex (Sheppard & Pearlman 1997). Reelin has homology to F-spondin and contains epidermal growth factor–like repeats similar to those of tenascin C,

tenascin X, restrictin, and the integrin beta chain (D'Arcangelo et al 1997). Because Reelin is expressed in a zone above the site where Purkinje cells cease migration (Miyata et al 1996), Reelin might curb the initial migration of the immature Purkinje cells. This action would suspend Purkinje cell precursors in a broad zone, where they interact with ingrowing axons (Mason et al 1990) and await the arrival of the granule cell (Miyata et al 1997). In *reeler* mice, lamination of the Purkinje cells fails, and neurons assume random orientations within the depth of the cerebellar cortex. Granule cell migration is unaffected by Reelin, as migrating granule cells both produce and migrate through zones of Reelin in *in vitro* assays.

In addition to these changes in the possible extracellular matrix (ECM) material in the cerebellar and cerebral cortex, *reeler* has been associated with defects in the radial glial system. Thus, *reeler* partially inhibits expression of the radial glial phenotype, leaving the cells shorter and disorganized (Pinto-Lord et al 1982, Hunter-Schaedle 1997). This is apparently an indirect effect of CR-50 antigen/Reelin. Cajal-Retzius cells make CR-50 antigen/Reelin (Soriano et al 1997) in the cerebral cortex and hippocampal formation. Thus, it appears that the neurons secrete other factors that promote glial differentiation, or factors that require the presence of Reelin to function (Soriano et al 1997).

Neuroanatomical studies on cerebellar development combine with molecular and cellular studies on Reelin to suggest a model for cerebellar organization. In this model, the early migration of the Purkinje cell and the cessation of migration to form the first cell layer, by mechanisms involving CR-50 antigen/Reelin, set the framework for the cerebellar cortex. After clonal expansion in the superficial EGL, granule cells migrate through the field of differentiating Purkinje cells and set forth three layers—an outer molecular layer of granule cell axons and Purkinje cell dendrites, a layer of Purkinje cells, and an inner layer of granule cells. The principal output neuron, the Purkinje cell, thus provides the organizing center of the cerebellar cortex.

A role for Purkinje cells in patterning the cerebellar cortex is supported by cerebellar structure in evolution. The cerebellar cortex first appears in amphibians, fish, and reptiles. In these lower vertebrates, the cerebellum is a single folium, or shelf, arching over the hindbrain (Gona 1976). As in higher vertebrates, there are three cell layers: the molecular layer, the Purkinje cell layer, and the granule cell layer. These trilaminar structures are formed by the same mechanism used to generate the more complex cerebellum of higher animals. Purkinje cells (and interneurons) migrate out from the ventricular zone (VZ), settle in a broad zone over the deep nuclei, and wait for the granule cell precursor population to traverse the roof of the anlage and migrate inward. Like higher vertebrates, the migratory pathway of the granule neurons follows a radial trajectory through the zone of immature Purkinje cells into a deeper layer (the

internal germinal layer). As one scales the evolutionary ladder, the structure of the cerebellum remains essentially the same: three layers formed by the coordinated migrations of two principal classes of neurons. The size of the cerebellum expands through the expansion of the pool of granule cell progenitors in the EGL, with the ratio of granule cells to Purkinje cells increasing with increased muscle mass and coordinated movements of the limbs and digits. In human cerebellum, this ratio is in excess of 400 granule cells per Purkinje neuron.

## ESTABLISHMENT OF GRANULE CELL IDENTITY

Recent molecular biological studies (Kuhar et al 1993) demonstrate that migration is one step in a cascade of gene expression for neuronal differentiation (Hatten & Heintz 1995). Prior to migration, cells have to enter a program of differentiation that utilizes cell movement. As migration is so intimately linked to the establishment of cell fate, it is necessary to discuss the mechanism of specification of the cell in question. In this review, the cerebellar granule cell is the focus. This cell is chosen because of the wealth of neuroanatomical, cell biological, and molecular biological information about its development.

Two general approaches to granule cell specification have been taken—the identification of transcription factors that mark the granule cell lineage, and the identification of locally acting cues that induce granule cell fate in early development. Recently, Ben-Arie et al (1997) examined the role of the mouse homologue of the *Drosophila* gene *atonal*, *Math1*. *Math1* encodes a basic helix-loop-helix transcription factor (bHLH) that is specifically expressed in cells within the cerebellar EGL, the precursors of the granule neuron. Targeted disruption of the *Math1* gene leads to a cerebellar cortex devoid of granule cells. Thus, *Math1* is essential for the genesis of the granule neuron, one of the two principle neurons of the cerebellar cortex. These experiments support the general conclusion that bHLH genes function in cell specification in the CNS and the particular conclusion that *Math1* functions directly in lineage determination within the granule neuron. As discussed below, *Math1* expression commences early in cerebellar development (E8–9), at the earliest time that cerebellar granule neuron precursors appear. Its expression is restricted to the dorsal ridge of the emerging cerebellar anlage, the ridge that will give rise to the rhombic lip (His 1891) (see Figure 2). *Math1* expression commences at the earliest appearance of the anlage and within precursors of the most abundant neuron in the cerebellum, the granule neuron.

To further examine transcription factors in granule cell development, screening was done for zinc-finger motifs that occur in higher vertebrate cerebellar development. The precedent for these experiments comes from experiments on invertebrate systems that have established a role for transcription factor function

in cell fate specification. To examine granule cell development, a zinc-finger motif-containing gene, *Ru49*, was identified (Yang et al 1996). *Ru49* has arisen recently on the evolutionary scale and, more importantly, has a pattern of expression that is restricted to granule neurons. Expression commences in granule cell precursors during the embryonic period and continues through the lifetime of granule cells. Recently developed technology with bacterial artificial chromosomes (Yang et al 1998) has allowed the generation of transgenic mice that overexpress *Ru49*, resulting in more granule cells and a larger cerebellar cortex (X Yang, N Heintz, unpublished data). These studies show a fundamental role for *Ru49* in granule cell specification.

Two other zinc-finger-containing transcription factors have been shown to mark granule cells in developing cerebellum. These are *Zic1* and *Zic2* (Nagai et al 1997). Like *Ru49*, *Zic1* and *Zic2* genes are expressed in granule cells. A fascinating feature of *Ru49* expression is the fact that the gene is also expressed in two other regions of the brain, the dentate gyrus and the olfactory bulb. These areas also contain cells named granule cells by Ramon y Cajal (1995). The common expression of *Ru49* in granule cells of cerebellum, the hippocampal formation, and the olfactory bulb suggests that *Ru49* has a fundamental role in the development of all these classes of granule cells. Moreover, it suggests that these cells, although divergent in molecular features such as neurotransmitters, have a common subroutine within the mechanisms that specify their fate (Yang et al 1996).

The other approach to granule cell specification is to apply the principles of spinal cord embryogenesis to the cerebellar cortex. Before considering this model, it is useful to review the cardinal steps in granule cell neurogenesis. The precursors of granule cells first appear in an area of the neuroepithelium just dorsal to the zone where Purkinje and other cerebellar neurons are generated (Figure 2). This zone, called the rhombic lip, constitutes the dorsal ridge of the cerebellar territory. Cells in this domain separate from the adjacent neuroepithelium, cross the lip, and migrate up onto the surface of the anlage. The thin layer of proliferating cells, which spreads across the roof of the anlage are called the external germinal layer (EGL).

In vitro experiments (Alder et al 1996) demonstrate that the cells in the rhombic lip are a single class of cerebellar cell, the granule cells. During their migration across the roof of the anlage, precursor cells acquire the ability to make inducing signals that regulate granule cell differentiation, and they become competent to receive these signals. Thus, local signals in the EGL regulate the expansion and differentiation of the precursor cell. After birth, rapid proliferation in the EGL expands the precursor clone dramatically. Thereafter, cells commence a program of radial migration into the anlage. During this journey, they undergo final steps of differentiation.

Migration in the cerebellar cortex occurs within the context of a program of gene expression that includes (a) genes that specify the cerebellar territory, (b) genes that specify DV polarity, and (c) genes that mark specific cell types generated in the dorsal region of the tissue (Hatten & Heintz 1995). Genetic analyses indicate that the engrailed genes (*En1*, *En2*) function in the formation of the cerebellar region, that the bone morphogenic proteins dorsalize cells within this region, and that the dorsal markers *Math1*, *Zic1*, and *Zic2* function in the specification and migration of the granule cell population (J Alder, KF Lee, T Jessell, M Hatten, unpublished data). Cellular antigen marker studies show that radial glial cells can be recognized by the expression of RC-2 (Misson et al 1988) and BLBP (Feng et al 1994), and Purkinje cell precursors by a number of markers, including Calbindin (Chedotal & Sotelo 1992) (see Table 1). This suggests that the cerebellar cortex utilizes positional information along the AP and DV axes for cell specification in early embryonic stages. What distinguishes the cerebellum from the hindbrain and spinal cord is the emergence of a radial pathway for migration of the principal neuron and a novel migratory pathway to provide a secondary germinal matrix of interneurons. After their migration across the roof of the anlage, the latter use the radial glia to migrate into the framework set up by the first generation of neurons, the Purkinje cells.

**Table 1** Cerebellar granule cell genes: expression pattern<sup>a</sup>

Embryonic EGL (E10–E15)	Postnatal EGL (P0–P10)	Parallel fibers	Migrating neurons (P2–P15)	IGL (P0–P10)	IGL (Adult)
Ru49 <sup>b,c</sup>	Ru49	TAG1 <sup>d</sup>	Astn <sup>e</sup>	Ru49	Ru49
Math1 <sup>f</sup>	Math1	Integrin $\beta$ 1	Thrombospondin <sup>g</sup>	Zic1,2 <sup>b,h</sup>	Zic1,2 <sup>b</sup>
Zic1,2 <sup>b</sup>	Zic1,2 <sup>b</sup>	Integrin $\alpha$ v $\beta$ 5 <sup>i</sup>	Neuregulin <sup>j</sup>	En2 <sup>k</sup>	En2
En2	En2	Vitronectin <sup>l</sup>		Astn	
Wnt 3 <sup>m</sup>	Notch2 <sup>l</sup>	Tenascin <sup>n</sup>		GC5 <sup>o</sup>	GABA <sup>o</sup> GC5 <sup>o</sup>

<sup>a</sup>EGL, External germinal layer; IGL, internal germinal layer

<sup>b</sup>Expressed in cerebellum, olfactory bulb, and hippocampal formation

<sup>c</sup>Yang et al 1996

<sup>d</sup>Furley et al 1990

<sup>e</sup>Zheng et al 1996

<sup>f</sup>Ben-Arie et al 1997

<sup>g</sup>O'Shea et al 1990

<sup>h</sup>Nagai et al 1997

<sup>i</sup>Murase & Hayashi 1998

<sup>j</sup>Anton et al 1997

<sup>k</sup>Millen et al 1995

<sup>l</sup>Liu & Hatten, manuscript in preparation

<sup>m</sup>Salinas et al 1994

<sup>n</sup>Humann et al 1992

<sup>o</sup>Kuhar et al 1993

## GRANULE CELL MIGRATION ALONG GLIAL FIBERS

The vast numbers of granule cells facilitates their purification for studies of neuronal migration along glial fibers. Two experimental approaches have been taken to directly observe migration along glial fibers: imaging purified cell populations in an in vitro system (Edmondson & Hatten 1987) and imaging labeled cells in vivo (Gao & Hatten 1994a,b; Anton et al 1996). Video observations were extended by correlating the behavior of migrating neurons with their cytology, as viewed in the electron microscope. In cells that were moving prior to fixation, a specialized migration junction, an interstitial junction, was present beneath the neuronal cell soma at the site of apposition with the glial fiber (Gregory et al 1988). This junction consisted of a widening of the intercellular space and filamentous material in this space that spans the cleft and membranes of each cell, contiguous with cytoskeletal elements. The interstitial junctions are seen only in cells that move along the glial process. In contrast, in resting cells, *puncta adherentia*, or attachment junctions, were found where the neuron apposes the glial fiber, and unlike the migration junction, these small focal densities lack any obvious connections to the cytoskeleton of the apposing cells. Thus, migrating neurons form a migration junction along the neuron-glial apposition. The close apposition of migrating neurons and glia suggests that membrane components of the cell surface mediate migration.

## MOLECULAR MECHANISMS OF GLIAL-GUIDED MIGRATION

A number of neuronal and glial receptor systems have been implicated in the directed migration of CNS neurons along radial glial fibers (Figure 3). Antibody perturbation studies on granule neuron migration in vitro demonstrate that the neural glycoprotein astrotactin provides a neural receptor system for migration along glial (Edmondson et al 1988, Fishell 1991). The molecular cloning of the major component of the astrotactin activity (Kuhar et al 1993) indicates that the predicted protein contains epidermal growth factor repeats and fibronectin type III domains (Zheng et al 1996). By Northern analysis, cDNAs for astrotactin encode a brain-specific transcript that is developmentally regulated and shows high levels of expression in developing brain and low levels in adult brain. Fluorescent in situ hybridization (FISH) analysis has localized *Astn* to chromosome 1 in humans. Sequential G-band to FISH analysis localizes the *Astn* gene to band 1q25.2 (Fink et al 1997a). This localization is of particular interest because recent mapping experiments localized one set of families with micrencephaly to 1q25. Micrencephaly is a diverse class of disorders that result in a smaller brain size, especially forebrain and cerebellar cortex. These

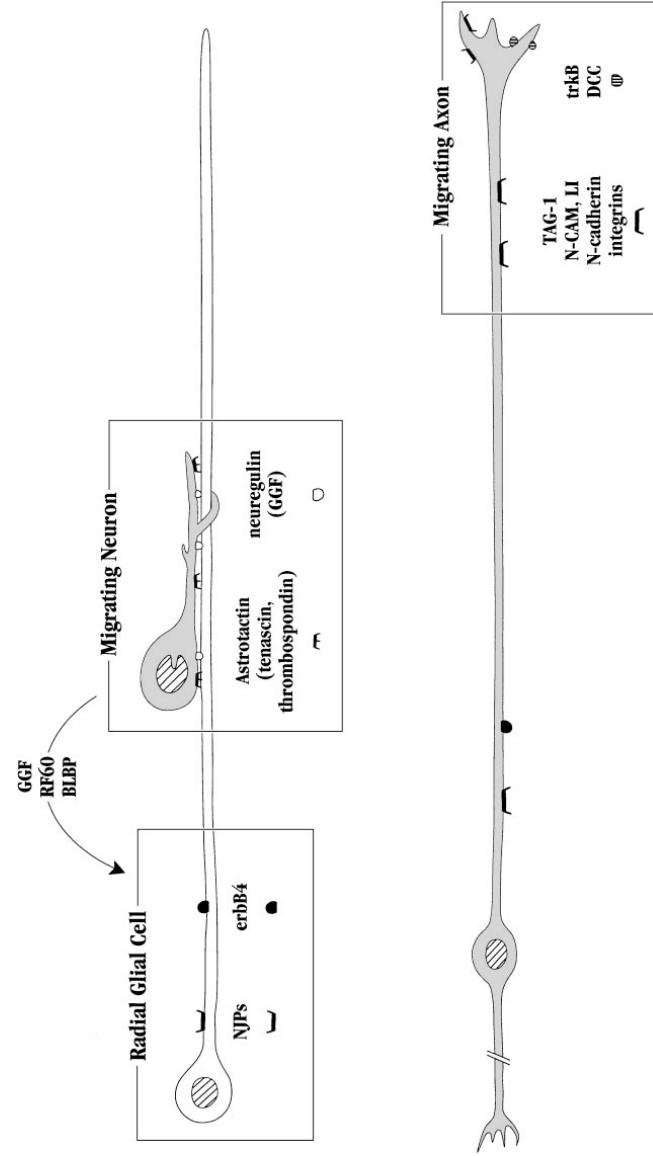


Figure 3 Model for central nervous system neuronal migration along radial glial fibers. As the neuron migrates, it extends a motile, leading process that wraps around the glial guide. Among cell adhesion receptor systems, astrotactin (Astn) provides neuron-glial ligand. Components of the extracellular matrix may also play a role. However these likely function in axon extension. The molecular components of the migratory process and the migrating axon, the parallel fiber, are contrasted.

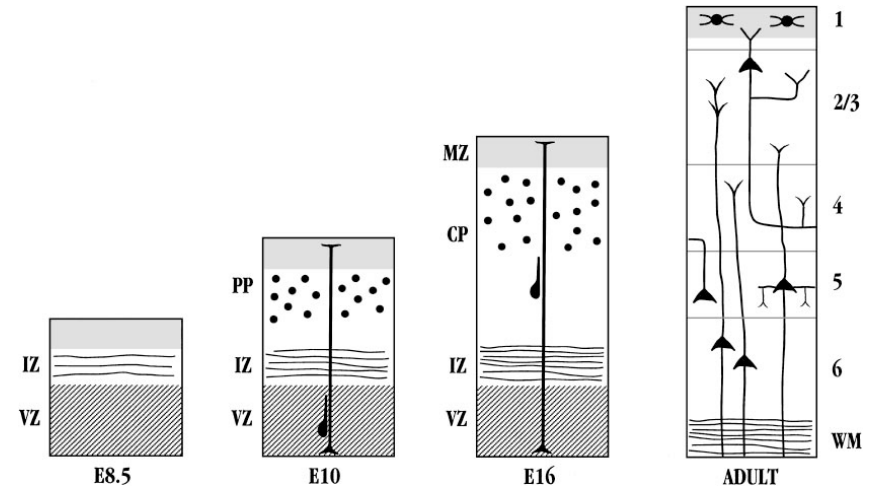
diseases are not to be confused with microcephaly, which can involve hypoplasia of head structures (Volpe 1995). Preliminary analysis of mice with a targeted null mutation of *Astn* indicates that the size of the neuronal layers in cortex and cerebellum are smaller, which suggests that *Astn*<sup>-/-</sup> may mimic micrencephaly (ME Hatten, unpublished observations). In vitro assays demonstrate an arrest of cell migration and abnormal development of the Purkinje cell.

Several components of the ECM have been proposed to influence granule cell migration. Studies on the disposition and role of thrombospondin (O'Shea et al 1990) show that thrombospondin is expressed on the granule cell axons. Antibody perturbation experiments in explant cultures of cerebellar cortex demonstrated reduced granule cell migration. Tenascin appears to have the opposite role, namely of stimulating neurite production and thereby stimulating migration (Husmann et al 1992). It is important to note that granule cell neurite extension and migration are closely linked processes. Both thrombospondin and tenascin influence migration indirectly by altering the rate of parallel fiber production. Thus, although important to migration, neither of these components can be said to function directly in migration. Similar results have been obtained in explant assays with a number of other molecules, including the axonal glycoproteins NCAM and L1. By definition, these components influence parallel fibers, not the cell soma as it translocates down the glial guide (Table 1).

Another class of molecules that functions in cerebellar migration is the growth factor GGF, or neuregulin. Recent studies (see Anton et al 1997, Rio et al 1997) demonstrate a role for neuregulin. This growth factor is expressed in granule cells as they migrate on Bergmann glial fibers. It binds to erbB4 on the glial cell surface (Rio et al 1997). Thus, the GGF-erbB4 signaling system functions in granule cell migration along Bergmann glial fibers in the cerebellar cortex.

## THE FUNDAMENTAL EMBRYONIC LAYERS OF CEREBRAL CORTEX

During embryogenesis, as proliferation in the neuroepithelium thickens the cortical wall, a system of radial glial fibers appears across the radial plane. Postmitotic neurons migrate away from the inner surface of the neural tube along the trajectory set forth by the radial glial fiber system (Rakic 1972). As the first neuronal populations migrate away from the VZ, a zone of axons appears between the germinative zone and the mantle of postmitotic cells (Figure 4). This intermediate zone (IZ) consists of pioneer axons laid down by the emigration of the first wave of neurons to become postmitotic away from the VZ. Recent studies by Easter and colleagues (1993) demonstrate axon extension at about E8.5 as the neuropore is closing, with early axon tracts in place by E10, the time when sequential neurogenesis and migration begins to set forth the



**Figure 4** Development of the cerebral cortex. In early phases of development, neurogenesis is ongoing in the compact germinal zones lining the ventricles [ventricular zone (VZ)] (left). Axons grow over this zone to form the intermediate zone (IZ). The next wave of postmitotic neurons migrates through the IZ to form the preplate (PP). Continued migration splits the PP into the marginal zone (MZ) and cortical plate (CP). Thereafter, successive waves of migration position cells within six layers. Cells within each of these layers have specific patterns of projections both within the cortex and to distant locations in the central nervous system. In adults, the axon tracts are termed the white matter (WM). Cajal-Retzius cells are located in the PP, MZ, and layer 1.

laminar structure of cortical. At E10–12 in mice, the overlying marginal zone consists of Cajal-Retzius cells, perhaps the first generated neuron of cortical regions of brain, neurons that will form the deep layer and subplate neurons (Luskin & Shatz 1985, Shatz et al 1988).

Within the forebrain, two specific patterns of transcription factor expression set forth the territory—*Otx* and *BFI*. By E8, expression of *Otx* and *BFI* is restricted to the emerging forebrain (Rubenstein et al 1998). Between E8–E9.5, the DV axis is established by expression of bone morphogenic proteins along the dorsal ridges and of *Shh* in the precordal mesoderm. Thereafter, territories of transcription factor expression appear (Rubenstein et al 1994, Rubenstein & Shimamura 1997). Remarkably, the same transcriptional regulation is often used across the evolutionary scale, from *Caenorhabditis elegans* to mammals. Neuronal migration occurs after regionalization sets forth a plan for cell fate specification, as a means to generate the cellular architecture specific to a particular brain region.

As one discusses migration, the issue of what makes the neuron stop migration always emerges. Until recently, cell-cell (neuron-glia) adhesion systems were assumed to stop the neuron along the glial pathway. Experiments on cerebellar neurons provide evidence that the stop signal for neuronal migration is not a simple de-adhesion but rather a cue provided by target axons projecting toward the neuron (Baird et al 1992). This model is supported by the fact that, in the developing brain, axons grow toward their targets during the period of cell migration. The second emerging class of stop signal is the ECM component Reelin. As discussed above, a zone of Reelin appears to stop the earliest-generated neurons in cortex, and the earliest-generated neurons in cerebellum.

Molecular genetic experiments show that *scrambler* and *yotari* have the same deficits in corticogenesis as *reeler*, hence the same phenotype (Gonzalez et al 1997, Goldowitz et al 1997, Yonishema et al 1997). Cloning of *scrambler* indicates that the gene encodes a mutated form of a mouse homologue of the *Drosophila disabled* gene, *mdab*. Expression studies indicate that CR-50 antigen/Reelin is expressed in the marginal zone of the emerging cortex, as well as in developing cerebellum. The similarity in the phenotype of *reeler* and *scrambler* has led to the hypothesis that their gene products are part of a signaling pathway that regulates neuronal lamination (Sheldon et al 1997, Ware et al 1997).

As discussed above, early steps in neuronal development, in particular programs of gene expression during neurogenesis, can set forth and/or alter the program of cell migration. An example of a class of gene that disrupts the cell cycle, thereby influencing cell patterning, is *cdk5*. Targeted disruption of this cyclin-dependent kinase gene leads to abnormal cell positioning; humans with the genes have abnormal corticogenesis and perinatal death (Ohshima et al 1996). More complete analysis of mice lacking *p35* by Chae et al (1997) shows aberrant cell migration. The reeler-like preplate does not form. Instead, the cells move tangentially in the intermediate zone and never move onto the glial fiber system. In the absence of glial-guided migration, all the cells move along axon tracts. This behavior is similar to that reported by O'Rourke et al (1997) (see below). However, it also lends further support to the general idea that radial migration is essential for lamination of the cortex.

## TANGENTIAL MIGRATIONS IN CEREBRAL CORTEX

Direct evidence has been provided (see O'Rourke et al 1992, 1997) for tangential movement on axons, across the plane of the glial fiber system. These studies, as well as that of Rakic (1995), show that although the radial plane and radial glial scaffold accommodate the bulk of the cells (80%–85%), a subpopulation of the cells moves tangentially within the intermediate zone (O'Rourke et al 1997). At present, it is not clear whether these cells represent a particular

class of neurons or, alternatively, whether all cells stray across the glial scaffold for a small portion of their migratory pathway.

In addition to dispersion across the neurite tracts of the intermediate zone, immuno-histochemical studies indicate that some of the cells moving along the glial fiber system move tangential to the radial plane of the neuraxis. This class of tangential dispersion arises from two features of the glial scaffold: (a) Radial glial fibers are not strictly radial in all areas of developing cortex, and (b) radial glial fibers branch in the superficial aspect of the developing cortical plate (Misson et al 1988). Retroviral labeling of neurons, in combination with RC2 labeling of glial fibers, has recently indicated the alignment of the vast majority of labeled, migrating neurons with glial fibers, despite variations in the pattern of alignment of the glial fibers (Misson et al 1991). These findings suggest, in agreement with earlier studies of Rakic (1971, 1972, 1978), that the radial glial fiber system provides the primary guidance system for CNS migrations through the thickening cortical plate. However, they extend previous studies by illustrating regional variations in the patterning of glial fascicles, with migratory patterns of neurons in those regions drifting out of the radial plane of the neuraxis convergent and divergent alignment of the radial glial system.

Gray & Sanes (1991) have addressed the more general issue of how migratory path effects the identity of clonally related cells in the development of chicken optic tectum. Their studies show that although descendants of a single progenitor begin their migrations in the same area of the VZ, subgroups of cells diverge, following distinct migratory pathways (radial migration along the glial pathway and tangential migration in the intermediate zone), and differentiate into distinct neuronal phenotypes. Although studies on chicken optic tectum suggest that precursor cells in the VZ are multipotential, with diverse migration routes away from these germinal zones spatially restricting particular neuronal phenotypes, they do not examine the role of the migratory pathway in phenotypic specification. On the one hand, specification could occur early, with migratory routes restricting different neuronal phenotypes. On the other, partially specified cells could randomly follow one or the other migratory pathway, with diverse epigenetic cues present along the two pathways inducing different neuronal phenotypes.

## NEURONAL MIGRATION IN NEUROLOGICAL MUTANT MICE

Studies on neurological mutant mice with brain malformations (Sidman 1968, 1973, 1983; Hatten & Heintz 1995; Heintz et al 1993) provide another approach to the discovery of genetic loci that contribute to neuronal migration in developing brain. Two of these mutants, *weaver* and *reeler*, have long been assumed to be models for cell migration. In *weaver*, granule cell precursors in the

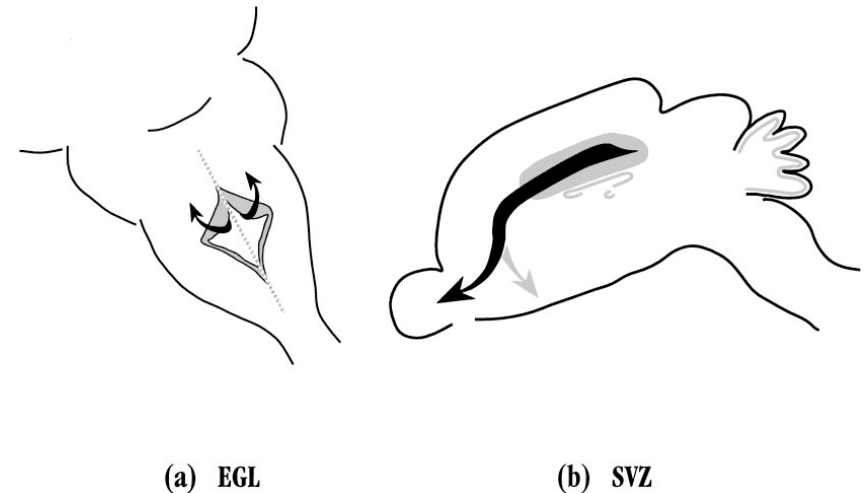


cerebellar cortex fail to migrate along glial fibers and die in ectopic positions. In vitro studies (Gao & Hatten 1994a,b) and the production of mouse chimeras (Goldowitz 1989) demonstrate that the *weaver* gene acts in the immature neuron. Positional cloning of *weaver* confirmed the cellular site of action of the gene, but surprisingly the developmental defect results from a gain of function point mutation in the G protein-gated inwardly rectifying potassium (GIRK2) channel (Kofuji et al 1996, Navarro et al 1996, Slesinger et al 1996). The latter leads to death of the neuron, prior to migration. Although studies on *weaver* point to a role for channels hitherto silent during development, they have not yielded insights into genetic pathways that control neuronal migration. In the *reeler* mouse, Cajal-Retzius cells remain at the top of the undivided preplate, or superplate (Sheppard & Pearlman 1997). Cortical plate neurons accumulate beneath the superplate in a highly disordered, nonlaminar fashion. Taken together, these observations have led to the suggestion that Reelin is an ECM-like protein that may interact with other adhesive proteins and mediate cell adhesion. All mutant alleles of *Reelin* have the same cortical phenotype, and all lack secreted Reelin. The human *Reelin* gene, located on chromosome 7q22, is nearly identical to that of mice. Thus far, no links have been established to human pathology (DeSilva et al 1997).

## SECONDARY GERMINAL MATRICES

As discussed above for the granule cell of the cerebellar cortex, secondary germinal matrices provide large populations of neurons that are generated in zones displaced from the VZ, and that intercalate into the laminar structure that results from the migration of large neurons from the VZ (Figure 5). Typically, these classes of neurons are small interneurons that provide local circuit connections for principal output neurons generated earlier. The cerebellar EGL represents a classic example of a displaced germinal zone that generates neurons well into the postnatal period. Neurons in the EGL derive from the rhombic lip, as discussed, and migrate across the surface of the anlage. There, they undergo clonal expansion into the second postnatal week, coming to number millions in mice and tens of millions in humans. In the postnatal period, cells in this superficial EGL begin to migrate into the cerebellar cortex. By then, the Purkinje cells have already settled into a broad zone, providing the template for lamination. Thus, the granule cells, a huge population of interneurons, migrates inward after the rudiments of the cerebellum are set forth, through the waiting Purkinje cells. Because they undergo proliferation in a displaced zone and migrate into a pre-existing laminar structure, they are a cardinal example of secondary neurogenesis.

Within the developing neocortex, a secondary matrix, termed the subventricular zone (SVZ), develops above the primary VZ. This zone gives rise to a large population of glia, both astrocytes and oligodendrocytes, and to neurons in the



**Figure 5** Secondary neurogenesis, occurring late in development, often in the perinatal period, after cells in the ventricular zone have undergone clonal expansion, migration, and the formation of neural layers. There are three primary sites of secondary neurogenesis. (a) The first, the external germinal layer (EGL) of the cerebellum: As the cerebellar anlage is forming, cells along the dorsal ridge sweep over the surface through structures called the rhombic lips (light gray) and move in a rostromedial direction. Continued proliferation in the displaced zone expands the clone of cells dramatically. (b) In the subventricular zone (SVZ), a similar process is ongoing. Cells within the SVZ continue clonal expansion well beyond the period of corticogenesis. During development, SVZ cells migrate into the olfactory bulb, where they form granule neurons (black arrow). The SVZ continues to supply cells via this pathway throughout life. These systems produce huge numbers of cells, which migrate long distances without glial guidance. After they cease proliferation they integrate into the existing laminar structure, as interneurons.

early postnatal period of murine corticogenesis. By retroviral marking methods, these cell populations migrate in a predominantly radial path (Gray et al 1990). Retroviral marking studies, like [<sup>3</sup>H]thymidine marking experiments, suggest that the time of origin of neuronal populations relate to the mode of migration of the cells. Whereas the first generated neurons appear to use a radial, glial pathway for positioning, later-generated cells often migrate tangentially along the axons in the IZ.

## MIGRATION OF SVZ CELLS INTO THE OLFACTORY BULB

First described by Altman in 1969 (Altman 1969), the subventricular zone (SVZ) maintains a proliferative population of stem cells throughout life (Garcia

et al 1998, Levison & Goldman 1993). Work by Alvarez-Buylla et al (1988) with songbirds showed that neurons originating in the SVZ migrate into the cortex during the season when new neurons are added to the hippocampus and vocal nuclei. In rat brain, it has been shown (see Lois et al 1996, Luskin 1993) that the rat SVZ serves as a fountainhead of cells for the developing olfactory bulb. This population of neurons, like that of the rhombic lip and dentate gyrus, continues clonal expansion well into the postnatal period. Neurons from this zone undergo a long-range, tangential migration into the olfactory bulb. It has been shown that glial cells do not guide this class of neuronal migration. Rather, the neurons migrate in a "daisy chain"-like array, one over the other (see Wichterle et al 1997, Doetsch et al 1997). Molecular genetic studies show that the mechanism of migration involves the sialated form of NCAM (PS-NCAM), as animals lacking PS-NCAM fail to migrate and accumulate along the perimeter of the cortex (Hu & Rutishauser 1996, Hu et al 1996, Ono et al 1994).

Molecular cloning of markers for granule cell development in the cerebellar cortex reveals a particularly interesting feature of SVZ neuronal development. Of nearly 100 cDNAs and genes cloned from cDNA libraries of purified granule neurons, many are expressed in all three regions of the nervous system where secondary neurogenesis is ongoing (N Heintz, M Hatten, unpublished observation). Thus, molecular markers for cerebellar granule neurons are generally expressed in the two other classes of cells, named granule cells by Ramon y Cajal (1995), those of the dentate gyrus and those of the olfactory bulb. This is astonishing given the differences between these neurons (granule cells of the cerebellum are excitatory neurons, whereas those of olfactory bulb are inhibitory, etc). It suggests that these three sets of neuronal precursors share common elements of a program of development, i.e. subroutines of development (Hatten et al 1997, Hatten & Heintz 1995). Thus, precursors of the cortical SVZ, like those of the cerebellar rhombic lip and the hippocampal dentate gyrus, proliferate in displaced germinal zones to generate huge numbers of granule neurons. In the cortical SVZ, this process takes on the additional importance of providing replacement neurons for adult olfactory bulb neurons (Alvarez-Buylla 1997).

### MIGRATION OF CELLS FROM THE LATERAL GANGLIONIC EMINENCE INTO THE NEOCORTEX

Although classical studies of brain histogenesis demonstrated the migration of cells from the lateral ganglionic eminence (LGE) to adjacent, ventral areas and to the thalamus via the internal capsule (Sidman & Rakic 1973), the idea that cells would migrate dorsally, from ventral brain regions up into the cortex, is novel. The first indication of this migratory movement came from evidence that early born neurons in the LGE and striatum migrate into the cortical

marginal zone (Anderson et al 1997). In addition, the LGE supplies a cohort of GABAergic neurons that migrate through the axon tracts into the IZ of the cortex (DeDiego et al 1996). There they move tangentially along the ingrown cortical axons and incorporate into cortex. Analysis of targeted mutations of genes that mark the LGE, including mouse homologues of the *Drosophila* distal-less genes *Dlx1* and *Dlx2* result in the accumulation of postmitotic precursor cells in the LGE. Thus, the axon tracts up into the neocortex provide a migratory pathway for LGE neuronal migration.

### HUMAN MIGRATION DISORDERS AND CORTICAL MALFORMATION

A number of human developmental malformations have been attributed to defects in neuronal migration (Dobyns & Truwit 1995). Neuronal migration disorders (NMDs) primarily affect development of the cerebral cortex, but the extent and nature of the cortical malformation varies greatly (Norman et al 1995). Characterization of the pathologic alterations and underlying defect in these syndromes will provide important insights into the histogenesis of the cortex (Table 2).

Lissencephaly represents a broad class of NMDs that result in a decrease in the number of neurons, seen as a dramatic decrease in the number of gyri in the cortex. It occurs as an isolated abnormality (isolated lissencephaly sequence) or in association with dysmorphic facial appearance in patients with Miller-Dieker lissencephaly (Albrecht et al 1996). These abnormalities have been attributed to defects in neuronal migration (Dobyns et al 1996). A hemizygous chromosomal deletion at 17p13 led to identification of *LIS-1* as the causative gene in this anomaly. In at least 40% of patients with isolated lissencephaly sequence, smaller deletions in this chromosomal region are found. The *LIS-1* gene contains WD-repeats, as seen in beta-subunits of G-proteins, and is a regulatory subunit of brain platelet activating factor acetylhydrolase (PAF-AH) (Hattori et al 1994), a G-protein-like trimer that regulates cellular levels of the lipid messenger PAF (Ho et al 1997). The importance of PAF-AH in the developing brain is supported by the high-level expression of mRNA transcripts for all three subunits during neuronal migratory epochs in cerebrum and cerebellum. The *LIS* gene product is prominent in Cajal-Retzius cells and ventricular neuroepithelium in developing human cortex (Clark et al 1997), and a PAF receptor agonist decreases migration of cerebellar granule cells in vitro. How the absence of the *LIS-1* gene product affects PAF-AH function, PAF signaling in the cell, and ultimately neuronal migration remains to be understood. In addition, *LIS-1* may have as yet unidentified interactions in the cell, as suggested by the ability of the WD40 repeat segments of *LIS-1* to interact with the cytoskeleton.

Another group of disorders within this general class of NMDs is X-linked (Dobyns et al 1996). In *X-LIS*, males have lissencephaly and females have a double cortex (Ross et al 1997, Des Portes et al 1998). The latter involves the disposition of a layer of gray matter beneath the white matter. The defective gene encodes the doublecortin protein. Doublecortin is homologous to the amino terminus of a predicted kinase domain, which suggests a role for signal transduction in this phenotype (Gleeson et al 1998). These disorders are caused by mutation of a single gene, *XLIS*. The second X-linked malformation syndrome is bilateral periventricular nodular heterotopia (BPNH) that consists of BPNH in females and prenatal lethality or a more severe phenotype in males. In this disorder, large masses of well-differentiated cortical neurons fill the adult subependymal zone. The gene for BPNH has been mapped by linkage analysis to Xq28 (Fink et al 1997a,b; Eksioglu et al 1996).

Zellweger syndrome is a second broad class of cortical malformation, causing death within approximately 6 months of life. Zellweger degeneration involves peroxisome biogenesis disorders. Like lissencephaly, Zellweger patients have characteristic gyral abnormalities in the cerebral cortex, with a stereotypic medial pachygyria (reduced number of gyri, which are abnormally large) and lateral polymicrogyria (excess number of small gyri). Zellweger syndrome is a genetically heterogeneous disorder that may arise from defects in at least 10 different genes (Moser et al 1995). Recently, two groups provided the first animal model for a human NMD by targeted deletion in mice of genes encoding the *PEX2* 35-kDa peroxisomal membrane protein (Faust & Hatten 1997) and the *PEX5* peroxisomal protein import receptor (Baes et al 1997). These mice provide models for Zellweger.

### MULTIPLE MODES OF MIGRATION GENERATE OTHER LAMINAR STRUCTURES: RETINA AND SPINAL CORD

Although the general scheme of proliferation portrayed for the cortical VZ is maintained throughout the developing CNS, the retina and spinal cord do not use the full complement of migration-based laminar formation seen for cortex, hippocampus, and cerebellum. In the retina, clonally related cells (Cepko et al 1990, 1997) derived from multipotent precursor cells disperse in radial arrays. The mode of migration of young neurons in the retina is apparently by an accentuation of the interkinetic, to-and-fro movements of the nuclei, with cells in various phases of the cell cycle. Such movements occur in early phases of cortical development, prior to the formation of the four embryonic layers. One class of retinal cell, the amacrine cells, exhibits somewhat longer-range migrations, up to several cell lengths. Such cells apparently move as free cells,

**Table 2** Genetics of cell migration<sup>a</sup>

Mutation	Symbol	Chromosome	Position	Description
Mice				
Reeler <sup>b</sup>	<i>rl</i>	5	8.0 cM	Migration arrest in early development with subsequent failure of cortical plate formation. <i>Reeler</i> encodes a large ECM molecule produced by Cajal Retzius cells in the molecular layer.
Scrambler <sup>c</sup>	<i>scr</i>	4	49.7 cM	Phenotype is identical to that of <i>reeler</i> . <i>Scrambler</i> is a mutation in a <i>disabled</i> gene that encodes a phosphoprotein that binds nonreceptor tyrosine kinases.
Yotari <sup>d,e</sup>	<i>yot</i>	4	49.7 cM	Allele of <i>scrambler</i> .
Disabled <sup>d</sup>	<i>mdabl</i>	4	49.7 cM	Allele of <i>scrambler</i> .
Astrotactin <sup>f</sup>	<i>astn</i>	1	81 cM	Slowed rate of neuronal migration of cerebellar granule cells in vitro. <i>Astn</i> encodes a protein with EGF repeats and FN III domains that functions as a neuronal receptor system for migration on glial fibers.
Weavers <sup>g</sup>	<i>wv</i>	16	67.6 cM	Failure of cerebellar granule cell migration via defective GIRK2 channel function.
Lissencephaly <sup>h</sup>	<i>Lis1</i>	ND	ND	Failure of forebrain neuronal migration via deletion of the beta subunit of platelet activating factor acetylhydrolase ( <i>PAFAH1B1</i> , also known as <i>Lis1</i> ).
Zellweger <sup>i</sup>	<i>PEX1</i> , <i>PEX2</i>	ND	ND	Failure of forebrain neuronal migration via defective peroxisomal biogenesis.
Rats				
Double cortex <sup>j</sup>	<i>fish</i>	ND	ND	Cortical neurons are seen in a bilateral heterotopia that is prominent below the frontal and parietal neocortex; heterotopias rare beneath the temporal cortex.
Humans				
MD syndrome <sup>k</sup>	<i>LIS1</i>	17	17p13.3	A class of spontaneous and inherited disorders (MD) with failure of migration in forebrain, fewer gyri, and smoother gyri in cerebral cortex. In a murine model, the mechanism involves the deletion of the beta-subunit of platelet activating factor acetylhydrolase ( <i>PAFAH1B1</i> ).

Lissencephaly <sup>l</sup>	LIS				Subset of MD with failure of migration in forebrain. Individuals that express the gene have a smooth brain, i.e. fewer gyri in the cerebral cortex.
X-Linked lissencephaly <sup>m</sup>	xLIS	X	Xq22.3-q23		Males show lissencephalic phenotype. Females have a double cortex phenotype with disorganized forebrain gray matter and an extra layer of cells located underneath the white matter. The defective gene encodes the doublecortin protein. Doublecortin is homologous to the amino terminus of a predicted protein kinase, which suggests a role for signal transduction.
Zellweger syndrome <sup>k</sup>	At least ten genes proposed	ND	ND		Failure of cortical migration, neuronal laminae do not form. In two murine models, the molecular mechanism involves defects in the <i>PEX2</i> or <i>PEX5</i> genes, both genes required for neuronal peroxisomal biogenesis.
Bilateral periventricular nodular band heterotopias <sup>n</sup>	BPNH	X	Xq28		Forebrain neurons form heterotopias in the subependymal zone. The cellular mechanism is unknown.
Microcephaly <sup>k</sup>	ND	1	1q25		A class of disorders resulting in reduced brain size due to smaller neuronal lamina. The pattern of lamination is normal; the thickness of the layers is reduced. (Not involving head structures.) One subgroup of families has been mapped.

<sup>l</sup>ECM, extracellular matrix; EGF, epithelial growth factor; NC, not determined; MD, Miller-Dieker

<sup>m</sup>D'Arcangelo et al 1995, 1998; Hirotsune et al 1995

<sup>n</sup>Gonzalez et al 1997, Ware et al 1997

<sup>o</sup>Yoneshima et al 1997

<sup>p</sup>Sheldon et al 1997

<sup>q</sup>Zheng et al 1996, Fink et al 1997a,b

<sup>r</sup>Kofuji et al 1996

<sup>s</sup>Hirotsune et al 1997

<sup>t</sup>Faust & Hatten 1997, Baes et al 1997

<sup>u</sup>Jee et al 1997

<sup>v</sup>McKusick 1994

<sup>w</sup>Pliz et al 1998

<sup>x</sup>Ross et al 1997, Des Portes et al 1998, Gleeson et al 1998

<sup>y</sup>Dobyns et al 1997, Fink et al 1997a,b

without an underlying cellular substrate. A system of radial glial fibers does not develop in the retina.

The spinal cord extends the range of cell movements seen in retina to combine interkinetic displacements, formation of a mantle layer, limited radial migration along glial fibers, and extensive tangential migration along axon tracts. Leber & Sanes (1995) have used retroviral marking methods to reveal extensive intermixing of precursor cells within the germinal zone of the spinal cord. The extent of precursor cell movement apparently becomes progressively restricted during development of the cord. An interesting feature of spinal cord development is the movement of cells along the rostrocaudal axis of the posterior portion of the CNS.

## SUMMARY

Whereas cell migrations in lower species follow the DV/AP directions and then, in *Drosophila* as bilateral symmetry emerges, cross the midline, the mammalian brain adds a radial component. This component underlies the establishment of laminar architecture, first seen in amphibians, birds, and fish, that accompanies the development of cortical architectonics. Molecular genetic studies indicate that the neuron-glial ligand astrotactin functions in neuronal migration. Positional cloning of neurological mutations in mice (*reelin*, *scrambler*, and *mdabl*), of genes that function in the formation of laminae (LIS), of genes involved in foliation, of NCAM, a gene that functions in neuronal migration along axons, and of genes associated with human disorders (NMDS) has led to new insights into the molecular basis of lamination in brain.

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## Literature Cited

- Albrecht U, Abu-Issa R, Ratz B, Hator M, Aoki J, et al. 1996. Platelet-activating factor acetylhydrolase expression and activity suggest a link between neuronal migration and platelet-activating factor. *Dev. Biol.* 180:579-93
- Alder J, Cho NK, Hatten ME. 1996. Embryonic precursor cells from the rhombic lip are specified to a cerebellar granule neuron identity. *Neuron* 17:389-99
- Altman J. 1969. Autoradiographic and histological studies of postnatal neurogenesis. III. Dating the time of production and onset of differentiation of cerebellar microneurons in rats. *J. Comp. Neurol.* 136:269-94
- Altman J, Bayer SA. 1985a. Embryonic development of the rat cerebellum. I. Delineation of the cerebellar primordium and early cell movements. *J. Comp. Neurol.* 231:1-26
- Altman J, Bayer SA. 1985b. Embryonic development of the rat cerebellum. II. Translocation and regional distribution of the deep neurons. *J. Comp. Neurol.* 231:27-41
- Altman J, Bayer SA. 1985c. Embryonic development of the rat cerebellum. III. Regional differences in the time of origin, migration, and settling of Purkinje cells. *J. Comp. Neurol.* 231:42-65
- Alvarez-Buylla A. 1997. Mechanism of migration of olfactory bulb interneurons. *Cell Dev. Biol.* 7:207-13

- Alvarez-Buylla A, Theelen M, Nottebohm F. 1988. Mapping of radial glia and of a new cell type in adult canary brain. *J. Neurosci.* 8:2707-12
- Anderson S, Eisenstat D, Shi L, Rubenstein J. 1997. Interneuron migration from basal forebrain to neocortex: dependence on DLX genes. *Science* 278:474-76
- Anton ES, Cameron R, Rakic P. 1996. Role of neuron-glia junctional domain proteins in the maintenance and termination of neuronal migration across the embryonic cerebral wall. *J. Neurosci.* 16:2283-93
- Anton ES, Marchionni MA, Lee K-F, Rakic P. 1997. Role of GGF/neuregulin signaling in interactions between migrating neurons and radial glia in the developing cerebral cortex. *Development* 124:3501-10
- Baes M, Gressens P, Baumgart E, Carmeliet P, Casteels M, et al. 1997. A mouse model for Zellweger syndrome. *Nat. Genet.* 17:49-57
- Baird D, Hatten M, Mason C. 1992. Cerebellar target neurons provide a stop signal for afferent neurite extension in vitro. *J. Neurosci.* 12:619-34
- Ben-Arie N, Bellen K, Armstrong D, McCall A, Gordadze P, et al. 1997. Math1 is essential for genesis of cerebellar granule neurons. *Nature* 390:169-72
- Caviness VS, Sidman R. 1973. Time of origin and corresponding cell classes in the cerebral cortex of normal and reeler mutant mice: an autoradiographic analysis. *J. Comp. Neurol.* 148:141-52
- Caviness VSJ. 1982. Neocortical histogenesis in normal and reeler mice: a developmental study based upon [<sup>3</sup>H]thymidine autoradiography. *Dev. Brain Res.* 4:293-302
- Caviness VSJ, Rakic P. 1978. Mechanisms of cortical development: a view from mutations in mice. *Annu. Rev. Neurosci.* 1:297-326
- Cepko C, Golden J, Szele F, Lin J. 1997. Lineage analysis in the vertebrate central nervous system. See Cowan et al 1997, pp. 391-439
- Cepko CL, Austin CP, Walsh C, Ryder EF, Halliday A, Fields-Berry S. 1990. Studies of cortical development using retrovirus vectors. *Cold Spring Harbor Symp. Quant. Biol.* 55:265-78
- Chae T, Kwon YT, Bronson R, Dikkes P, Li E, Tsai LH. 1997. Mice lacking p35, a neuronal specific activator of cdk5, display cortical lamination defects, seizures and adult lethality. *Neuron* 18:29-42
- Chedotal A, Sotelo C. 1992. Early development of olivocerebellar projections in the fetal rat using CGRP immunocytochemistry. *Eur. J. Neurosci.* 4:1159-79
- Clark GD, Mizguchi M, Antalfy B, Barnes J, Armstrong D. 1997. Predominant localization of the lis family of gene products to Cajal-Retzius cells and ventricular neuroepithelium in the developing human cortex. *J. Neuropathol. Exp. Neurol.* 56:1044-52
- Cowan WM, Jessell TJ, Zipursky SL, eds. 1997. *Molecular and Cellular Approaches to Neural Development*. New York: Oxford Univ. Press
- Culican SM, Baumrind NK, Yamamoto M, Pearlman AK. 1990. Cortical radial glia: identification in tissue culture and evidence for their transformation to astrocytes. *J. Neurosci.* 10:684-92
- D'Arcangelo G, Curran T. 1998. Reeler: new tales on an old mutant mouse. *BioEssays* 20:235-44
- D'Arcangelo G, Miao G, Chen S, Soarles H, Morgan J, Curran T. 1995. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. *Nature* 374:719-23
- D'Arcangelo G, Nakjima K, Miyata T, Ogawa M, Mikoshiba K, Curran T. 1997. Reelin is a secreted glycoprotein recognized by the CR-50 monoclonal antibody. *J. Neurosci.* 17:23-31
- DeDiego I, Smith-Fernandez A, Fairen A. 1996. Cortical cells that migrate beyond area boundaries: characterization of an early neuronal population in the lower intermediate zone of prenatal rat. *Eur. J. Neurosci.* 6:983-97
- DeSilva U, D'Arcangelo G, Braden V, Miao G, Curran T, Green E. 1997. The human reelin gene— isolation, sequencing, and mapping on chromosome. *Genome Res.* 7:157-64
- Des Portes V, Pinard J, Millart P, Vinet M, Koulakoff A, et al. 1998. A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. *Cell* 92:51-61
- Dobyns WB, Andermann E, Andermann F, Czapanaky-Beilman D, Dubeau F, et al. 1996. X-linked malformations of neuronal migration. *Neurology* 47:331-39
- Dobyns WB, Guerrini R, Czapanaky-Beilman DK, Pierpont ME, Breningstall G, et al. 1997. Bilateral periventricular nodular heterotopia with mental retardation and syndactyly in boys: a new X-linked mental retardation syndrome. *Neurology* 49:1042-47
- Dobyns WB, Truwit CL. 1995. Lissencephaly and other malformations of cortical development: update. *Neuropediatrics* 26:132-47
- Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A. 1997. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. *J. Neurosci.* 17:5046-61
- Doniach T. 1995. Basic FGF as an inducer of anteroposterior neural pattern. *Cell* 83:1067-70
- Easter SS Jr, Ross LS, Frankfurter A. 1993. Initial tract formation in the mouse brain. *J. Neurosci.* 13:285-99
- Edmondson J, Liem R, Kuster J, Hatten M. 1988. Astrotactin: a novel neuronal cell surface antigen that mediates neuron-astroglial interactions in cerebellar microcultures. *J. Cell Biol.* 106:505-17
- Edmondson JC, Hatten ME. 1987. Glial-guided granule neuron migration in vitro: a high-resolution time-lapse video microscopic study. *J. Neurosci.* 7:1928-34
- Eksioglu YZ, Scheffer IE, Cardenas P, Knoll J, Dimario F, et al. 1996. Periventricular heterotopia—an X-linked dominant epilepsy locus causing aberrant cerebral cortical development. *Neuron* 16:77-87
- Faust PL, Hatten ME. 1997. Targeted deletion of the PEX2 peroxisome assembly gene in mice provides a model for Zellweger syndrome, a human neuronal migration disorder. *J. Cell Biol.* 139:1293-305
- Feng L, Hatten ME, Heintz N. 1994. Brain lipid-binding protein BLBP: a novel signaling system in the developing mammalian CNS. *Neuron* 12:895-908
- Feng L, Heintz N. 1995. Differentiating neurons activate transcription of the brain lipid-binding protein gene in radial glia through a novel regulatory element. *Development* 121:1719-30
- Fink J, Hirsch B, Zheng C, Dietz G, Hatten M, Ross M. 1997a. Astrotactin (ASTN), a gene for glial-guided neuronal migration, maps to human chromosome 1q25.2. *Genomics* 40:202-5
- Fink JM, Dobyns WB, Guerrini R, Hirsch BA. 1997b. Identification of a duplication of Xq28 associated with bilateral periventricular nodular heterotopia. *Am. J. Hum. Genet.* 61:379-87
- Fishell G, Hatten ME. 1991. Astrotactin provides a neuronal receptor system for CNS migration. *Development* 113:755-65
- Fishell G, Mason CA, Hatten ME. 1993. Dispersion of neural progenitors within the germinal zones of the forebrain. *Nature* 362:636-38
- Fraser S, Keynes R, Lumsden A. 1990. Segmentatain in the chick embryo hindbrain is defined by cell lineage restriction. *Nature* 344:431-35
- Furley AJ, Morton SB, Manalo D, Karagozios D, Dodd J, Jessell TM. 1990. The axonal glycoprotein TAG-1 is an immunoglobulin superfamily member with neurite outgrowth-promoting activity. *Cell* 61:157-70
- Gao WQ, Hatten ME. 1994a. Neuronal differentiation rescued by implantation of weaver granule cell precursors into wild-type cerebellar cortex. *Science* 260:367-70
- Gao WQ, Hatten ME. 1994b. Immortalizing oncogenes subvert the establishment of granule cell identity in developing cerebellum. *Development* 120:1059-70
- Garcia-Verdugo J, Doetsch F, Wichterle H, Lim D, Alvarez-Buylla A. 1998. Architecture and cell types of the adult subventricular zone: in search of the stem cells. *J. Neurobiol.* 36:234-48
- Gleeson J, Allen K, Fox J, Lamperti E, Berkovic S, 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
- Goldowitz D. 1989. The weaver granular phenotype is due to intrinsic action of the mutant locus in granule cells: evidence from homozygous weaver chimeras. *Neuron* 2:1565-75
- Goldowitz D, Cushing R, Laywell E, D'Arcangelo G, Sheldon M, et al. 1997. Cerebellar disorganization characteristic of reeler in scrambler mice despite persistence of Reelin. *J. Neurosci.* 17:8767-77
- Gona AG. 1976. Autoradiographic studies of cerebellar histogenesis in the bullfrog tadpole during metamorphosis: the external granular layer. *J. Comp. Neurol.* 165:77-87
- Gonzalez JL, Ruso CJ, Goldowitz D, Sweezy HO, Davison MT, Walsh CA. 1997. Birthdate and cell marker analysis of scrambler: a novel mutation affecting cortical development with a reeler-like phenotype. *J. Neurosci.* 17:9204-11
- Gray GE, Leber SM, Sanes JR. 1990. Migratory patterns of clonally related cells in the developing central nervous system. *Experientia* 46:929-40
- Gray GE, Sanes JR. 1991. Migratory paths and phenotypic choices of clonally related cells in the avian optic tectum. *Neuron* 6:211-25
- Gregory W, Edmondson J, Hatten M, Mason C. 1988. Cytology and neuron-glia apposition of migrating cerebellar granule cells in vitro. *J. Neurosci.* 8:1728-38
- Guthrie S. 1996. Patterning in the hindbrain. *Curr. Opin. Neurobiol.* 6:41-48
- Harland RM. 1997. Neural induction in Xenopus. See Cowan et al 1997, pp. 1-25
- Hatten M, Liem R. 1981. Astroglial cells provide a template for the positioning of developing cerebellar neurons in vitro. *J. Cell Biol.* 90:622-30
- Hatten ME. 1993. The role of migration in central nervous system neuronal development. *Curr. Opin. Neurobiol.* 3:38-44
- Hatten ME, Alder J, Zimmerman K, Heintz N. 1997. Genes involved in cerebellar cell specification and differentiation. *Curr. Opin. Neurobiol.* 7:40-47
- Hatten ME, Heintz N. 1995. Mechanisms of neural patterning and specification in the

- developing cerebellum. *Annu. Rev. Neurosci.* 18:385-408
- Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K. 1994. Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor acetylhydrolase. *Nature* 370:216-18
- Heintz N, Norman DJ, Gao W-Q, Hatten ME. 1993. Neurogenetic approaches to mammalian brain development. In *Genome Maps and Neurological Disorders*, ed. Davies, Tilghman, pp. 19-44. Cold Spring Harbor, NY: Cold Spring Harbor Press
- Hemmati-Brivanlou A, Kelly OG, Melton DA. 1994. Follistatin, an antagonist of activin, is expressed in the Spemann organizer and displays direct neuralizing activity. *Cell* 77:283-95
- Hirotsune S, Pack SD, Chong SS, Robbins CM, Pavan WJ, et al. 1997. Genomic organization of the murine Miller-Dieker/lissencephaly region: conservation of linkage with the human region. *Genome Res.* 7:625-34
- Hirotsune S, Takahara T, Sasaki N, Hirose K, Yoshiki A, et al. 1995. The reeler gene encodes a protein with an EGF-like motif expressed by pioneer neurons. *Nat. Genet.* 10:77-83
- Ho YS, Swenson L, Derewenda U, Serre L, Wei YY, et al. 1997. Brain acetylhydrolase that inactivates platelet-activating factor is a g-protein-like trimer. *Nature* 385:89-93
- Hu H, Rutishauser U. 1996. A septum-derived chemorepulsive factor for migrating olfactory interneuron precursors. *Neuron* 16:933-40
- Hu H, Tomasiewicz H, Magnuson T, Rutishauser U. 1996. The role of polysialic acid in migration of olfactory bulb interneuron precursors in the subventricular zone. *Neuron* 16:735-43
- Hunter KE, Hatten ME. 1995. Radial glial cell transformation to astrocytes is bidirectional: regulation by a diffusible factor in embryonic forebrain. *Proc. Natl. Acad. Sci. USA* 92:2061-65
- Hunter-Schaedle K. 1997. Radial glial cell development and transformation are disturbed in reeler forebrain. *J. Neurobiol.* 33:459-72
- Husmann K, Faissner A, Schachner M. 1992. Tenascin promotes cerebellar granule cell migration and neurite outgrowth by different domains in the fibronectin type III repeats. *J. Cell Biol.* 116:1475-86
- Jessell TM, Lee KJ. 1999. The specification of dorsal cell fates in the vertebrate central nervous system. *Annu. Rev. Neurosci.* 22:261-94
- Jessell T, Lumsden A. 1997. Inductive signals and the assignment of cell fate in the spinal cord and hindbrain. See Cowan et al 1997, pp. 290-333
- Joyner AL. 1996. Engrailed, Wnt and Pax genes regulate midbrain-hindbrain development. *Trends Genet.* 12:15-20
- Kofuji P, Hofer M, Millen KJ, Millonig JH, Davidson N, et al. 1996. Functional analysis of the weaver mutant GIRK2 K+ channel and rescue of weaver granule cells. *Neuron* 16:941-52
- Kolliker A. 1890. Zur Feineren Anatomie des centralen Nervensystems Zweiter Beitrag das Rückenmark. *Ziss. Zool.* 51
- Kuhar SG, Feng L, Vidan S, Ross ME, Hatten ME, Heintz N. 1993. Changing patterns of gene expression define four stages of cerebellar granule neuron differentiation. *Development* 117:97-104
- Leber S, Sanes JR. 1995. Migratory paths of neurons and glia in the embryonic chick spinal cord. *J. Neurosci.* 15:4556-71
- Lee KS, Schottler F, Collins JL, Lanzino G, Couture D, et al. 1997. A genetic animal model of human neocortical heterotopia associated with seizures. *J. Neurosci.* 17:6236-42
- Levison S, Goldman J. 1993. Both oligodendrocytes and astrocytes develop from progenitors in the subventricular zone of postnatal rat forebrain. *Neuron* 10:201-12
- Lois C, Garcia-Verdugo J-M, Alvarez-Buylla A. 1996. Chain migration of neuronal precursors. *Science* 271:978-81
- Lumsden A. 1990. The cellular basis of segmentation in the developing hindbrain. *Trends Neurosci.* 13:329-35
- Lumsden A, Keynes R. 1989. Segmental pattern of neuronal development in the chick hindbrain. *Nature* 337:424-28
- Lumsden A, Keynes R. 1996. Patterning the vertebrate neuraxis. *Science* 274:1109-15
- Luskin M, Shatz C. 1985. Studies of the earliest generated cells of the cat's visual cortex: co-generation of the cells of the marginal zone and subplate. *J. Neurosci.* 5:1062-75
- Luskin MB. 1993. Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. *Neuron* 11:173-89
- Mason C, Edmondson J, Hatten M. 1988. The extending astroglial process: development of glial cell shape, the growing tip, and interactions with neurons. *J. Neurosci.* 8:3124-34
- Mason CA, Christakos S, Catalano SM. 1990. Early climbing fiber interactions with Purkinje cells in postnatal mouse cerebellum. *J. Comp. Neurol.* 297:77-90
- McKusick VA. 1994. *Mendelian Inheritance in Man. Catalogs of Human Genes and Genetic Disorders*. Baltimore, MD: Johns Hopkins Univ. Press. 11th ed.
- Millen KJ, Hui CC, Joyner AL. 1995. A role for En-2 and other murine homologues of

- Drosophila* segment polarity genes in regulating positional information in the developing cerebellum. *Development* 121:3925-45
- Misson JP, Austin CP, Takahashi T, Cepko CL, Caviness VS Jr. 1991. The alignment of migrating neural cells in relation to the murine neopallial radial glial fiber system. *Cereb. Cortex* 1:221-29
- Misson J-P, Edwards MA, Yamamoto M, Caviness VS Jr. 1988. Identification of radial glial cells within the developing murine central nervous system: studies based upon a new immunohistochemical marker. *Dev. Brain Res.* 44:95-108
- Miyata T, Nakajima K, Aruga J, Takahashi S, Ikenaka K, et al. 1996. Distribution of a reeler gene-related antigen in the developing cerebellum: an immunocytochemical study with an allogenic antibody CD-50 on normal and reeler mice. *J. Comp. Neurol.* 372:214-28
- Miyata T, Nakajima K, Mikoshiba K, Ogawa M. 1997. Regulation of Purkinje cell alignment by reelin as revealed with CR-50 antibody. *J. Neurosci.* 17:3599-609
- Moser AB, Rasmussen M, Naidu S, Watkins PA, McGuinness M, et al. 1995. Phenotype of patients with peroxisomal disorders subdivided into sixteen complementation groups. *J. Pediatr.* 127:13-22
- Murase SI, Hayashi Y. 1998. Concomitant expression of genes encoding integrin alpha v beta 5 heterodimer and vitronectin in growing parallel fibers of postnatal rat cerebellum: a possible role as mediators of parallel fiber elongation. *J. Comp. Neurol.* 397:199-212
- Nagai T, Aruga J, Takada S, Gunther T, Sporle R, et al. 1997. The expression of the mouse Zic1, Zic2, and Zic3 gene suggests an essential role for Zic genes in body pattern formation. *Dev. Biol.* 182:299-313
- Navarro B, Kennedy ME, Velmirovic B, Bhat D, Peterson AS, Clapham DE. 1996. Nonselective and G betagamma-insensitive weaver K+ channels. *Science* 272:1950-53
- Norman M, McGillivray B, Kalousek D, Hill A, Poskitt K. 1995. Neuronal migration disorders and cortical dysplasias: Part I: migration disorders. In *Congenital Malformations of the Brain: Pathologic, Embryologic, Clinical, Radiologic and Genetic Aspects*, ed. M Norman, pp. 223-77. New York: Oxford Univ. Press
- Ohshima T, Ward JM, Huh CG, Longenecker G, Veeranna-Pant HC, 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* 93:11173-78
- Ono K, Tomasiewicz H, Magnuson T, Rutishauser U. 1994. NCAM mutation inhibits tangential neuronal migration and is phenocopyed by enzymatic removal of polysialic acid. *Neuron* 13:595-609
- O'Rourke NA, Chen A, McConnell SK. 1997. Postmitotic neurons migrate tangentially in the cortical ventricular zone. *Development* 124:997-1005
- O'Rourke NA, Dailey ME, Smith SJ, McConnell SK. 1992. Diverse migratory pathways in the developing cerebral cortex. *Science* 258:299-302
- O'Shea KS, Rheinheimer JST, Dixit VM. 1990. Deposition and role of thrombospondin in the histogenesis of the cerebellar cortex. *J. Cell Biol.* 110:1275-83
- Pilz DT, Matsumoto N, Minnerath S, Mills P, Gleeson JG, et al. 1998. *LIS1* and *XLIS (doublecortin)* mutations cause most human classical lissencephaly, but different patterns of malformation. *N. Engl. J. Med.* In press
- Pinto-Lord M, Evrard P, Caviness VJ. 1982. Obstructed neuronal migration along radial glial fibers in the neocortex of the reeler mouse: a Golgi-EM analysis. *Brain Res.* 256:379-93
- Rakic P. 1971. 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. 1972. Mode of cell migration to the superficial layers of fetal monkey cortex. *J. Comp. Neurol.* 145:61-84
- Rakic P. 1978. Neuronal migration and contact guidance in the primate telencephalon. *Postgrad. Med. J.* 54(Suppl. 1):25-40
- Rakic P. 1995. Radial versus tangential migration of neuronal clones in the developing cerebral cortex. *Proc. Natl. Acad. Sci. USA* 92:11323-27
- Ramon y Cajal S. 1911. *Histology of the Nervous System of Man and Vertebrates*, Vol. I. Transl. L Swanson, N Swanson, 1995. Oxford, UK: Oxford Univ. Press
- Reid C, Tavazoie S, Walsh C. 1997. Clonal dispersion and evidence for asymmetric cell division in ferret cortex. *Development* 124:2441-50
- Retzius G. 1892. Die Neuroglia des Gehirns beim Menschen und bei Säugethieren. *Biol. Unters.* 3:1-24
- Rio C, Rieff H, Pelmin Q, Corfas G. 1997. Neuregulin and erbB receptors play a critical role in neuronal migration. *Neuron* 19:39-50
- Roelink H, Augsberger A, Heemskerk J, Korsch V, Norlin S, et al. 1994. Floor plate and motor neuron induction by vhh-1, a vertebrate homologue of hedgehog expressed by the notochord. *Cell* 76:761-75
- Ross ME, Srivastava AK, Featherstone T, Gleeson JG, Hirsch B, et al. 1997. Linkage and physical mapping of X-linked

- lissencephaly/SBH (XLIS): a gene causing neuronal migration defects in human brain. *Hum. Mol. Genet.* 6:555-62
- Rubenstein JLR, Martinez S, Shimamura K, Puelles L. 1994. The embryonic vertebrate forebrain: the prosomeric model. *Science* 266:578-80
- Rubenstein JLR, Shimamura K. 1997. Regulation of patterning and differentiation in the embryonic vertebrate forebrain. See Cowan et al 1997, pp. 356-90
- Rubenstein JLR, Shimamura K, Martinez S, Puelles L. 1998. Regionalization of the prosencephalic neural plate. *Annu. Rev. Neurosci.* 21:445-75
- Salinas PC, Fletcher C, Copeland NG, Jenkins NA, Nusse R. 1994. Maintenance of Wnt-3 expression in Purkinje cells of the mouse cerebellum depends on interactions with granule cells. *Development* 120:1277-86
- Schmechel D, Rakic P. 1979a. Arrested proliferation of radial glial cells during midgestation in rhesus monkey. *Nature* 227:303-5
- Schmechel D, Rakic P. 1979b. A Golgi study of radial glial cells in developing monkey telencephalon: morphogenesis and transformation into astrocytes. *Anat. Embryol.* 156:115-52
- Shatz C, Chun J, Luskin M. 1988. The role of the subplate in the development of the mammalian telencephalon. In *Cerebral Cortex*, ed. A Peters, E Jones, 7:35-58. New York: Plenum
- Sheldon M, Rice D, D'Arcangelo G, Yonishima H, Nakajima K, et al. 1997. Scrambler and yotari disrupt the disabled gene and produce a reeler-like phenotype in mice. *Nature* 389:730-33
- Sheppard A, Pearlman A. 1997. Abnormal reorganization of preplate neurons and their associated extracellular matrix: an early manifestation of altered neocortical development in the reeler mutant mouse. *J. Comp. Neurol.* 378:173-79
- Sidman RL. 1983. Experimental neurogenetics. In *Genetics of Neurological and Psychiatric Disorders*, ed. S Kety, LP Rowland, RL Sidman, SW Matthyse, pp. 19-46. New York: Raven
- Sidman RL. 1968. Development of interneuronal connections in brains of mutant mice. In *Physiological and Biochemical Aspects of Nervous Integration*, ed. F Carlson, pp. 163-93
- Sidman RL, Rakic P. 1973. Neuronal migration with special reference to developing human brain: a review. *Brain Res.* 62:1-35
- Slesinger PA, Patil N, Liao YJ, Jan Y-N, Jan LY, Cox DR. 1996. Functional effects of the mouse weaver mutation on G protein-gated inwardly rectifying K+ channels. *Neuron* 16:321-31
- Soriano E, Alvarado-Mallart RM, Dumesnil N, Delrio JA, Sotelo C. 1997. Cajal-Retzius cells regulate the radial glia phenotype in the adult and developing cerebellum and alter granule cell migration. *Neuron* 18:563-77
- Volpe JJ. 1995. *Neurology of the Newborn*. Philadelphia: Saunders. 3rd ed.
- Walsh C, Cepko C. 1994. Clonal dispersion in proliferative layers of developing cerebral cortex. *Nature* 362:632-35
- Ware ML, Fox JW, Gonzalez JL, Davis NM, Derouvroit CL, et al. 1997. Aberrant splicing of a mouse disabled homolog mdab1 in the scrambler mouse. *Neuron* 19:239-49
- Wichterle H, Garcia-Verdugo J, Alvarez-Buylla A. 1997. Direct evidence for homotypic, glia-independent neuronal migration. *Neuron* 18:779-91
- Xu L, Sanchez MR, Sali A, Heintz N. 1996. Ligand specificity of brain lipid-binding protein. *J. Biol. Chem.* 271:24711-19
- Yang XW, Model P, Heintz N. 1998. Homologous recombination based modification in *Escherichia coli* and germline transmission in transgenic mice of a bacterial artificial chromosome. *Nat. Biotechnol.* 15:859-65
- Yang XW, Zhong R, Heintz N. 1996. Granule cell specification in the developing mouse brain as defined by expression of the zinc finger transcription factor RU49. *Development* 122:555-66
- Yonishema H, Nagata E, Matsumoto M, Yamada M, Nakajima K, et al. 1997. A novel neurological mutation mouse, yotari, which exhibits reeler-like phenotype but expresses CR-50 antigen/reelin. *Neurosci. Res.* 29:217-23
- Zheng C, Heintz N, Hatten ME. 1996. CNS gene encoding Astrotactin, which supports neuronal migration along glial fibers. *Science* 272:417-19
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