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Elusive Radial Glial Cells: Historical and Evolutionary Perspective

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KEY WORDS neurogenesis; gliogenesis; corticogenesis; neuronal migration; brain evolution

ABSTRACT Since the discovery of radial glial cells in the human fetal forebrain, this specialized cellular population has been identified in most regions of the vertebrate brain during restricted developmental periods. However, their size, longevity, and significance for guiding migrating neurons have increased with the evolutionary expansion of the mammalian neocortex, reaching a peak in the gyrencephalic human forebrain. The phenotypic distinction of radial glial cells from the more specialized neuronal progenitors in the proliferative zones and from the migrating neurons in the intermediate zone of the primate fetal forebrain, based initially on morphological criteria, has been supported by their ultrastructural, molecular, and physiological characteristics. In addition, modern in vivo and in vitro approaches revealed that these specialized embryonic cells can also generate neuronal cell lines, which either immediately, or after several divisions, migrate along radial shaft processes of the mother cells that span the expanding and convoluted cerebral wall. The multiple functions of radial glial cells and their species-specific adaptations indicate a pivotal role in evolution, development, and pathology of the cerebral neocortex. *GLIA 43:19–32, 2003.* © 2003 Wiley-Liss, Inc.

HISTORY AND DEFINITION

Radial glial cells have a long and eventful history. Their oval soma with elongated fibers that span the full width of the developing cerebral wall, and which impregnate well with most variants of the Golgi method, has been described in the human fetal brain at the end of the 19th century (Magini, 1888; Retzius, 1893; von Lenhossék, 1895; Ramón y Cajal, 1899). However, phenotypic distinction between immature neuronal and glial cells with the classical Golgi method alone was rather difficult, as apparent by Ramón y Cajal's uncharacteristic uncertainty concerning the nature of these cells (Ramón y Cajal, 1881, 1883, 1890, 1899, 1909). Thus, in his initial study of the developing frog and chick embryo, he thought that the neuroepithelial cells spanning the width of the neural tube may actually be neuroblasts, which contribute neurons to both the ventral and dorsal horns of the spinal cord (Fig. 1A and B). However, after examining the developing telencephalon in several mammalian species (Fig. 1C and D), he observed the distinct characteristics of these elongated cells, including the presence of a series of transitional cell forms as attributed to astrocytes [also described about the same time by von Lenhossék (1895)], and then he changed his mind. He recognized the cells with voluminous radial fibers studded with lamellate expansions and terminating with endfeet at both sides of the cerebral wall as a separate cell class, different from the pyriform neuroblasts that arise from the primitive spheroidal cells that give rise to bipolar neurons migrating to the cerebral cortex. Thus, although all ventricular cells in all CNS regions originate from the primitive neuroepithelium, they eventually diverge into specialized neuronal and glial precursors, as has been at the time advocated by His (1889) based on the Nissl-stained sections of the embryonic human telencephalon. Using the Golgi silver impregnation method, Ramón y Cajal basically agreed, but in addition suggested that radial cells eventually transform

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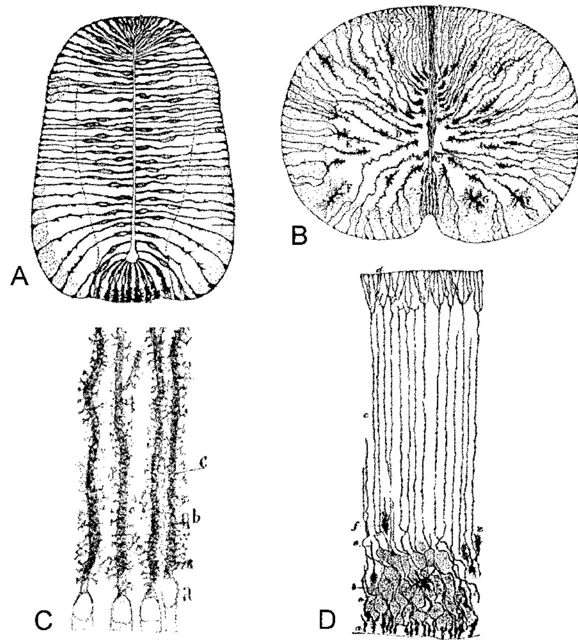

Fig. 1. **A:** Primordial epithelium, including spongioblast (radial glial) cells of the spinal cord of the chick embryo-3rd day of incubation when, according to Ramón y Cajal, they become stainable by the Golgi method. **B:** Epithelial (radial glial) and displaced astroglial precursors and more mature astrocytes in the spinal cord of the newborn mouse stained by the Golgi method display different phases of morphogenetic transformation of a more differentiated glial cell line. **C:** Characteristic lamellate expansion on the radial shafts of epithelial (radial glial). **D:** Epithelial (radial glial) and neuroglial cells of the cerebral cortex in neonatal rabbit stained with the Golgi method. Adapted from Ramón y Cajal (1909).

into spiderlike cells, which differentiate into fibrillary or protoplasmic types of astrocytes of the white and gray matter of the cerebrum, respectively.

Other investigators of that era, who also used the Golgi method on embryonic forebrain tissue, recognized the distinct morphology of these elongated cells and referred to them by a variety of terms such as "epithelial cells" (Golgi, 1885; Ramón y Cajal, 1909), "radial cells" (Magini, 1888), "fetal ependymal cells" (Retzius, 1893, 1894), and "spongioblasts" (von Lenhossék, 1895; Kölliker, 1896). They also noticed that each cell has only one basal endfoot ("pied ventriculere" of Ramón y Cajal) at the ventricular surface, whereas at the pial side their radial fiber often, particularly at later stages, may form several branches that terminate with multiple endfeet at the pial surface. Additional terms, such as "tanycytes," "faserglia," "Müller cells," and "Bergmann glia" that were introduced to denote the modified radial glial cell, which persist in some regions of the adult brain, have added to the confusion in the terminology. However, although the methods available at the time were not adequate to provide definitive phenotypic classification, based on the morphological criteria, most investigators have classified them as embryonic or fetal glia (Schmechel and Rakic, 1979a; Varone and Somjen, 1979; Fedoroff and Vernadakis, 1986; Rakic, 1988; Nieuwenhuys et al., 1998; Bentivoglio and Mazzarello, 1999; deAzevedo et al., 2003; Kriegstein and Parnavelas, 2003).

The major advance in defining the nature and function of radial glail cells came with the introduction of new methods in developmental biology such as electron microscopy, ^{3}H-thymidine (^{3}H-TdR) autoradiography, and immuncytochemistry, which provided higher resolution of cellular events and allowed more reliable identification of cell classes. Furthermore, the use of cell cultures, transgenic technology, and retroviral gene transfer methods allowed a more accurate analysis of cell lineage relationships as well as their function in the developing mammalian brain. Thus, the use of electron microscopy and immunohistochemistry applied to primate embryos has confirmed the glial phenotype of radial cells (Rakic, 1971b, 1972; Choi and Lapham, 1978; Levitt and Rakic, 1980; Levitt et al., 1981; Gadisseux and Evrard, 1985; Rakic, 1988; Hatten and Mason, 1990; deAzevedo, 2003). For example, in the human and macaque fetal cerebrum, electron microscopic and immunohistochemical identification of glial acidic fibrillarly protein (GFAP) confirmed the existence of radial GFAP-positive cells with a distinct entity from GFAP-negative cells during the course of corticogenesis (Fig. 2) (Choi and Lapham, 1978; Levitt and Rakic, 1980; Levitt et al., 1981, 1983; Choi, 1986; deAzevedo et al., 2003).

The presence of GFAP in the cell cytoplasm in the central nervous system of all vertebrate species studied, exclusive of cyclostomes, has provided a useful and reliable marker for identification of the astrocytic cell phenotype, including radial glial cells (Onteniente et al., 1983; Dahl et al., 1985; Bignami, 1991; Zupanc, 1999). The intermediate filament vimentin is also a helpful label for the identification of radial glia (RG) cells as a separate cell line, particularly in primates, since the adjacent radial glial cell can be characterized by immunoreactivity to RC1, RC2, vimentin, Rat 401, and Ran-2. However, unlike in primates, radial glial cells in rodents are not GFAP-positive until the completion of corticoneurogenesis (Dahl et al., 1981; Cameron and Rakic, 1991), and their antigenic properties are changed during the emergence of a secondary phenotype indicated by a substitution in the intermediate filament protein composition from vimentin to GFAP (Bovolenta et al., 1984; Pixley and De Vellis, 1984; Rickmann et al., 1987; Hutchins and Casagrande, 1989; Voigt, 1989). However, in addition to the presence of GFAP in the cytoplasm, radial cells at the late stages of corticoneurogenesis in primates display a number of morphological and ultrastructural characteristics that make them distinct from the adjacent migrating neurons. These include lamellate expansions and cone-shaped endfeet that are interconnected by specialized intermembrane junctions, forming a continuous pial surface (glia limitans) coated with a basement membrane composed of extracellular matrix molecules (Rakic, 1985). In contrast, bipolar migrating neurons have a more voluminous leading process filled with a darker cytoplasm that usually terminates with

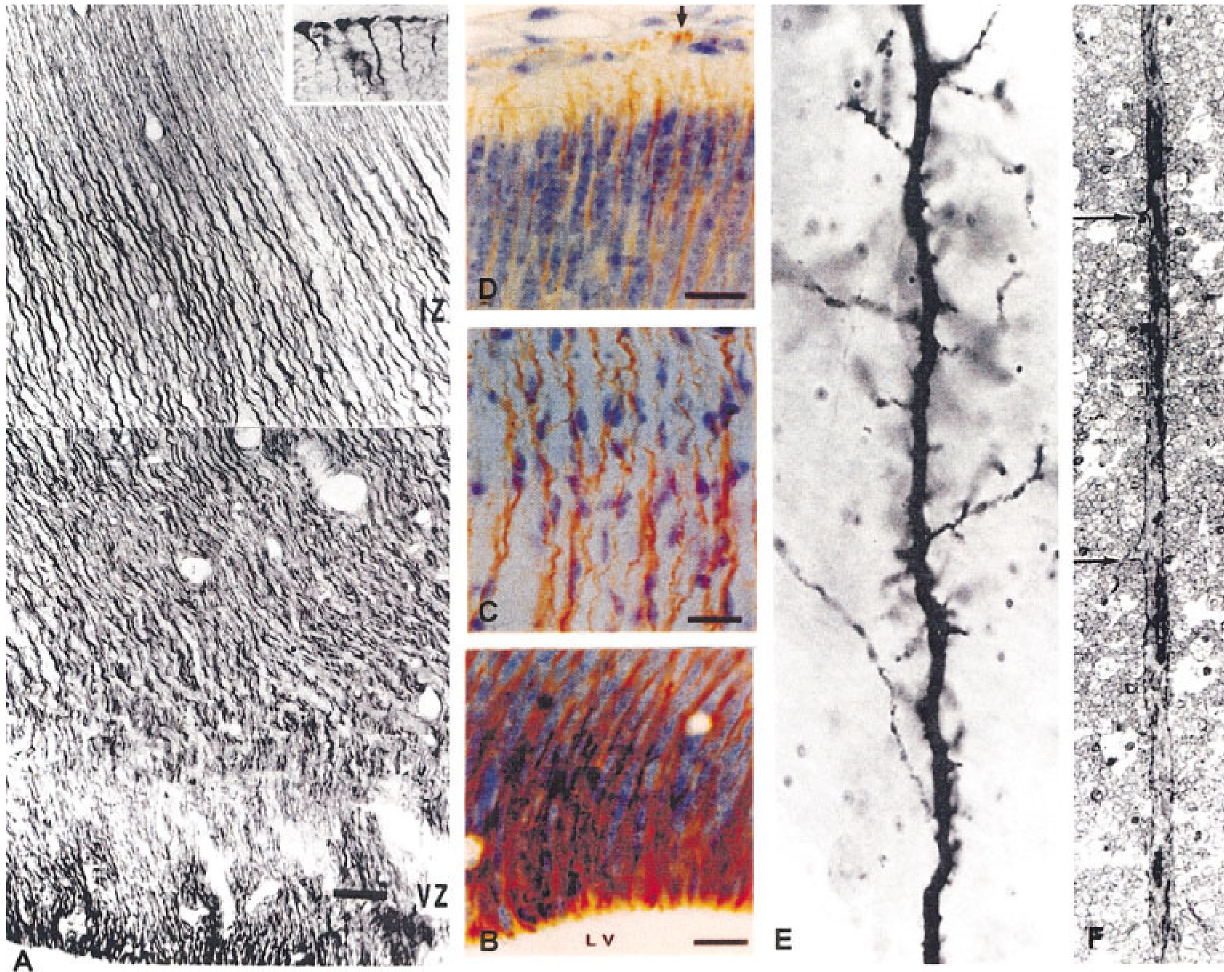

Fig. 2. **A–E:** Radial glial cells in the E70 monkey fetal cerebrum immunostained with the antibodies to GFAP. A: Photomicrograph of a portion of the fetal cerebral wall exposes the richness of the RG fiber scaffolding at the midpoint of cortical neurogenesis. The radial fibers continue to run from the ventricular zone near the lateral cerebral ventricle (LV) across the intermediate zone (IZ) all the way to the cortical plate (not shown), where many of them terminate with the typical endfeet at the pial surface (inset). B–D: Verichrome photographs of the GFAP-stained RG fibers taken from the three levels of the cerebral wall, starting from the surface of the lateral ventricle (LV) in B, across the intermediate zone (C) to the pial surface (D). The GFAP-negative migrating neurons (blue) are distinguishable from the GFAP-positive RG cells (brown). RG fibers impregnated with Golgi method (**F**) and viewed with electron microscope. Adapted from Levitt and Rakic (1980) and Rakic (1984).

an arboroid tip while the trailing process is much thinner and resembles an axon (Rakic et al., 1974).

It may not be a coincident that radial glial cells were first described in the human fetal forebrain, as it is there that they reach the peak in size and phenotypic differentiation. It should be emphasized that the term "radial glia" and the concept of glial scaffolding have derived from analysis of relatively advanced developmental stages of the gyrencephalic primate forebrain when their phenotype is well differentiated (Rakic, 1972). Unlike rodents, in primates, particularly at later stages, separate glial and neuronal cell lines are easily identifiable by both transmission electron microscopy (EM) and immunocytochemical methods (Levitt et al., 1981, 1983; Kadhim et al., 1988; Cameron and Rakic, 1991; deAzevedo et al., 2003). However, during the onset of corticogenesis in both monkey and human, when the migratory pathway is as short as it is in rodents, the distinction between radial glail cells and postmitotic neurons is more difficult, and the classical Golgi method could not provide distinction between cell types (Morest, 1970a, 1970b; Sidman and Rakic, 1973). These technical limitations have been acknowledged in our early reports: "At early stages the radial guides cannot be classified clearly as glia or neurons. . . . Thus, at all stages of development, neural migration and growth is predominantly along the radial path, with guidance provided at first by undifferentiated columnar epithelial ventricular cells. Later, this role is served by immature glia and/or the processes of previously generated neurons, and even later by more clearly differentiated glial cells. The elongated radial glial cells themselves ultimately disappear, many transforming into astrocytes" (Sidman and Rakic, 1973). Therefore, even in the human forebrain, at early stages a simple translocation of nucleus can account for

the cell's displacement, as has been described in many other brain structures (Morest, 1970a; Snow and Robson, 1995; Das et al., 2003). The difference between neuronal and glial cell types in the embryonic primate telencephalon becomes more evident at the later stages when the cerebral wall enlarges. For example, during migration of neurons to the superficial strata of the cortical plate (prospective layers 2 and 3) in the macaque monkey, it is easy to detect GFAP in the cytoplasm of the RG fiber, while the cytoplasm of the leading and trailing processes of the adjacent migrating cell is devoid of this protein (Levitt and Rakic, 1980; Levitt et al., 1983). Similar diversity has been observed in the human fetal cerebrum at midgestation (Fig. 7) (deAzevedo et al., 2003). It may be biologically significant that, as the size of the cerebral wall expands during evolution, radial glial scaffolding also becomes more differentiated, more permanent, and functionally more significant (Schmechel and Rakic, 1979a, 1979b; Levitt and Rakic, 1980; Levitt et al., 1981, 1983; Rakic, 2003).

The hundred million years of continuous mammalian evolution has resulted in numerous modifications of developmental programs that produce not only quantitative (e.g., the number of neurons and columns or timing and sequence of cellular events) but also qualitative changes (e.g., the elaboration of new neuronal types, addition of specialized cytoarchitectonic areas, and formation of new connections) (Preuss, 2000). These differences are not only of theoretical but also of biomedical significance, since many of the new traits may be particularly vulnerable to genetic and environmental factors (Steward at al., 1999; Gurwitz and Weizman, 2001; Rakic, 2002). In the case of RG cells, it should be recognized that while their basic properties may be conserved across vertebrate orders, there are also important structural, molecular, and functional differences between different regions within the same species (Rakic, 1984; Cooper and Steindler, 1986; Steindler et al., 1989; Silver et al., 1993; Malatesta et al., 2003) as well as between the same regions of different species (Rakic, 1984, 1985). Even among the mammalian species, comparative analysis of the mouse, monkey, and human cerebrum shows that the radial glial cells have undergone substantial evolutionary transformation (Rakic, 2003), and new discoveries about their diverse functions in the developing as well as in mature brain are added at a rapid pace (Barres, 1991, 1999; Malatesta et al., 2003; Tramontin et al., 2003). Thus, although the term "radial glial cell" does not encompass all of its structural and functional features, it has served a useful purpose for relating their basic phenotype during individual development to the continuity of cell morphogenetic transformation during regional and species-specific evolutionary adaptations. Historically, the descriptive term "radial glia" was adopted in order to avoid narrow functional connotations, which inevitably change with new discoveries, while recognizing their ubiquitous radial orientation as well as the morphological, ultrastructural, and molecular characteristics that make them distinct from other, more specialized neuronal and glial cell progenitors (Rakic, 1971a, 1972). This designation is now generally accepted (Varone and Somjen, 1979; Bentivoglio and Mazzarello, 1999; Hatten, 1999, 2002; Kriegstein and Parnavelas, 2003).

ROLE IN CELL PRODUCTION

Classical histological methods have clearly indicated that RG cells have the capacity to divide, and it has been suspected that they may serve as precursors that directly or indirectly give origin to all major classes of neurons and astrocytes (Ramón y Cajal, 1909; Sidman and Rakic, 1973; Cameron and Rakic, 1991). However, because Golgi methods preferentially impregnate RG cells compared to less mature migrating neurons, it was difficult to determine the exact timing and uncover the molecular mechanisms that lead to divergence of these cells into different types during development. This technical problem may also be the reason why the tangential migration of bipolar neuroblasts was less emphasized until the new experimental methods enabled detection and better visualization of bipolar migrating neurons in the developing cerebral wall (Marin and Rubenstein, 2001). Thus, until recently, there has been the persisting question as to whether, in addition to RG cells, the cerebrum simultaneously contains more restricted neuronal and glial cell progenitors as well as bipolar migrating neurons. However, modern methods enable identification of several classes of progenitors that can produce distinct neuronal subclasses with considerable species-specific differences in their relative proportions (Letinic et al., 2002; Malatesta et al., 2003). As in other tissues, these differences are probably controlled by genes that act on the progenitor cells at or prior to their exit from their cell's mitotic cycle generating a different outcome, depending on the given evolutionary context (Bang and Goulding, 1996; Shirasaki and Pfaff, 2002).

A schematic drawing of the major models that were over the past few decades proposed for cortical neurogenesis is provided in Figure 3. It should be recognized that most of the models, as well as the broad conceptual generalizations in the literature on this subject, are based on the research performed using different methods on different species, on different regions of the brain, and at different stages of development, which has lead to conclusions that are not generally applicable. For example, during the early stages of corticogenesis, when the migratory pathway in most species, including the human, is relatively short, nuclear displacement through the short radial process of postmitotic cells may be sufficient for the cell to reach the preplate layer situated at the interface with the marginal zone (Sidman and Rakic, 1973). However, the enormous enlargement and dramatic morphogenetic change from the smooth (lysencephalic) to a convoluted (gyrencephalic) primate cerebrum are associated with accelerated differentiation of RG cells (Sidman and

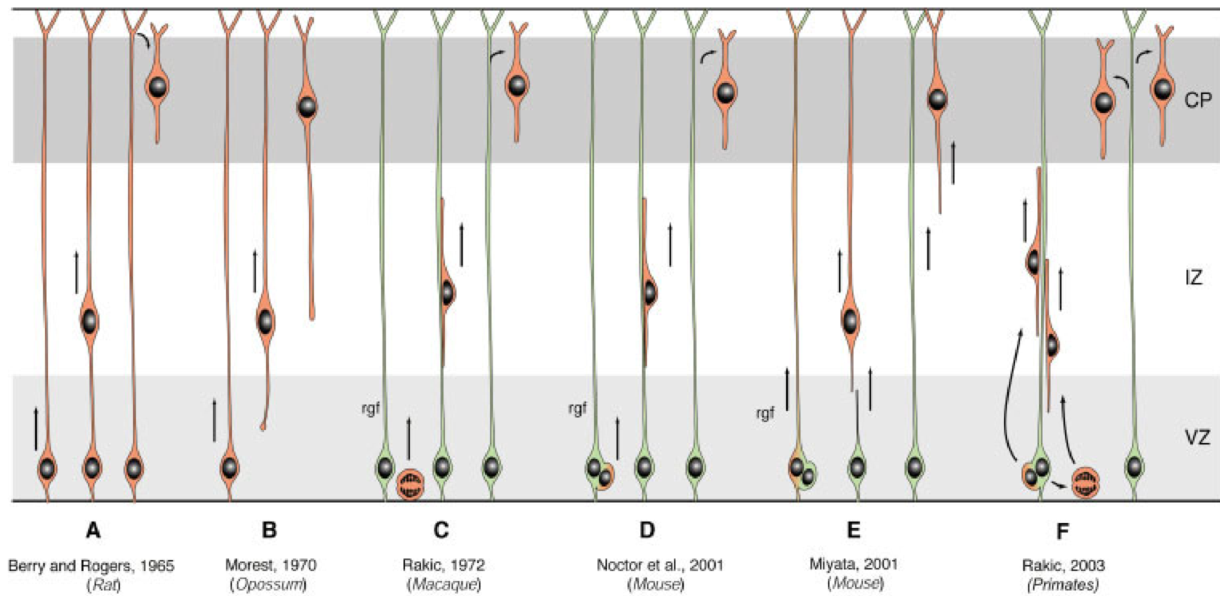

Fig. 3. Schematic diagram of the evolving concepts of the relationship between radial glial fiber (rgf) of the radial glial cells and migrating neurons in the developing mammalian cerebral wall based on studies with increasingly more sophisticated methods applied on the embryonic forebrain of species ranging from the mouse and opossum pouch young to human and nonprimates. Adapted from Rakic (2003).

Rakic, 1973; Schmechel and Rakic, 1979a; Levitt and Rakic, 1980; Levitt et al., 1981, 1983; Kadhim et al., 1988; deAzevedo et al., 2003). The separate neuronal and RG cell lines at these stages are easily identifiable by either EM and immunocytochemical methods in both human or monkey forebrain (e.g., Fig. 2) (Rakic, 1972; Rakic et al., 1974; Levitt and Rakic, 1980; Levitt et al., 1981, 1983; Cameron and Rakic, 1991; deAzevedo et al., 2003). The length of the RG fiber in the macaque monkey cerebrum toward the end of corticoneurogenesis may reach 3,000–7,000 μm while the leading process of bipolar migratory neurons of 50–200 μm (Rakic, 1972) is similar to those observed in smaller forebrains (Misson et al., 1988a, 1988b) or other structures such as the optic tectum or retina (Domesick and Morest, 1977; Snow and Robson, 1995; Das et al., 2003). At this stage in the primate forebrain, many RG cells stop transiently to divide while their shaft serves as scaffolding for a cohort of migrating neurons (Schmechel and Rakic, 1979a, 1979b).

The stability of RG scaffolding may be an essential evolutionary adaptation, which enables proper allocation of neurons to the expanded and convoluted cerebral cortex (Rakic, 1995a). At late stage of cortical development in the human fetus, a large number of interneurons, originating from the proliferative ventricular (VZ) and subventricular (SVZ) zones of the dorsal telencephalon, migrate radially to the superficial layers of the cerebral cortex (Letinic et al., 2002). It remains to be determined if a similar population of interneurons and glial cells exist in rodents, or if they are more difficult to be identified due to the lack of cell class-specific markers in these species (Tan, 2002). For example, the use of genetic labeling and in vivo imaging revealed the presence of ganglionic eminence-derived bipolar, tangentially migrating neurons in the intermediate and marginal zone of the rodent cerebrum (Lavdas et al., 1999; Marin and Rubenstein, 2001) that were apparently missed in the Golgi-stained preparations that impregnate only 1–3% of cells.

Although it has been recognized that the primary or conversional RG phenotype can revert to the neuroepithelial form and generate neurons (Cameron and Rakic, 1991), recent studies in vitro and in vivo provided more direct evidence that RG give origin to cortical neurons (Malatesta et al., 2000, 2003; Hartfuss et al., 2001; Noctor et al., 2001, 2002; Tamamaki et al., 2001; Alvarez-Buylla and Garcia-Verdugo, 2002; Gaiano and Fishell, 2002; Tramontin et al., 2003). Using a retrovirus carrying the GFP reporter gene as a marker, we have confirmed that RG can both generate and guide the migration of cortical neurons (data not shown). In addition, we have generated transgenic mice (RG-Cre) harboring a Cre gene driven by a human GFAP promoter that is normally expressed in mouse radial glial cells. When crossed with ROSA26R transgenic mice, embryos carrying both transgenes showed lacZ expression in both radial glial cells, pyramidal neurons, and astrocytes indicating that both cortical neurons and astrocytes can be derived from radial glial cells (data not shown). The newly generated cells assume a bipolar shape and migrate along the radial fiber of the mother cell, which remains attached to the ventricular surface (Noctor et al., 2001). Thus, in a sense, the daughter cells are guided by the radial fibers of their mother's cells to the appropriate location in the developing cortical plate (Fig. 3D and F). In the human fetal cerebrum during the midgestation, a single RG fiber

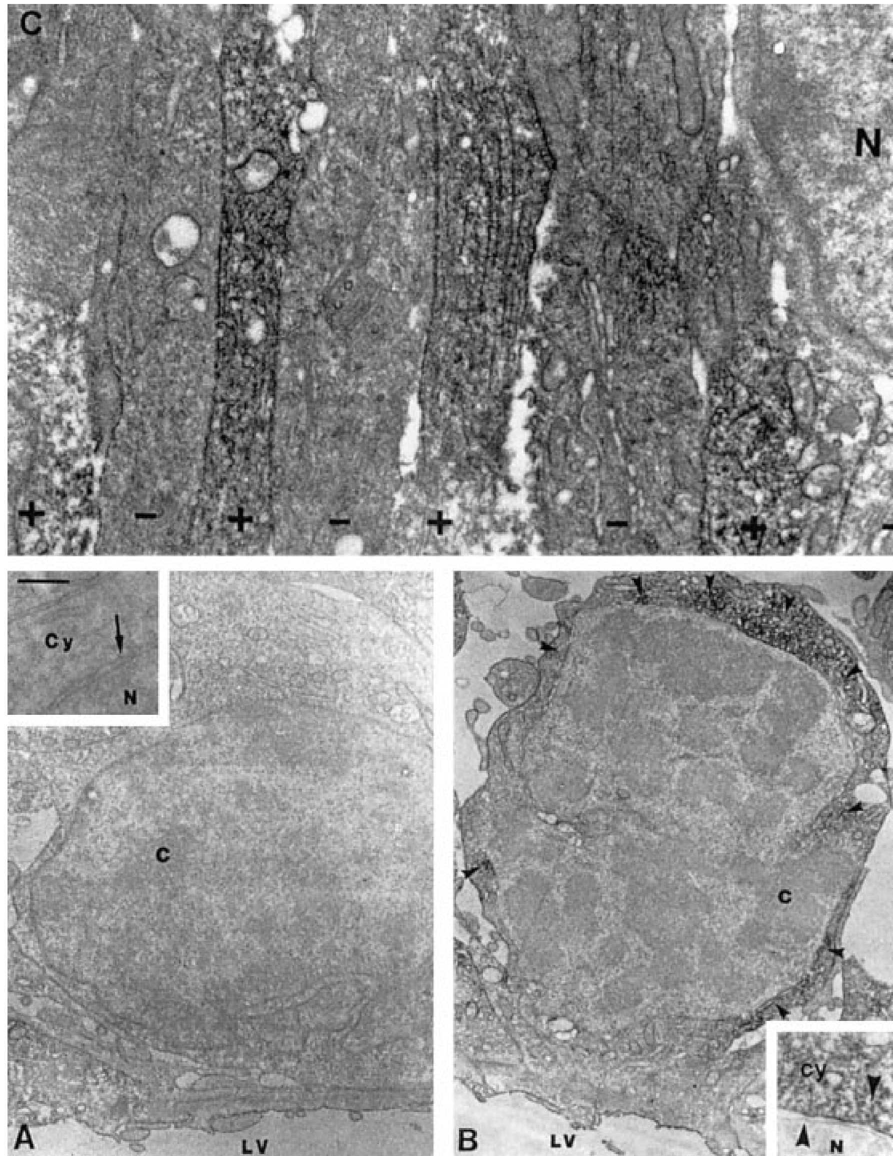

Fig. 4. GFAP–negative (**A**) and GFAP-positive (**B**) mitotic figures in the prophase phase of cell division, situated within the ventricular zone directly at the surface of the lateral cerebral ventricle (LV) of the E80 monkey fetus. The absence of any immunoreactivity on the cytoplasm (cy) is confirmed at higher power (inset in A) and the dense reaction HR product characteristic of anti-GFAP PAP staining is enlarged in the inset in B. **C:** Electron micrographs of the portion of the ventricular zone in an E61 monkey fetus processed with the PAP immunohistochemical method using antibody to GFAP reveal the presence of GFAP-positive (+) and GFAP–negative (−) processes and a soma of a GFAP-negative postmitotic neuron (N). Adapted from Levitt et al. (1981, 1983).

may guide simultaneously several generations of migrating neurons (Fig. 7).

The model presented in Figure 3F integrates the available evidence of cell genealogy in the mammalian cerebral wall including the findings in primates (Rakic, 2003). Studies in both human (Carpenter et al., 2001; Letinic et al., 2002; deAzevedo et al., 2003) and nonhuman primates (Levitt and Rakic, 1980; Levitt et al., 1981, 1983) show the existence of at least two stem cell lines in the VZ and a highly expanded SVZ: one glial and the other neuronal (e.g., Figs. 2 and 4). Unlike in rodents, cells isolated from the human VZ/SVZ, even at early stages of corticogenesis, generate separate neuron-restricted precursors and glia-restricted precursors (Carpenter et al., 2001). The presence of $GFAP^{+}$ and $GFAP^{-}$ in the cytoplasm of mitotic figures at the ventricular surface suggested that both cell types divide (Fig. 4) (Levitt et al., 1981, 1983). Furthermore, retroviral gene transfer labeling of cell lineages in human embryonic slices shows that multiple divisions of neuronal stem cell progenitors occur in the VZ/SVZ before they begin radial migration to the neocortex (Letinic et al., 2002). Similarly, a diversity of progenitors may also exist in rodents, but could be overlooked because of the smaller number or lack of cell class-specific markers for their identification at early stages (McCarthy et al.,

2001; Tan, 2002). There are several lines of evidence that neuron-restricted progenitors are even further specified. For example, more specialized stem cells of both glial and neuronal lineages that produce different classes of projection and local circuit neurons can be identified by retroviral labeling (Parnavelas et al., 1991; Tan et al., 1998). Likewise, heterochronous transplantation of VZ cells indicate that progenitors produce layer-specific pyramidal neurons depending on the time when they are dissociated from the embryo (McConnell, 1988). The molecular heterogeneity of remnant stem cells in the human fetal cerebrum has also been demonstrated by molecular phenotyping of clonal neurospheres (Suslov et al., 2002).

Several other models have suggested alternative cellular dynamics in the embryonic cerebral wall. For example, according to one recent model, the RG cell divides and the daughter cell that retains the radial shaft actually becomes a migrating neuron, while the other daughter cell remains in the VZ as a progenitor, which then extends a new radial fiber to the cortex in order to recapitulate the same event during each cycle (Fig. 3E) (Miyata et al., 2001). This model is a modification of earlier models (Fig. 3B and C) (Berry and Rogers, 1965; Morest, 1970a, 1970b). Note that these three models are in mutual disagreement in regard to which of the daughter cells becomes a neuron and which remains as a stem cell, as well as where in the developing cerebral wall the daughter cell separates from the mother cell (compare, for example, Fig 3A and E). More importantly, they would not apply to primates where the EM and immunohistochemical evidence indicates a coexistence of separate RG fibers and bipolar migrating neurons that are not attached to either cerebral surface (Levitt and Rakic, 1980; Levitt et al., 1981, 1983; deAzevedo et al., 2003). Some of these models neglect existence of separate neuronal and glial lines that are discernable also in the rodent forebrain with the modern methods of cell class identification (Marin and Rubenstein, 2001; McCarthy et al., 2001; Haydar et al., 2003; Malatesta et al., 2003). Furthermore, these models require that, after each division, the stem cell extends a new radial process to the increasingly distant cortical plate and forms a new endfoot at the pial surface. The amount of protein synthesis essential for achieving this task is unlikely to be accomplished during the 30 min of the G_1 phase of the cell cycle, even for the short radial shaft of the rodent telencephalon. However, it is an even more unlikely scenario for generating several thousand micron long shafts in the large primate forebrain after each cell division. In addition, since in primates the RG fibers are GFAP-positive and the leading process GFAP-negative, a large amount of GFAP would need to be synthesized in a short time only to be lost when the nucleus starts to move. It should be kept in mind that the models illustrated in Figure 3 were based on studies of different animal species and by different methods. Therefore, it remains an open question whether they reflect genuine interspecific differences or technical limitations in distinguishing between cell phenotypes in rodents. However, the real interspecies distinction appears to be that RG cells in the primate telencephalon precociously express GFAP (Choi, 1986; Levitt and Rakic, 1980; Kadhim et al., 1988; deAzevedo et al., 2003), as well as that some RG cells become frozen in the G_1 phase and stop proliferating while their shafts serve as transient scaffolding (Schmechel and Rakic, 1979b).

As originally suggested by Ramón y Cajal, the fetal type of RG cells in most regions of the mammalian brain disappears soon after birth. Analyses of Golgi-stained and GFAP-immunolabeled sections of the monkey and human cerebra indicate that RG cells in the telencephalon become transformed into fibrillary astrocytes and/or protoplasmic astrocytes (Choi and Lapham, 1978; Rakic, 1978, 1995b; Schmechel and Rakic, 1979a; Levitt and Rakic, 1980; Choi, 1986; Rickmann et al., 1987). The timetable of the disappearance of RG cells in the primate neocortex, hippocampus, and cerebellum correlates with the emergence of protoplasmic and fibrillary astrocytes (Fig. 5) (Rakic, 1971a; Schmechel and Rakic, 1979a; Eckenhoff and Rakic, 1984). The cellular or the molecular events that underlie this transformation are not known. In primary cultures, neuronal cells have been shown to exert an inhibitory effect on glial cell proliferation and, additionally, appear to regulate changes in the astroglial cell shape from epithelial-like to radial or stellate (Sobue and Pleasure, 1984; Hatten, 1985; Ard and Bunge, 1988; Culican et al., 1990). The morphological transformation of GFAP-positive RG cells into classical astrocytic cell forms, as well as alternative RG forms, appears to coincide with the loss of RC1, RC2, and Rat-401 antigens, which are not expressed in adulthood (Hockfield and McKay, 1985; Misson et al., 1988a, 1988b; Evrard et al., 1990). A correlative analysis of antigenic and morphologic transformation in vivo (Misson et al., 1991) and in vitro (Culican et al., 1990) demonstrates that the morphological transformation of radial glial cells occurs concomitantly with a gradual acquisition of GFAP immunoreactivity and with a corresponding loss of RC1 immunoreactivity.

Modified RG cells may be found in some regions of the adult CNS where a selective microenvironment may allow for their maintenance (Reichenbach, 1989; Rakic, 1995b). In some structures of the mammalian brain, RG cells adapt to the local functional requirements and spatial conditions and transform into specialized astrocytic cell types (e.g., the Bergmann glial cells of the cerebellum, tanycytes of the hypothalamus, or Müller cells of the retina). These specialized cells retain the basic morphological, immunological, and biochemical features of RG cells that include expression of GFAP (Craft et al., 1979; Bartlett et al., 1981; Fedoroff and Vernadakis, 1986; Evrard et al., 1990; Robinson and Dreher, 1990; Rakic, 1995b). Thus, they may be considered as genealogical, morphological, and biochemical descendents of the transient fetal RG cells. However, in some nonmammalian vertebrate species,

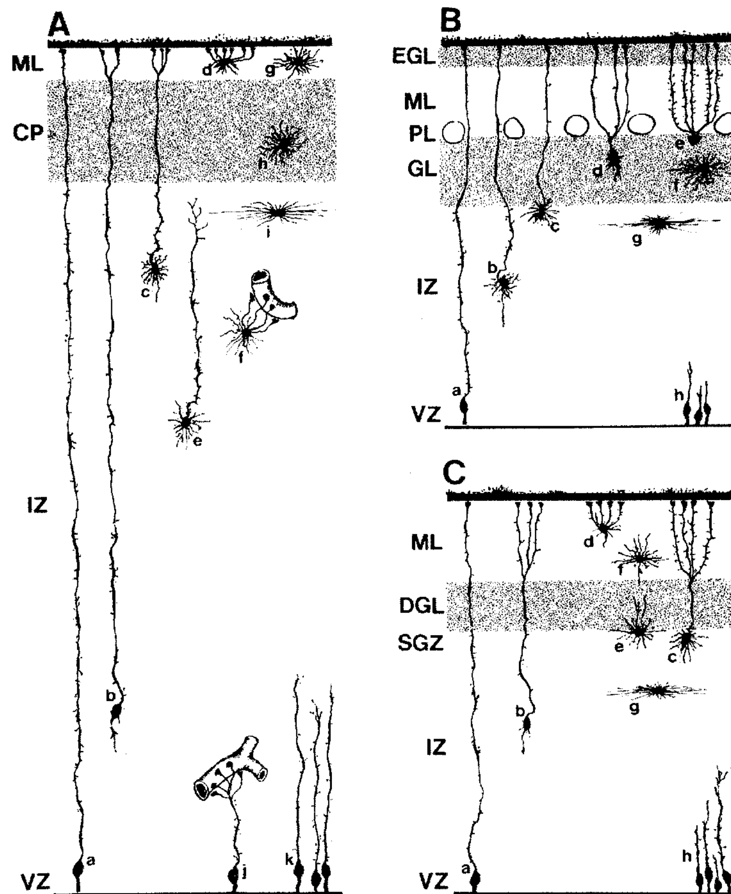

Fig. 5. Semischematic diagram illustrating the morphogenetic transformation of fetal RG cells into various astrocytic forms in the cerebral hemisphere (**A**), cerebellar hemisphere (**B**), and dentate gyrus of the hippocampus (**C**). CP, cerebral cortical plate; EGL, external granule layer; GL, granular layer (internal) of the cerebellum; DGL, dentate gyrus-granular layer of the hippocampal region; IZ, intermediate zone; ML, molecular layer; PL, Purkinje cell layer; SGZ, subgranular zone of the dentate gyrus; VZ, ventricular zone. Further explanation and designation of various transitional cell forms (a–k) is provided in the text. Adapted from Rakic (1984).

RG cells may persist throughout the adult life span (Ramón y Cajal, 1909; King, 1966; Zupanc, 1999). The available data in vivo and in vitro indicate that the fate of the RG cells depends on the context and functional requirements, which differ between regions and between species.

It was recently discovered that the remnants of RG cells in the adult rodent forebrain are capable of transformation into neurons that can be incorporated into olfactory and hippocampal formations (Doetsch et al., 1999; Chanas-Sacre et al., 2000; Laywell et al., 2000; Gage, 2002; Rakic, 2003; Tramontin et al., 2003) and/or may influence neurogenesis (Song et al., 2002). The use of the gain of function approach has revealed that notch activity may be involved in cell decision-making, by promoting glial differentiation and/or by inhibiting neurogenesis (Gaiano and Fishell, 2002; Sestan and Rakic, 2002). The available data also indicate that both cell-cell interactions and cell lineages are likely to determine the fate of RG cells (Doetsch et al., 1999; Kukekov et al., 1999; Laywell et al., 2000) and that the RG cell can, under certain conditions, serve as a mutipotent stem cell. Thus, while during their transient existence, fetal RG cells contribute actively to brain construction, the remnant of their progeny may be involved in brain functioning in health and disease during the entire life span.

ROLE IN NEURONAL MIGRATION

Neurons of the cerebral cortex are not generated in the cortex itself; rather, they immigrate in a precise inside-out sequence from the proliferative ventricular and subventricular zones. This sequence was initially implied on the basis of histological observations of the distribution of mitotic figures, bipolar cells, and sequence of neuronal differentiation in the embryonic human cortex by Vignal, Stefanowska, Retzius, and Cajal (Sidman and Rakic, 1982) and this concept has been confirmed experimentally by ^{3}H-thymidine autoradiography in mice (Angevine and Sidman, 1961) as well as in primates (Rakic, 1974). The short journey from the VZ to the preplate beneath the marginal zone in the small lysencephalic brain does not exceed the

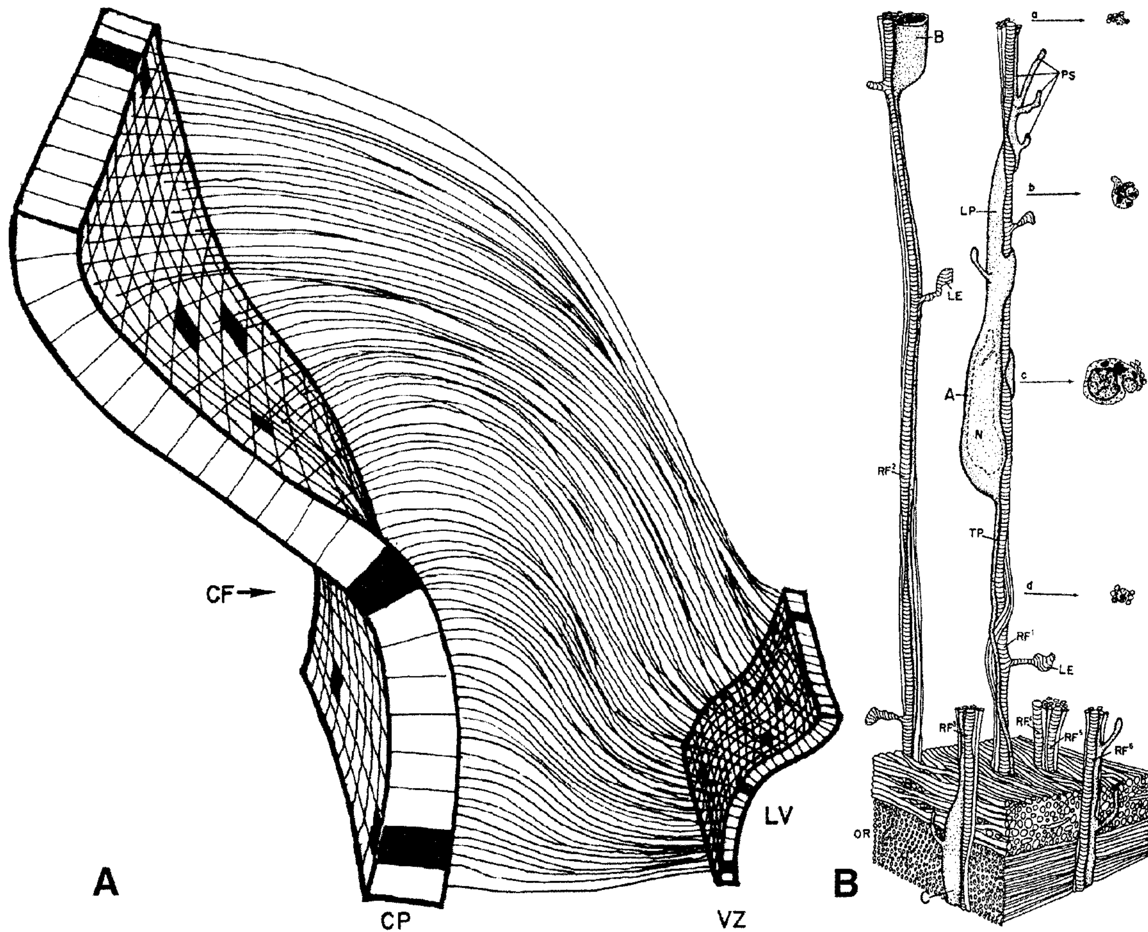

Fig. 6. **A:** Schematic three-dimensional reconstruction of the portion of the medial cerebral wall at the level of the incipient calcarine fissure (CF) in the 80-day-old monkey fetus. The reconstruction illustrates how the corresponding points in the ventricular zone (VZ) are connected by the array of elongated RG fibers that span the full thickness of the cerebral wall to the increasingly distant cortical plate (CP) situated below the convoluted pial surface. Adapted from Rakic (1978). **B:** Three-dimensional reconstruction of migrating neurons based on electron micrographs of semiserial sections of the occipital lobe of the monkey fetus. The reconstruction was made at the midlevel of the 2.500 μm wide intermediate zone. The lower portion of the diagram contains uniform, parallel axons of the optic radiation (OR), while the irregularly disposed fiber systems occupying the upper part of the diagram are deleted to expose the RG fibers (striped vertical shafts RF1-6) and their relations to the migrating neurons A, B, and C and other vertical processes. The soma of migrating cell A, with its nucleus (N) and leading process (LP), is situated within the reconstructed space, except for the terminal part of the attenuated trailing process and the tip of the vertical ascending pseudopodium. The perikaryon of cell B is cut off at the top of the reconstructed space, whereas the leading process of cell C is shown just penetrating between axons of the optic radiation (OR) on its way across the intermediate zone. LE, lamellate expansions; PS, pseudopodia. Adapted from Rakic (1972).

total length of the migrating cells and is not substantially different from the displacement of cell nuclei in other tissues, such as the optic tectum or retina (Morest 1970a; Snow and Robson, 1995; Das et al., 2003). However, the negotiation of the long, curvilinear migratory trajectories in the large gyrencephalic cerebrum, at later stages of development, requires an additional strategy. The use of a combination of Golgi impregnation, ^{3}H-thymidine autoradiography, and reconstruction from EM serial sections revealed that during late stages of corticogenesis in the macaque cerebrum, cohorts of bipolar postmitotic cells originating in the same sites within the proliferative mosaic of the VZ follow a radial pathway consisting of single or, more often, multiple RG fibers, which span the expanding and increasingly more convoluted cerebral wall (Fig. 6) (Rakic, 1972).

The expansion and elaboration of the neocortex in primate evolution is associated with enormous increase in size of the subventricular zone (Kostovic and Rakic, 1990; Smart et al., 2002). This zone in the human generates most of the cortical interneurons (Letinic et al., 2002). For example, in the wide intermediate zone of the human fetus during midgestation, as many as 30 generations of migrating neurons can be simultaneously aligned along the single radial glial shaft (Fig. 7) (Sidman and Rakic, 1973, 1982). Although postmitotic neurons in the large gyrencephalic primate brain may need several weeks to reach their final destinations, clonally related cells that originate at the same spot in the VZ/SVZ follow the same guide and eventually settle within the same cortical column (Kornack and Rakic, 1995; Rakic, 1995c). The regularity of the well-defined migratory streams (e.g., Fig. 7) suggests

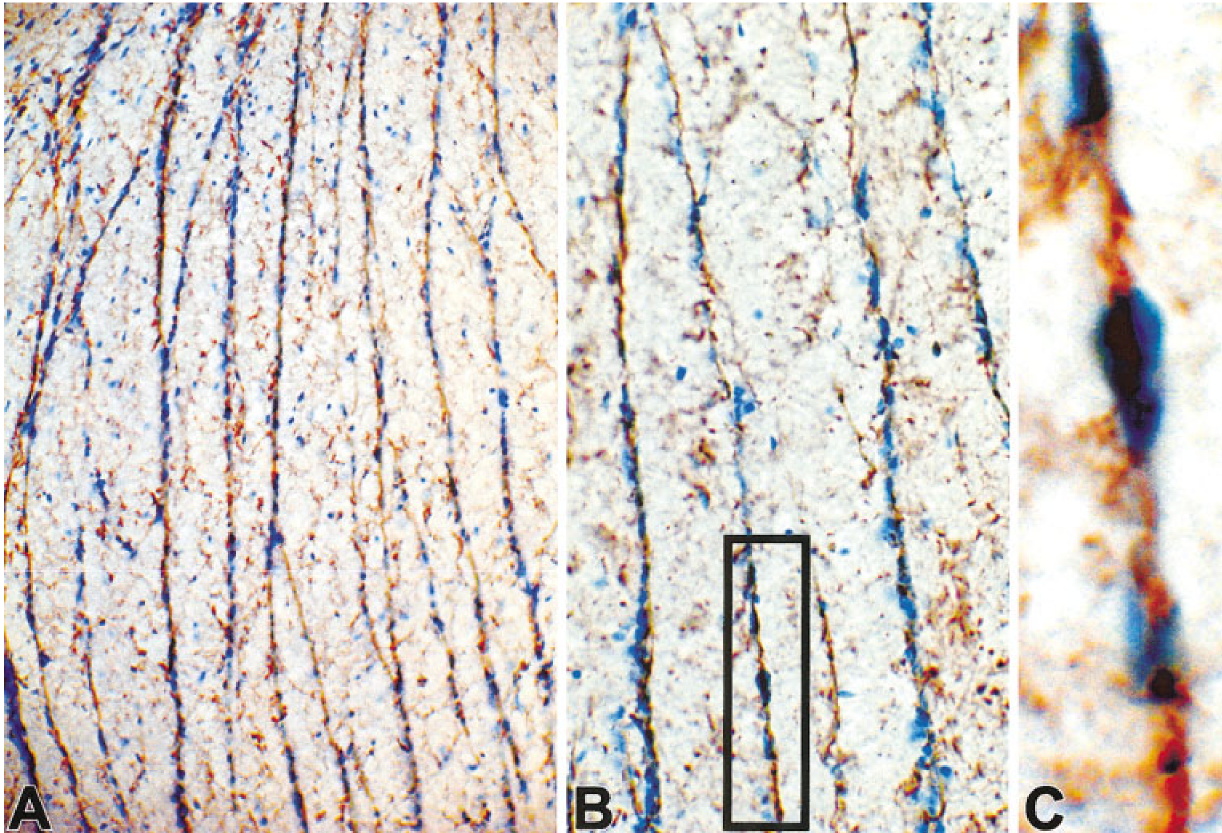

Fig. 7. **A:** Cohorts of migrating neurons visualized by toluidine blue stain (blue) are aligned along immunostained, GFAP-positive RG shafts (brown) crossing the portion of the intermediate zone of the frontal lobe of the cerebral wall in the 18-week-old human fetus. **B:** The adjacent section counterimmunostained with vimentin (brown) showing rows of similarly aligned vimentin-negative neuron aligned along vimentin-positive RG shafts. **C:** A higher magnification of the segment of the migratory pathway outlined with a rectangle in B. The image illustrates that the nuclei of the migrating neurons are not enclosed within the cytoplasm of the RG shaft. The migrating cells cannot be reproduced in the same focal plane as they are situated at the opposite sides of the RG shaft (data not shown).

both the stability of the RG cells as well as the existence of a differential binding affinity mediated by heterotypic, gliophilic adhesion molecules present on apposing neuronal and RG cell surfaces (Rakic, 1985, 1988; Rakic et al., 1994). In contrast, migrating cells that did not obey the glial constraints and were moving tangentially along axonal tracts were considered as neurophilic (Rakic, 1985).

In the past three decades, a variety of surface molecules that might be involved in recognition, adhesion, and cessation of neuronal migration have been selectively and transiently identified in the leading process of postmitotic neurons and at the surface adjacent to the RG fibers (Schachner et al., 1985; Fishell and Hatten, 1991; Komuro and Rakic, 1993, 1998; Cameron and Rakic, 1994; Rakic et al., 1994; Anton et al., 1996, 1997, 1999; Rakic et al., 1996; Hatten, 2002). Thus, separate sets of molecular classes may be involved in the recognition, selective adhesion, and maintenance of neuron-glial interactions during extension of the leading process. Among the candidate molecules involved in radial migration are neuregulin, which binds to the glial surface via ErbB2 and 4 (Anton et al., 1997; Rio et al., 1997; Schmid et al., 2003), and integrins, which provide the optimal level of basic neuron-glial adhesion needed to maintain neuronal migration on the RG (Anton et al., 1999). However, a gliophilic-to-neurophilic switch in the preference of adhesive interactions of developing cortical neurons occurs in the absence of functional α_3 integrins (Anton et al., 1999; Schmid and Anton, 2003). Recently, it has been shown that many of tangentially migrating neurons originate in the ganglionic eminence of the ventral telencephalon (Lavdas et al., 2001; Marin and Rubenstein, 2001; Letinic and Rakic, 2002). Tangentially migrating neurons may use a different set of recognition molecules than those migrating radially (Denaxa et al., 2001; Wichterle et al., 2001; Marin and Rubenstein, 2002).

Active movement of cells to their distant locations requires not only recognition of the migratory pathway and the directed growth of the leading process, but also the displacement of the nucleus and surrounding somatic cytoplasm with its nucleus to the new location. A series of Golgi impregnated cell images in Ramón y Cajal's classical drawings have illustrated convincingly this point (Ramón y Cajal, 1909), which gained support from many subsequent studies using the same method (Morest, 1970b). The use of electron microscopy in the

early 1970s revealed that after mitotic division the newly born neuron becomes separated from the progenitor and extends its leading process preferentially along adjacent existing glial shafts. We found that the newly formed nucleus becomes translocated within the cytoplasmic cylinder of its own leading process (Rakic, 1971a, 1971b, 1972). Thus, our initial ultrastructural observations indicated that "as the nucleus moves further within the vertical cytoplasmic process, the organelles become redistributed. The cytoplasm close to the nucleus contains free ribosomes, rosettes of five to six ribosomes, smooth endoplasmic reticulum, Golgi apparatus and mitochondria, whereas further from the nucleus the cytoplasm is replete with longitudinally oriented microtubules and microfilaments" (Rakic, 1971a). Thus, the content of the cytoplasmic organelles and membrane structure of the leading process was found to be more similar to the growing dendrites than to axonal growth cones or RG shafts (Rakic, 1971b, 1972; Garcia–Segura and Rakic, 1985), the distinction indicated also by their morphology (Ramón y Cajal, 1909). Importantly, the leading process does not contain GFAP, which allows quick translocation of the nucleus within the cytoplasm of the leading process. The coordinated extension of the leading process followed by nuclear translocation is particularly prominent in the primate telencephalon at later stages of corticogenesis where the migratory pathway exceeds manifold the length of the leading process of the migratory neuron.

The cytological and molecular mechanism of the physical translocation of the cell nucleus and perikaryal cytoplasm within the leading process of migrating neurons only recently began to be explored experimentally in vivo and in vitro (Komuro and Rakic, 1995, 1998; Rakic et al., 1996; Behar et al., 1999; Hirai et al., 1999; Hatten, 2002; Nadarajah et al., 2003). Collectively, these data indicate that the combination of amplitude and frequency components of intracellular calcium ion fluctuations may provide an intracellular signal controlling the rate of neuronal cell migration (Komuro and Rakic, 1996). The time-lapse imaging of migrating neurons in slice preparations in both the cerebral and cerebellar cortex extended this mechanism by showing that the leading process extends more slowly and steadily while the nucleus moves in an intermittent stepwise manner (Komuro and Rakic, 1995). Thus, the extension of the leading process and translocation of the nucleus and surrounding cytoplasm within the membrane envelope need to be orchestrated by a synchronized polymerization and disintegration of the microtubules that creates a rearrangement of the cytoskeletal scaffolding (Rivas et al., 1995; Rakic et al., 1996).

The role of polymerization and depolymerization of the microtubule protein during neuronal migration is consistent with the hypothesis that major classes of migratory defects involve abnormalities of the mictrotubule assembly (Reiner et al., 1993; Wynshaw-Boris and Gambello, 2001; Gleeson and Walsh, 2002). Furthermore, many of the candidate molecules regulate distinct aspects of neuronal migration and respond differently to environmental cues by inducing changes in the cytoskeleton, which in turn results in translocation of nuclei, eventually resulting in directed locomotion of entire cells (Rakic et al., 1996). However, a species-specific difference was observed in the effect of the deletion of doublecortin (Dbx) mutation, which has a profound effect on neuronal migration in the human telencephalon but does not effect formation and neurogenetic gradients of the mouse cerebral cortex (Corbo et al., 2002). We hypothesize that the modifications in the expression pattern of transcription factors in the forebrain may underlie species-specific programs for the generation of distinct lineages of cortical interneurons (Letinic et al., 2002), which may be differentially affected in genetic and acquired disorders related to neuronal migration in human (Rakic, 1985; Jones, 1997, 2002; Gleeson and Walsh, 2000; Lewis, 2000).

In conclusion, RG cells in the mammalian telencephalon are involved in both production and migration of cortical neurons. It may be counterintuitive that nonneuronal cells would play such a pivotal role in production and placement of neuronal cells during development and evolution of the cerebral cortex. However, it should be kept in mind that during invertebrate evolution, the first neurons have originated from the nonneuronal epithelial cells of the dorsal ectodermal epithelium (Kappers et al., 1965; Nieuwenhuys et al., 1998). Thus, the sequence of cell diversification in the forebrain from nonneuronal to neuronal lines recapitulates the sequence that has occurred during evolution of the central nervous system.

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