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Commentary

Radial versus tangential migration of neuronal clones in the developing cerebral cortex

Pasko Rakic

Section of Neurobiology, Yale University School of Medicine, New Haven, CT 06510

The cerebral cortex is a striking example of an ingenious and economic design of nature. Although the surface area of the neocortex is vastly different in the wide variety of mammals, the consistent feature of the cortex is its organization into horizontal and vertical arrays of neurons that form anatomically and physiologically distinct laminar and columnar compartments (1, 2). The application of a variety of neurobiological methods in the past two decades has provided the basis for a formulation of the dynamic cellular principles underlying cortical development (for review, see ref. 3). All cortical neurons in primates, including humans, are generated during the first half of gestation within the proliferative zone lining the surface of the cerebral ventricle (4). After their final mitotic division, cortical neurons migrate away from the place of their origin, toward the pial surface, where each successive generation passes one another and settles in an inside-out pattern within the cortical plate (5). This sequential pattern is particularly pronounced in the large convoluted primate cerebrum, where migratory pathways are long and tortuous (3). Postmitotic neurons during their migration tend to selectively follow the membrane surface of elongated nonneuronal, radial glial fascicles that transiently span fetal cerebral wall (6). This finding led to the concept of differential neuron–glial cell adhesion and stimulated a search for the molecular mechanisms underlying directed neuronal migration (7, 8). It also led to the formulation of radial unit hypothesis of cortical development.

Radial Unit Hypothesis

According to the radial unit hypothesis (3), the tangential (horizontal) coordinates of cortical neurons are determined by the relative position of their precursor cells in the proliferative ventricular zone, while their radial (vertical) position is determined by the time of their origin. Therefore, cells within a given radial column may originate from several progenitors but share the same birthplace and migrate along a common pathway (3). According to this theory, the number of radial columns determines the size of the cortical surface, whereas the number of cells within the columns determines cortical thickness. Further, this model holds that the >1000-fold increase in the cortical surface without a comparable increase in its thickness during mammalian evolution can be accounted for by changes in the proliferation kinetics of founder cells that increase the number of radial units without significantly changing the number of neurons within each unit (9). Thus, mutation of a few (as yet, undiscovered) regulatory genes that control the timing and ratio of symmetric and asymmetric modes of cell divisions in the proliferative zone, coupled with radial constraints in the deployment of migrating neurons, could create an expanded cortical plate with an enhanced capacity for establishing new patterns of connectivity that are validated through natural selection (9). Radial migration of neurons after final division is not unique to the cerebral cortex, as cells are similarly deployed in the developing retina, spinal cord, tectum, and diencephalon (e.g., refs. 10–14). However, the radial unit hypothesis of cortical development has provided a particularly useful framework for understanding the development and evolution of functional modules (1, 2, 9), as well as the pathogenesis of certain genetic disorders (15–18).

Challenge to the Radial Unit Hypothesis

While most developmental neurobiologists agree that the laminar and radial organization of the cerebral cortex can be predicted by knowing the time of neuron origin, the mode of cell proliferation, and the pattern of neuronal migration, a debate has arisen concerning the role of clonal allocation in building cortical architecture. The point of disagreement is whether, after their mitotic division, clonally related neurons are restricted in their distribution to a given sector of the cortex—e.g., a particular column—or become dispersed through widely spaced regions.

In the last several years the foundation of the radial unit hypothesis has been contested by interpretations of results from retroviral-mediated labeling of cell lineages, some of which initially suggested that most postmitotic neurons in the rodent cerebral wall do not obey radial constraints and presumably have no assigned positions in the cortex. Although it was well known from application of Golgi and electron microscopic methods that a small number of bipolar, presumably migrating neurons in the intermediate zone are oriented nonradially or stretch between adjacent glial fascicles (see, for example, figure 1 in ref. 19 and figure 3g in ref. 20), the tangential dispersion of cells received renewed attention only after the introduction of the retroviral labeling method for tracing clonal allocation of neurons (21, 22). These studies, which use replication-defective retroviral vectors that encode a histochemical marker gene, allowed clonal analysis of cells in the mammalian brain (23). Subsequently, identification of an extensive library of retroviral tags in individual cells, using PCR amplification, indicated that some progenitors may give rise to cortical neurons in distant cytoarchitectonic areas (24). This dispersion of clonally related cells has been interpreted as evidence that immature neurons of the entire cortical plate may be without intrinsic information concerning their regional fate (25, 26).

In contrast, examination of clonal allocation in chimeric mice confirmed that a large number of clonally related neurons in the developing cerebrum obey radial constraints (27, 28). In addition, other retroviral studies revealed radial migration or radial distribution of clonally related cells (29, 30). Therefore, the remaining questions seem to be which mode of cell allocation is predominant and what is the significance of two modes for building the cytoarchitecture of the cortex. The papers that appear in this issue of the *Proceedings* (31) together with recent reports published in *Development (Cambridge, U.K.)* (32) and *Neuron* (33, 34) provide new information relevant to these issues.

New Evidence from Transgenic Mice

The findings of Soriano *et al.* (31) seem to support the predominance of the radial mode of migration and also provide evidence that this allocation may be clonally based. These authors examined the distribution of β-galactosidase (β-gal) expression in the β2nZ3'1 transgenic mouse line, which shows ectopic expression in some brain cell clones. This transgenic line was intended to study transcriptional regulation of the β_2-microglobulin gene for a different experimental purpose, but exam-

ination of the β-gal histochemically stained sections of the telencephalon provided an unexpected pattern of cell allocation that was relevant to the issue of neuronal migration in the cortex: the progeny of β-gal$^+$ progenitors in the β2nZ3'1 transgenic mouse migrated radially and remained restricted within a given radial domain of the neocortex. A similar radial alignment of β-gal$^+$ cells was observed in the developing hippocampal region. In neither region were labeled clones distributed perpendicularly to the orientation of radial columns. In embryonic mice, clearly defined cohorts of labeled cells were radially deployed within the entire span between the proliferative ventricular and marginal zones near the pial surface. Furthermore, within the migratory intermediate zone β-gal$^+$ cells were aligned along fascicles of elongated radial fibers that could be identified by glia-specific antibodies. These observations support the predominance of radial migration in the mouse telencephalon.

Soriano *et al.* (31), in addition, offer several new lines of evidence that lineage may be a relevant parameter for gene regulation in the specification of the radial architecture of the cerebral cortex. (*i*) They show that β-gal$^+$ cells in the proliferative ventricular zone incorporate the thymidine analog, bromodeoxyuridine, indicating that these clones become specified already in the S phase of their last mitotic division. (*ii*) Precociously and intensely β-gal$^+$ cells were interspersed with β-gal$^-$ cells within the same radial stripes, confirming that radial columns are polyclones that share the same place of origin (3). Furthermore, the cellular heterogeneity of radial columns and, in particular, their random position across cerebral hemisphere in different animals from the same transgenic line indicate that the transgene expression is unlikely to be due to area-restricted transcriptional regulation induced by specific afferent inputs to the cortex.

Perhaps the most compelling evidence that the majority of neuronal clones remain restricted within radial columns was provided by the distribution of clonally related cells in H253 transgenic mice in which the gene encoding β-gal was integrated serendipitously into the X chromosome (32). Since the random inactivation of one X chromosome occurs during midgestation, transgenic female mice generate a mixed population of β-gal$^+$ and β-gal$^-$ cells in the ventricular zone and, therefore, can serve as a paradigm to study their subsequent distribution (28). Immunocytochemistry revealed that a majority of cortical neurons, originating from the same progenitor (β-gal$^+$ or β-gal), migrate in register with their place of origin in the ventricular zone and, in the cortex, form distinct radial stripes with relatively sharp borders (Fig. 1). However, the clarity of stripes varied greatly between individual animals because an uneven number of β-gal$^+$ cells were situated within the largely unlabeled stripes (compare Fig. 1 *A* and *B*). This "mixing" was interpreted by Tan *et al.* (32) as a measure of dispersion of clonally related cells beyond radial boundaries. On the basis of this model (Fig. 2*A*) up to 30% of cells may be dispersed nonradially as progenitors or after leaving the cell division cycle.

There is, however, an alternative interpretation according to which the observed mixture of β-gal$^+$ and β-gal$^-$ cells in the H253 transgenic mice reflects the polyclonal composition of radial columns rather than the lateral dispersion of postmitotic neurons (Fig. 2*B*). Because the radial unit hypothesis predicts that ontogenetic columns are formed by as many as 10 founder cells (3) and because the inactivation of the X chromosome in individual cells is random, it would be expected that each column in this transgenic preparation would derive from a mixture of labeled and unlabeled progenitors, even without any lateral migration (Fig. 2*B*). However, the probability that columns composed exclusively of β-gal$^+$ cells alternate with all β-gal$^-$ columns, which would expose radial columns most clearly, is very low. In practice, according to a Gaussian distribution, the most common outcome should be around the middle values, with ratios of labeled/unlabeled cells between 4:6 and 6:4 (Fig. 2*C*). When adjacent columns have the same ratios (e.g., 5:5), there would be no contrast in the staining between them, resulting in double- or triple-width columns. In contrast, when adjacent columns have different ratios, the borders become visible, and the bigger the difference in ratios of labeled/unlabeled cells between adjacent columns, the more obvious the border between them in this transgenic preparation (compare Fig. 1 *A* and *B*). The occasional juxtaposition of a highly labeled column (e.g., 9:1) and mostly unstained column (e.g., 2:8) is the most informative, as it sets up the lowest limit of the possible tangential dispersion (Fig. 2*D*). So, if the most lightly labeled radial stripe in H253 transgenic animals contains 10% β-gal$^+$ cells, I suggest that no more than 10% of cells cross over laterally. However, even this is an overestimate because the β-gal histochemical stain does not allow a distinction between cell types; glial cells make up a substantial proportion of labeled cells in the basically unlabeled columns. In the developing ferret as much as 12% of spindle-shaped cells in the cerebral wall are oriented perpendicular to the radial pathway and were observed to migrate tangentially (35). However, it is not clear whether all horizontally oriented cells survive or even enter the cortex. It is likely that some of these cells remain below the cortex as interstitial neurons (36, 37). Thus, the dispersion of clonally related neurons is probably smaller than

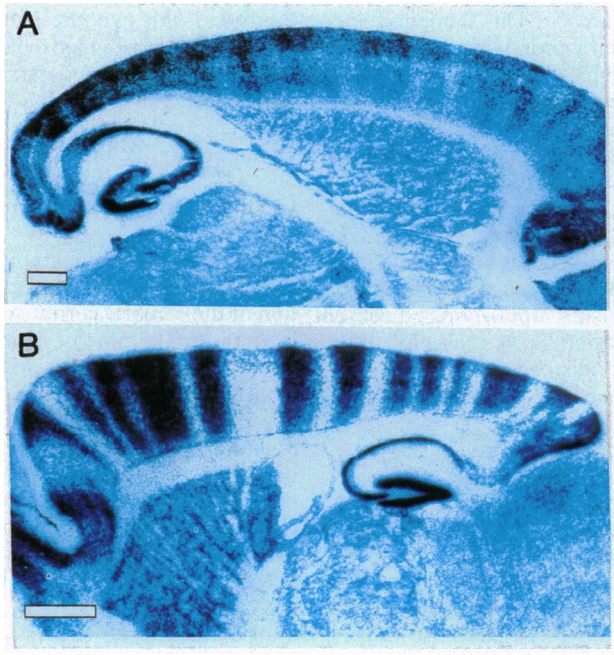

FIG. 1. Parasaggital sections of the cerebrum from two H253 transgenic mice showing mixture of labeled (β-gal$^+$) and unstained (β-gal$^-$) cells forming radial columns running from the white matter to the pial surface. Differential marking was accomplished by insertion of *lacZ* into one of the two X chromosomes and taking advantage of the natural inactivation of the transgene during the middle of gestation in female descendants from this line. As a result, the expression of β-gal, which is encoded by *lacZ*, occurs in approximately half the cells in female mice. Note the big difference in mixture of labeled and unlabeled cell in the two cases, with more explicit columns being revealed in *B* than in *A*. (Bar = *A*, 200 μm; *B*, 600 μm.) Reprinted with permission from ref. 32 (copyright, Company of Biologists Ltd., Cambridge, U.K.).

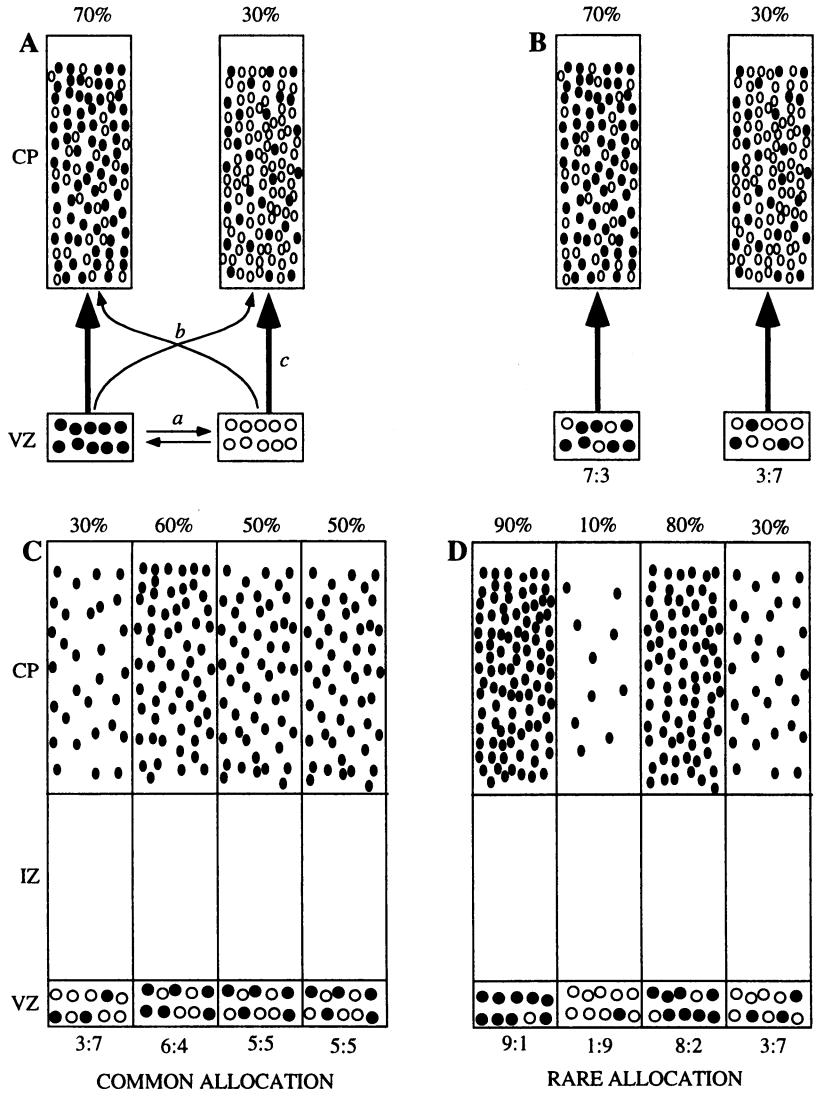

FIG. 2. (*A* and *B*) Graphic representation of the two models for interpretation of the labeling pattern seen in transgenic mice, such as those illustrated in Fig. 1 *A* and *B*. These models assume that each radial unit is formed by 10 founder cells that have ≈50% probability of either expressing β-gal. According to the model illustrated in *A*, presence of β-gal$^+$ in largely unlabeled columns of the cortical plate (CP) is obtained by crossing over of some cells between radial columns either within the ventricular zone (*a*) or after leaving the cell division cycle (*b*). The model illustrated in *B* is based on the assumption that each radial unit is composed of a number of progenitor cells at the time of X chromosome inactivation. Because inactivation of X chromosome occurs independently in each cell, the final number of the polyclonal founder group, in terms of expressing or not expressing β-gal, should be fitted with a Gaussian model. Therefore, more common composition of labeled/unlabeled cells around middle values (*C*) reveals radial columns in the cortex less well than the more rare ratios with extreme values (*D*). CP, cortical plate; IZ intermediate (migratory) zone; VZ, ventricular (proliferative) zone; numerals beneath VZ sectors represent the ratio of β-gal$^+$/β-gal$^-$ founder cells. The percentage (%) above radial columns in the cortical plate indicates fraction of β-gal$^+$ cells.

assumed, and radial allocation is the predominant mode of distribution. Furthermore, the mixed-composition model proposed in Fig. 2*B* explains the variability of labeling patterns observed between H253 transgenic animals as illustrated in Fig. 1 *A* and *B*.

New Evidence from Retroviral Gene Transfer Method

The large number of labeled cells in mosaic mice provides a broad view of the radial borders in the cortex. In contrast, retroviral-mediated gene transfer methods that label fewer cells is better suited to examine details of clonal allocation. In their most recent study, Walsh and his colleagues (34) use a retroviral library that encodes for alkaline phosphatase and allows better identification of cell types. They provide some new information about phenotypic differentiation but, most importantly, offer a new interpretation of the dispensation of clonally related neurons. According to their model, there are two nonoverlapping types of cortical clones in the rat cortex: one that forms tight groups of cells within the cortex and the other that distributes neurons over a distance of >1.5 mm. Further, they suggest that progenitors generating the first type of clones do not move while dividing within the ventricular zone. In contrast, widespread clones are explained by displacement of progenitors within the ventricular zone. This model is in agreement with [^{3}H]thymidine, bromodeoxyuridine, and retroviral studies that there are at least two types of progenitors in the ventricular zone (3, 33, 38–40). Furthermore, this model agrees with Fishell *et al.* (41) that some progenitors before their last division may change position within the ventricular zone. Therefore, according to this model, the dispersion of clones is due to the lateral displacement of progenitors rather than the tangential migration of their progeny. The basic implication of these results is that both types of progenitors eventually produce postmitotic cells that migrate radially to the cortex, a conclusion in harmony with the radial unit hypothesis.

Recent cell lineage analysis in the developing cerebrum of the macaque monkey using retroviral-mediated gene transfer method sheds new light on the issue of radial versus horizontal allocation of cortical neurons (33). A mixture of two recombinant retroviruses was used to label progenitor cells in the ventricular zone and to determine histochemically the distribution of their progeny during and after the period of cortical neurogenesis. One advantage of the retroviral approach in the large primate cortex is that labeled cells are distributed among myriads of unlabeled cells, making identification of clones reliable. This analysis revealed β-gal$^+$ clones that are clearly aligned radially (Fig. 3*A*). It was suggested that the radial arrays, typically composed of three to four sibling cells, are generated sequentially from an asymmetrically dividing stem cell in the ventricular zone (33). With each round of mitosis, the stem cell produces two daughters; one leaves the ventricular zone, and the other remains as a self-renewing progenitor. Because of their sequential mode of production, postmitotic cells leave in tandem to occupy successively more superficial positions in the cortex (Fig. 4*A*). The radial ordering suggests that a coupling between the "point source" in the ventricular zone and a restrictive migratory route to the cortical plate is established and maintained during cell production. These conclusions are in accord with the generally accepted view that asymmetrically dividing progenitors generate successive "siblings," which then migrate in sequence, along a common radial path to the cortex (3, 29, 39). However, it is remarkable that clonally related cells retain radial alignment, even in the

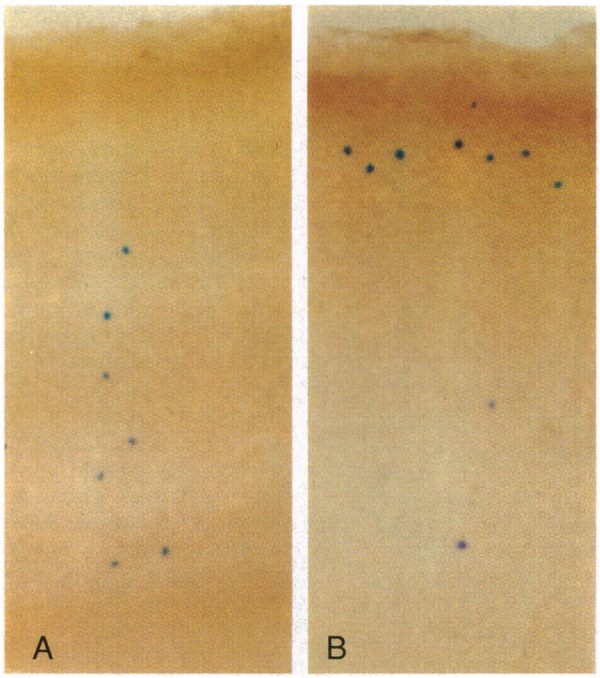

FIG. 3. Examples of radial (*A*) and horizontal (*B*) arrays of β-gal$^+$ clones in cerebral cortex (top, pial surace; bottom, layer VI) of monkey fetus injected with retroviral probes into the lateral ventricle 2 mo earlier. As elaborated in text, a radial array is composed of sequentially generated "sibling" cells that arrive at the cortex along the same migratory route. In contrast, a horizontal array may be composed of "cousins" that are generated simultaneously from multiple, related progenitors and migrate in concert to a common cortical lamina. Reprinted with permission from ref. 33 (copyright, Cell Press, Cambridge, MA).

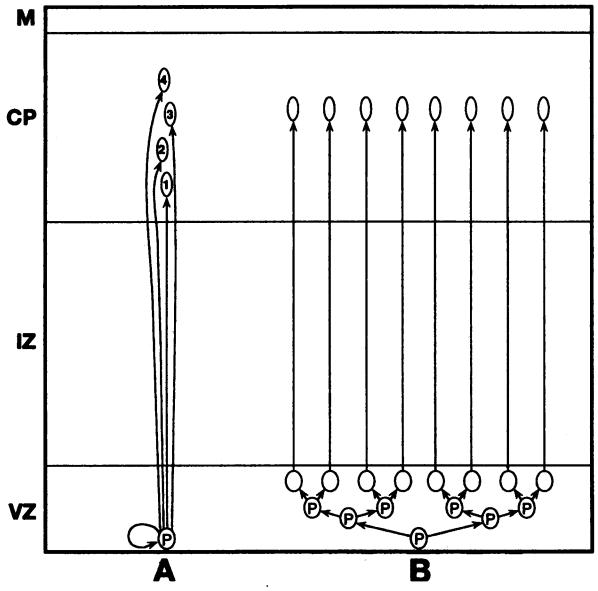

FIG. 4. Two models of clone allocation patterns in the macaque cerebral cortex and their relation to modes of mitotic divisions and migratory histories. (*A*) The first model consists of an array of "sibling" cells generated sequentially from an asymmetrically dividing stem cell in the ventricular zone (VZ). With each round of mitosis, the stem cell produces two daughters; one leaves the VZ, and the other remains as a self-renewing progenitor. Because of their sequential mode of production, the cells leave the VZ in tandem to occupy successively more superficial positions in the cortex (ovals 1, 2, 3, 4). The radial ordering suggests that a coupling between the "point source" in the VZ and a restrictive migratory route to the cortical plate (CP) is established and maintained during cell production. (*B*) The second mode produces a horizontal array that is composed of "cousin" cells that are generated simultaneously from multiple, related progenitors and migrate in concert to a common cortical lamina. The progenitors may be descendants of a single, symmetrically dividing ancestor. The unlabeled ovals in the VZ represent either the daughters of terminal symmetric divisions before they begin to migrate or asymmetrically dividing cells, each generating a cell that contributes to horizontal rows. IZ, intermediate zone; M, marginal zone; P, proliferative cell. Reprinted with permission from ref. 33 (copyright, Cell Press, Cambridge, MA).

large, convoluted primate cerebral cortex, where the site of cell origin and its final destination in the cortex are separated by long and meandering routes.

In addition to the radially deployed clones, some clonally related cells in the primate cortex were distributed horizontally, though, as shown in Fig. 3*B*, they were closely spaced and confined within a single lamina. This pattern of clonal distribution has not been observed previously in rodents, perhaps because, unlike in primates, the time of cell origin in rodents is less lamina-specific (5). The distribution of the clonally related cells in the same strata of the monkey cortex indicates that they have migrated simultaneously rather than sequentially (33). Examination of the cortex at a shorter time interval after retroviral injections suggested that symmetric divisions produce multiple, laterally displaced progenitors which, in turn, simultaneously generate "cousin" cells that migrate, in unison, to the same cortical layer (Fig. 4*B*). These results support the concept that the laminar fate of cortical cells is determined around the time of their origin (3, 42, 43). However, analysis in monkey embryos further indicates that simultaneously generated cells can be clonally related, leading to the hypothesis that different mitotic lineages in the primate ventricular zone produce distinct radial or laminar patterns of clone deployment (33). It should be underscored that both patterns of clonal distribution are fully compatible with radial cell migration to the cortex.

Conclusion and Perspective

The experimental evidence reviewed above indicates that the predominant mode of cell allocation in the cerebral cortex is both radial and clonally based. The presumed role of restricted radial allocation of clones may be to preserve positional information essential for the development of functionally distinct areas (3). However, it should be recognized that the transgenic mice or retroviral gene transfer method documents only a cell's ultimate fate and does not inform about the developmental potential of clonally related cells (34). Other approaches have demonstrated the emergence of area-specific molecules in the cortex before or independently of thalamic input (e.g., refs. 44–48). For example, the use of transgenic mice combined with transareal transplantation has indicated that the expression of genes specific for somatosensory cortex occurs in this region irrespective of interaction with the type of afferents from the thalamus (47). It is also noteworthy that specific functions can be restored after transplantation of embryonic cells derived from homologous, but not heterologous, areas (49).

The finding of restricted clonal allocation in the telencephalon does not imply autonomous specification of cerebral cortex. Intrinsic regional differences in gene expression may only form a protomap that serves to direct or attract specific sets of afferents (3). Normal differentiation and the final size of various cytoarchitectonic areas are clearly regulated by interaction with specific afferents originating from subcortical structures and other cortical areas. For example, ocular dominance columns in the visual cortex (50, 51) and barrel fields in the somatosensory cortex (52) develop normally only through instruction from the periphery. Furthermore, the size of the thalamocortical input determines the size of the corresponding cortical area (3, 53–55). Thus, the laminar and areal specification of cortex involves both intrinsic and extrinsic regulation of cellular events; it assumes the presence of a larger number of participating neurons from which the final pattern of the cortical map is carved (3, 56).

While the significance of radial allocation of neurons has been proposed for both the ontogenetic and phylogenetic development of cortical architecture (3, 9), the role of dispersed clones in the telencephalon is less clear. Because the fraction of dispersed cells is relatively small, it could simply reflect imperfection of the biological mechanism involved in cell migration. Alternatively, some of these cells may subserve a specialized role. It has been reported that tangentially moving cells in various parts of the telencephalon may be destined for brain regions—such as the olfactory bulb, basal ganglia, and diencephalon (37, 57–59). A subclass of postmitotic cells that migrate tangentially to radial pathways was described also in the developing avian tectum (12, 60). Collectively, these studies indicate that tangential migration does not necessarily signify the lack of clonal phenotypic restriction, as initially suggested, but rather the commitment of postmitotic neurons to a different mode of migration, one that is regulated by different sets of recognition and adhesion molecules (8, 61). The use of retroviral labeling and transgenic mice in combination with other methods such as labeling with [^{3}H]thymidine, cell-class-specific markers, and anatomical tracings may help to determine the fate and developmental significance of some of these cells.

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