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Neurons from radial glia: the consequences of asymmetric inheritance

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Recent work suggests that radial glial cells represent many, if not most, of the neuronal progenitors in the developing cortex. Asymmetric cell division of radial glia results in the self-renewal of the radial glial cell and the birth of a neuron. Among the proteins that direct cell fate in *Drosophila melanogaster* that have known mammalian homologs, Numb is the best candidate to have a similar function in radial glia. During asymmetric divisions of radial glial cells, the basal cell may inherit the radial glial fibre, while the apical cell sequesters the majority of the Numb protein. We suggest two models that make opposite predictions as to whether the radial glia or nascent neuron inherit the radial glial fiber or the majority of the Numb protein.

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Current Opinion in Neurobiology 2003, **13**:34–41

This review comes from a themed issue on
Development
Edited by Magdalena Götz and Samuel L Pfaff

0959-4388/03/$ – see front matter
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DOI 10.1016/S0959-4388(03)00013-8

Abbreviations
CNS central nervous system
VZ ventricular zone

Introduction

Mammalian cerebral cortex arises from expansion of the neural tube shortly after gastrulation, the neural plate is formed under the joint influence of signals from the node and the axial mesoderm and subsequently folds to become neural tube. During the establishment of the anterior–posterior (A–P) and dorsal–ventral (D–V) axis, no neurogenesis occurs but symmetrical cell divisions result in a dramatic expansion of the nervous system and the establishment of the neural axis [1]. From embryonic day 10 onwards, the mode of cell division within the telencephalon changes, such that increasing numbers of progenitors undergo asymmetric divisions and begin to give rise to neural progeny. By birth, the vast majority of neuronal production is complete. Just a few small populations of neural stem cells are maintained in niches that persist through adulthood. Over the past decade, numerous studies have begun to reveal both cellular and molecular mechanisms that underlie these developmental steps. In this review, we examine the different stages of central nervous system (CNS) development, focusing on cell-autonomous signals. We identify certain general principals that hold true with regard to asymmetric divisions across these developmental stages, and propose two possible but not mutually exclusive hypotheses of how asymmetric division occurs during neural development.

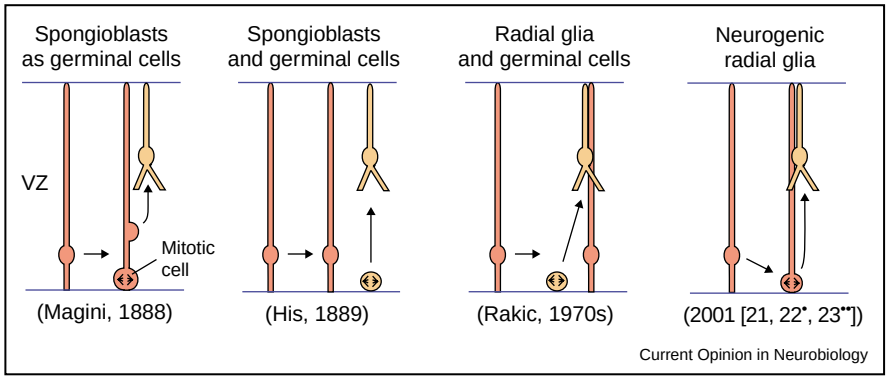
Establishment of regional pattern while in a stem cell state

The genetic evidence suggests that intrinsic determinants such as Notch and Numb are dispensable before mammalian neurogenesis; although they are later required for the proper ordering of symmetric and asymmetric cell divisions [2]. Indeed, mutants lacking genes required for specific lineal decisions, such as Notch [3] and Numb [4], develop relatively normally until the onset of neurogenesis. In contrast, extrinsic cell signals, such as Wnts, Bone morphogenetic proteins (BMPs) and Sonic Hedgehog (Shh), are all essential for neural patterning during this period [5]. At the onset of neurogenesis, the mode of cell divisions and the corresponding molecular requirements for cell division change abruptly. Self-renewing progenitors begin to undergo both asymmetric and symmetric terminal divisions at the same time as the first neurons are being generated. Despite our scant knowledge of the basis for these changes, recent work has revealed both the identity of the cells that give rise to mature neurons and the molecular basis by which these divisions are regulated.

Mitotic cells provide hints concerning the regulation of the mode of division

Before considering the molecular basis of how cell division generates diversity, it is worth reviewing what is known about the neuronal progenitor cells themselves. Over the past century, developmental neurobiologists have struggled to identify the cells that give rise to neurons. Early efforts revealed that cells in mitosis were generally found apically in the ventricular zone (VZ), lining the ventricles, whereas differentiating neurons were located basally near the brain's surface. Theories of neurogenesis attempted to describe how precursor cells both divide repeatedly at the ventricular surface and give rise to a vast population of newborn neurons that travel to remote sites of differentiation. Golgi preparations were

Figure 1



Changing concepts of cortical neurogenesis. Over the past century, concepts concerning the relationship between spongioblasts (radial glial cells) and germinal cells (neuronal progenitors) have undergone many changes. Current evidence indicates that they are, in fact, the same cells. Orange: germ cells/neurons; red: spongioblasts/radial glia.

presumed to contain the key to understanding neurogenesis, as they provided a snapshot of the morphologically diverse cells present within the developing cortex and could be placed into a presumed temporal sequence. A major stumbling block, however, was that cells with different morphology could represent either distinct cell types or dynamic morphological changes within a single cell type. This uncertainty gave rise to two general schools of thought: first, that spongioblasts (also termed epithelial or radial neuroglial cells) were themselves germinal cells, or second, that germinal cells and spongioblasts were two distinctly different cell types (see Figure 1).

Golgi was the first to describe epithelial cells in the developing neural tube that extended radial fibres from the ventricular surface to the pial surface [6]. These cells were subsequently termed 'spongioblasts' by His [7]. His presumed that it was not the spongioblasts but the rounded germinal cells visible at the ventricular surface that generated neurons. Cajal believed that neuroepithelial cells and neuronal progenitor cells were different cell populations (reviewed in [8]). However, Magini [9], observed varicosities along the filaments of the radial neuroglial cells and concluded that these represented immature nerve cells. Further, he speculated that these radial neuroglial cells could be the cells that gave rise to neurons [9].

Focusing primarily on cell-cycle-specific differences in nuclear morphology, Sauer [10] described the process of interkinetic nuclear migration and suggested that spherical germinal cells and spongioblasts are one cell type at different cell cycle stages. Later, attention shifted to the question of how newborn neurons migrate to the cortex [11,12]. Morest [13] presented evidence to show that neurons grow radial processes and subsequently translocate to the cortex. In the early 1970s, Rakic [14,15] described the guidance role of radial fibres during neuronal migration. He coined the term 'radial glia' to acknowledge both the radial morphology and the glial nature of the previously termed epithelial or radial neuroglial cells. After it was established that radial glia had a structural role in neuronal migration [16], they came to be considered as a type of glial support cell. Neuronal and glial lineages were believed to be distinct and, thus, mitotic radial glial cells were presumed to generate only astroglia [17–20].

The distinction between radial glial cells and neuronal progenitors has recently collapsed because of the demonstration that radial glial cells can generate cortical neurons [21,22•,23••,24]. It now appears that the majority of cortical pyramidal neurons are generated by mitotic radial glia [25•], and that neuronal progeny use parental radial fibres for migrational guidance [23••]. Surprisingly, this concept is reminiscent of the scheme originally proposed by Magini more than 100 years ago [9].

Time-lapse imaging of cell cycle progression reveals the dynamic changes in precursor cell morphology that occur during neuronal production in the VZ. One of the first time-lapse studies of cortical neurogenesis documented the orientation of the cleavage planes of dividing cells at the ventricular surface, but did not describe the cellular morphology of the precursor cells [26]. More recently, time-lapse studies of dividing radial glia in slice cultures have demonstrated that radial glial cells maintain their pially directed radial processes throughout division [22•,23••]. The radial fibres become attenuated during mitosis and varicosities develop along their length, presumably because of the streaming of cytoplasm toward the nucleus. The idea that radial glial fibres are retained during mitosis is supported by the examination of radial glia in M-phase that are labeled with an antibody to the phosphorylated form of vimentin [27]. These M-phase

radial glial cells have visible radial processes that can extend to the pial surface [25•,28].

Therefore, dividing radial glia appear to maintain their radial processes during division. However, the fate of the radial fibre following mitosis is not entirely clear. Some neurons that are 'born' from asymmetrical radial glial cell divisions may inherit the radial process from their parent cells [22•]. In these cases, the newborn neuron loses its ventricular attachment and is able to radially translocate its nucleus within the radial fibre, much like a cell undergoing interkinetic nuclear migration. Neurons can thus reach the cortical plate without undergoing the traditional migration process known as 'locomotion' whereby neurons inch along radial fibers [13,29,30]. Following an asymmetrical division in which a newborn neuron inherits the radial process, the parent radial glial cell would remain a rounded cell at the ventricular surface and would need to re-extend a radial process to the pial surface. Cells with a soma at the ventricular surface and a radial process partially extended toward the pial surface have been observed in the embryonic VZ [22•,25•,31,32]. Regardless of whether the neuron or the radial glial cell inherits the radial fibre, the persistence of a radial fibre throughout cell division imposes an inherent asymmetry on the mitoses occurring at the ventricular surface.

Definitions of symmetric and asymmetric divisions

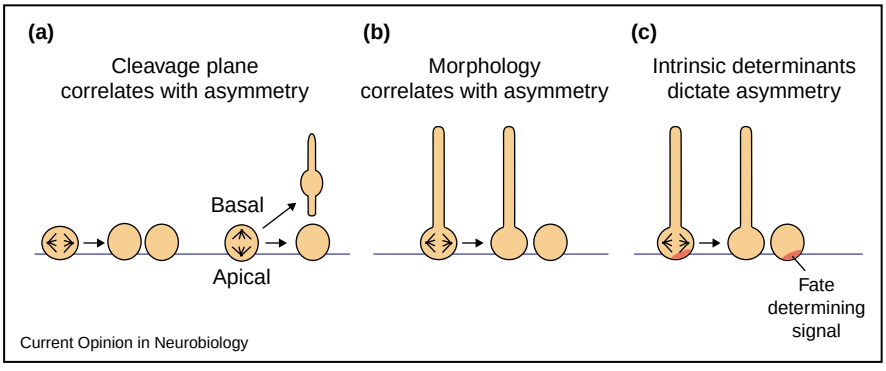
Although the terms symmetric and asymmetric are frequently used when discussing cell divisions, the precise meaning that is implied by these terms has varied widely. It is therefore helpful to establish definitions for the purpose of this review. In previous work, asymmetric divisions have been defined according to three different characteristics: first, the inclination of the plane of division with respect to an epithelial surface, second, the asymmetry of the daughter cell's morphology, or third, the asymmetry of inherited intrinsic fate-determining signals (see Figure 2). Here, we consider divisions to be asymmetric when the radial glial fibre is selectively inherited by one daughter cell. We speculate that this is a consequence of the unequal inheritance of the Numb protein.

In the *Drosophila* CNS, the plane of division of the founder neuroblast is predictive of either a symmetric or an asymmetric division. Mitotic divisions with the cleavage plane parallel to the epithelium (horizontal) are often asymmetrical, whereas mitotic divisions with a cleavage plane orthogonal to the epithelium (vertical) are generally symmetrical [33]. In the pseudostratified neuroepithelium of vertebrates, a similar correlation has been proposed [26]. This is supported by the observation that only the apical daughter maintains an attachment to the ventricular surface during a horizontal division. In contrast, in a vertical cell division, both daughter cells may maintain ventricular attachment. In vertebrates, we do not know whether the outcome of divisions is determined or simply predicted by the orientation of the division.

The implications of invertebrate neurogenesis for molecular mechanisms and models of asymmetric inheritance

Genetic studies performed on *Drosophila* suggest that the unequal inheritance of specific determinants is the key to intrinsically determined asymmetric cell divisions in this species. In *Drosophila*, in which lineages are relatively invariant, it has been possible to identify specific genes that act causally to specify asymmetric cell divisions. The discovery of mutations that perturb cell fate in *Drosophila* led to the cloning of a set of required genes, including Glial-cells-missing (GCM), Prospero, Numb, Miranda, Partner of Numb, Inscutable and Notch [2,34–36]. Notably, most of these appear to be genes that act cell-autonomously. Moreover, when the localization of the proteins encoded by genes was visualized, it became evident that some were inherited unequally during asymmetric cell divisions.

Figure 2



Possible predictors of asymmetric divisions. Asymmetric divisions have been defined by: **(a)** the orientation of the cleavage plane with respect to an epithelial surface, **(b)** the asymmetric morphology of the daughter cells, or **(c)** the asymmetric inheritance of intrinsic fate-determining signals.

Although homologs to some of these cell-fate genes have been found in mammals, it is clear that their functions are not necessarily conserved across species. For example, two homologs of GCM have been found in vertebrates; however, neither of these genes is expressed significantly in the nervous system, and loss-of-function analyses suggest that they do not instruct a glial identity as they do in *Drosophila* [37,38]. In contrast, the function of other genes, such as that encoding the Notch receptor, appears to be better conserved in mammals. Notch is a strong inducer of glial fate in the peripheral nervous system (PNS) and the CNS of both *Drosophila* and vertebrates [2,39,40,41]. Recent work has demonstrated that Notch activation in CNS progenitor cells results in a radial glial identity, which is of particular interest with regards to the role of radial glia as neuronal precursor cells [39].

With respect to factors that control the fate of asymmetrically dividing cells, the best candidate to date is the protein Numb. Both *in vitro* and *in vivo* genetic loss-of-function analyses have suggested that the asymmetric segregation of Numb determines cell identity in the nervous system [42,43,44,45••,46]. Our understanding of the role of this protein in mammals has been complicated by the fact that it appears to differ during progressive phases of neurogenesis. Loss-of-function analysis suggests that Numb acts to prevent differentiation in early neurogenesis [47•], whereas recent *in vitro* studies suggest that Numb can promote cells to adopt a neuronal identity during later neurogenesis [45••]. It is not particularly surprising that the role of intrinsic determinants varies according to both lineage and time during development. Indeed, the outcome of Notch signaling is also context dependent. For example, as discussed above, Notch signaling promotes progenitors to adopt a radial glial identity during neurogenesis [39]. Notch also plays a central role in the differentiation of oligodendrocytes, and regulates both dendritic and axonal growth in differentiating neurons [48–50].

Many aspects of Numb's function in determining cell fate remain unclear. At present, *in vivo* data that support the idea that Numb directs progenitors to adopt a neuronal fate during cortical neurogenesis has been lacking. Even whether Numb is localized to the apical or basal side of VZ cells has varied according to the species examined. Studies in mice have found that Numb is localized in the apical VZ [44], whereas other studies have found that it is located basally in chicks [51]. The evidence now suggests that the primary progenitor population during cortical development are radial glia [25•], however, the dynamics of asymmetric cell division in this population are still uncertain.

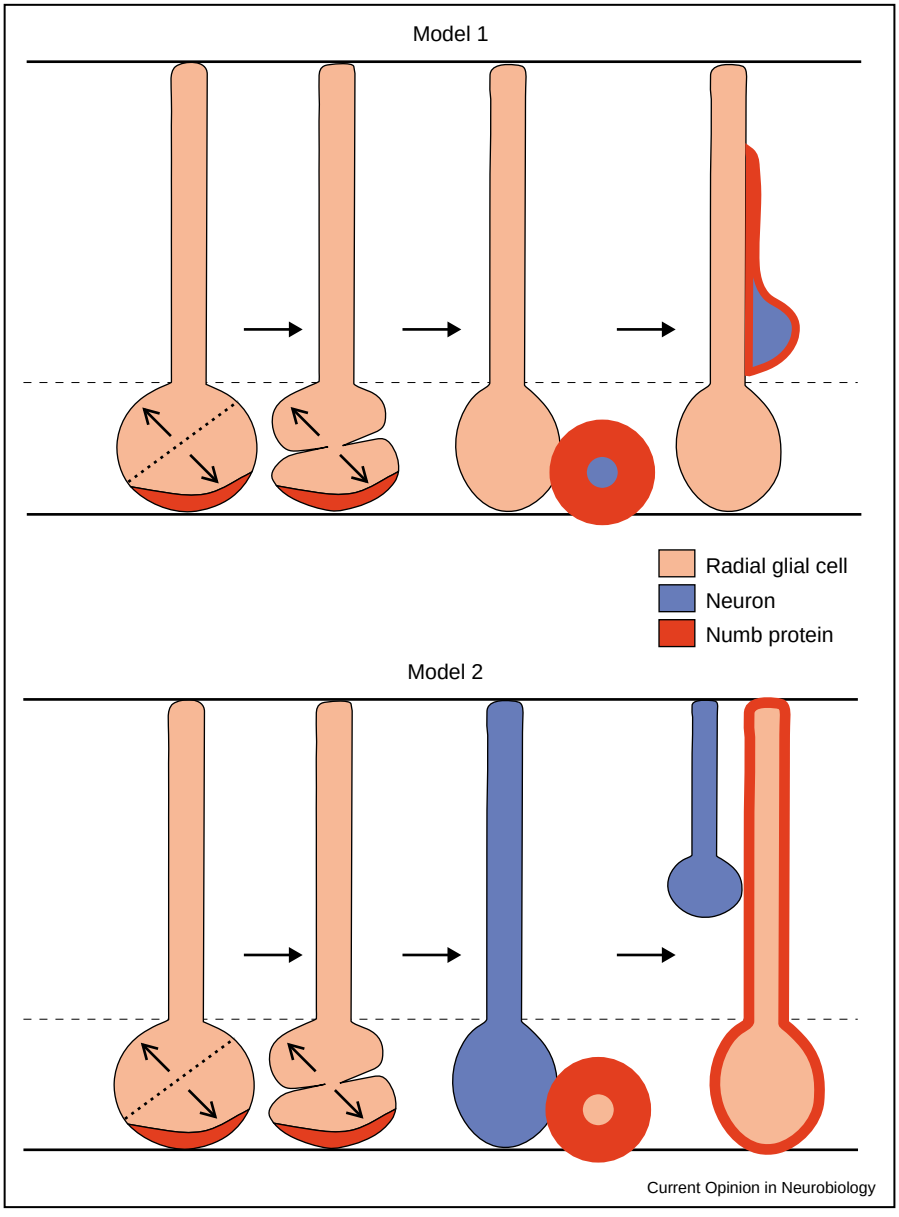
To simplify matters, we will focus only on the situation in mice, in which Numb is thought to be localized to the apical ventricular zone. Notably, time-lapse analysis of cell divisions in the cortex suggest that the plane of cell division during neurogenesis cannot be neatly divided into horizontal or vertical cell divisions [26,52]. Despite this, one might predict that the more basal cell in an asymmetric division is more likely to inherit the radial fibre, whereas the more apical cell is more likely to inherit the majority of the Numb protein. Following this line of reasoning, one can envision two scenarios that differ with regard to which of the two asymmetric progeny inherits the majority of the Numb protein. These two models make opposite predictions of how Numb directs neuronal fate during development (Figure 3). If, as Miyata *et al.* [22•] suggest, the postmitotic neuron inherits the radial process, one would imagine that the radial glial cell inherits most of the Numb protein. In contrast, if the radial glial cell maintains possession of the fibre during asymmetric divisions, the neuronal offspring would sequester the majority of Numb protein. Clearly these two outcomes imply different roles for Numb. If one assumes that Numb is acting instructively in mammals, as it does in *Drosophila*, the first scenario predicts that Numb inhibits neuronal differentiation, whereas the latter scenario predicts that Numb promotes neuronal identity (Figure 3). At present, insufficient data exists to determine the precise role of Numb. Indeed, given *in vitro* data, which suggest that Numb's role changes according to the stage of development, it remains possible that both outcomes occur. This would suggest that Numb inheritance is either stochastic or dependent upon additional factors that remain unidentified.

Adult neuronal stem cell populations

At the beginning of neurogenesis, the CNS is almost entirely composed of stem cell progenitors, whereas at the end of neurogenesis the CNS is characterized by a near absence of stem cell progenitors (Figure 4). Despite the fact that the vast majority of neurons in the brain are postmitotic by birth, it is now clear that pockets of neural stem cells persist throughout life within the hippocampus and olfactory bulb, and perhaps even more broadly [53–56]. The fact that adult neurogenesis is confined to small populations of stem cells within restricted regions has direct implications for the regulation of this process. It is clear that these regions of neurogenesis represent unique niches and, as such, are as highly specialized as their counterparts in the ovary, testis and skin. Recent work [57] (AP McMahon, G Fishell, unpublished data) has shown that the morphogen Sonic Hedgehog is essential for the maintenance of these niches in the perinatal brain. Presently, we have only a rudimentary general understanding of the molecular basis by which these niches are maintained.

The cell types and cytoarchitecture of stem-cell niches in the adult brain are better understood than those in the immature brain. Recent work from the Gage and Alvarez-Buylla laboratories (reviewed in [54,58•]) has defined

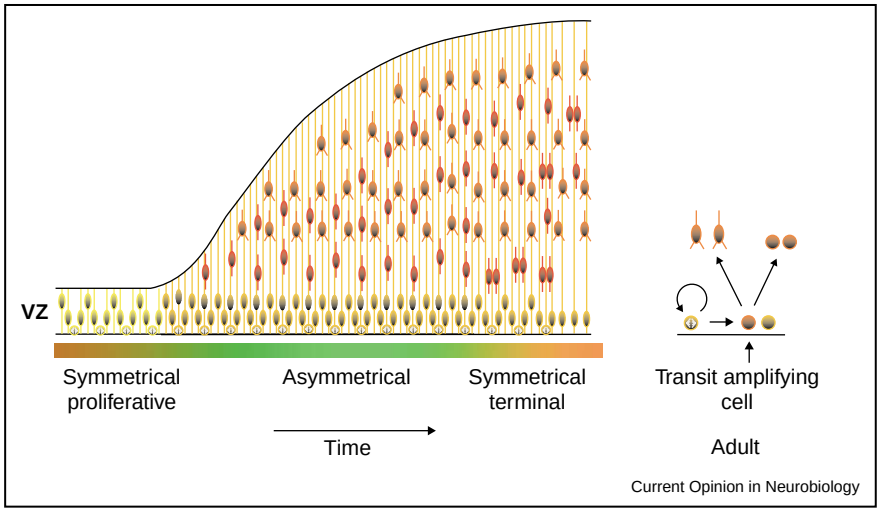
Figure 3



Two models of asymmetric divisions in the cerebral cortex. Two models are proposed for asymmetric cell divisions of neurogenic radial glial cells on the basis of the apical localization of Numb protein and maintenance of the radial glial fiber during mitosis. In Model 1, the radial glial cell inherits the radial fiber and the daughter neuron inherits Numb. In Model 2, the neuron inherits the radial glial fiber (and translocates to the cortex) whereas the radial glial cell inherits Numb.

both the cell types that participate in adult neurogenesis and the specialized environment in which they reside [59,60]. Proliferating cells in these areas require a strategy that must balance the need to generate large numbers of newborn neurons with the need to maintain the founder stem-cell population. It appears that the cellular mechanisms used to achieve this are similar to those used in other tissue types, perhaps most notably the haematopoietic system. Two distinctly different populations of progenitor cells appear to contribute to adult neurogenesis: the stem cells proper and intermediate transit amplifying cells. To maintain a population of progenitor cells, the stem cells proper must restrict themselves largely or completely to asymmetric cell divisions. The generation of the considerable numbers of neurons required to form a nervous system is left to the daughter population of transit amplifying cells, which have arisen from stem cells (Figure 4). They divide symmetrically to generate large populations of transit amplifying cells that ultimately undergo a terminal division to give rise to two newly born neurons. By

Figure 4



Patterns of neurogenic cell divisions in embryonic and adult cortex. Before neurogenesis, symmetrical divisions serve only to increase the precursor pool, but during neurogenesis asymmetrical divisions generate neurons. As neurogenesis proceeds, terminal symmetric divisions also contribute to neuronal production, particularly near the end of neurogenesis [62]. In areas of adult neurogenesis, 'stem cells' undergo asymmetric divisions to generate intermediate 'transit amplifying cells', which then undergo symmetrical divisions to generate neurons.

partitioning progenitors into stem cells and transit amplifying cells, the relatively small stem-cell niches are able to continuously produce extraordinary numbers of postmitotic cells. It is intriguing to speculate on the mechanisms by which adult stem cells self-renew while simultaneously giving rise to a daughter transit amplifying cell. It is quite possible that, similar to the asymmetric divisions seen in radial glia during embryonic development, the unequal inheritance of Numb may contribute to the asymmetric divisions in adult stem cells.

Conclusions

Our understanding of neurogenesis has come a long way from the days when 'germ cells' and 'spongioblasts' were thought to mysteriously give rise to the CNS. The progression from neuroepithelium to radial glia to adult stem cell is now well characterized, as are the dynamics of the asymmetric cell divisions. Similarly, genetic studies in *Drosophila* have provided excellent candidate genes for exploring the molecular basis of this process in mammals. Although the precise role of these genes in vertebrates is yet to be discovered, it seems likely that they will ultimately emerge as some of the key intrinsic determinants that direct asymmetric cell divisions in the brain. Nonetheless, the outstanding challenges remain considerable, and include determining the heterogeneity of neural progenitors.

Even assuming that radial glia comprise the entire cortical-progenitor population, work from several laboratories [17,61] suggests that there are several subtypes of radial glial cells whose numbers change in both space and time during development. It will be important to reveal the degree of heterogeneity in radial glial cells, and the extent to which different populations of radial glia vary in both their mode of cell division and the cells they produce. With regard to the molecular basis of asymmetric cell divisions, it seems certain that other intrinsic determinants beyond Numb act to direct neural cell fate. Furthermore, both the nature of the information bestowed by determinants such as Numb and whether their activity is stochastic or influenced by other epigenetic factors are not yet clear. The outline of the problem has, however, now been clarified. Radial glial cells appear to be an important source of neurons in the developing cortex and are lineally related to adult neural stem cells. During neurogenesis at least, their mode of division is likely to be primarily asymmetric. On the basis of these insights, future work can now focus on how the asymmetric inheritance of fate determinants and epigenetic signals combine to direct cell fate during neurogenesis.

Acknowledgements

We thank T. Weissman and M. Götz for helpful comments.

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