THE CELL BIOLOGY OF NEUROGENESIS

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Abstract | During the development of the mammalian central nervous system, neural stem cells and their derivative progenitor cells generate neurons by asymmetric and symmetric divisions. The proliferation versus differentiation of these cells and the type of division are closely linked to their epithelial characteristics, notably, their apical–basal polarity and cell-cycle length. Here, we discuss how these features change during development from neuroepithelial to radial glial cells, and how this transition affects cell fate and neurogenesis.

DEVELOPMENTAL CELL BIOLOGY

MACROGLIAL CELLS
Collective term for astrocytes, oligodendrocytes and Schwann cells.

ASTROCYTES
The main type of glial cell, which has various supporting functions, including participating in the formation of the blood–brain barrier. A subpopulation of astrocytes functions as adult neural stem cells.

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During development, neural stem cells give rise to all the neurons of the mammalian central nervous system (CNS). They are also the source of the two types of MACROGLIAL CELL in the CNS — ASTROCYTES and OLIGODENDROCYTES[1–5]. Usually, two criteria are applied to define a cell as a stem cell — self-renewal, ideally for an unlimited number of cell divisions, and multipotency, that is, the ability to give rise to numerous types of differentiated cell. However, as it is not clear to what extent multipotent stem cells exist during the development of the CNS[1–3,5–16], we use the term stem cells here to describe neural cells that are self-renewing, but not necessarily for an unlimited number of cell divisions, and that might be multipotent or unipotent.

The self-renewal of neural stem cells can occur either by symmetric cell divisions, which generate two daughter cells with the same fate, or by asymmetric cell divisions, which generate one daughter cell that is identical to the mother cell and a second, different cell type. Notably, during development, neuroepithelial cells, which can be considered stem cells, first undergo symmetric, PROLIFERATIVE DIVISIONS, each of which generates two daughter stem cells[17,18]. These divisions are followed by many asymmetric, self-renewing divisions, each of which generates a daughter stem cell plus a more differentiated cell such as a NON-STEM-CELL PROGENITOR or a neuron (FIG. 1). Neural non-stem-cell progenitors typically undergo symmetric, differentiating divisions, each of which generates two neurons — terminally differentiated, postmitotic cells. These types of division were first deduced from retroviral cell-lineage-tracing experiments[19–25] and were subsequently shown directly in live time-lapse observations with brain slices[26–31] and isolated cells *in vitro*[32–37].

This review mainly discusses the cell-biological basis of the symmetric versus asymmetric division of neural stem and PROGENITOR CELLS, concentrating on the developing CNS of rodents (from which most of the available data were derived) and focusing on issues such as CELL POLARITY, CLEAVAGE-PLANE ORIENTATION, apical cell constituents, INTERKINETIC NUCLEAR MIGRATION and cell-cycle length. Before addressing these issues, we first briefly describe the main categories of neural stem and progenitor cells, as well as some of their basic cell-biological features.

Neural stem and progenitor cells

Neuroepithelial cells. Before neurogenesis, the NEURAL PLATE and NEURAL TUBE are composed of a single layer of cells, neuroepithelial cells, which form the neuroepithelium. The neuroepithelium looks layered ('pseudostratified'), because the nuclei of neuroepithelial cells migrate up and down the apical–basal axis during the cell cycle (interkinetic nuclear migration; see below and FIG. 2a). Neuroepithelial cells show typical epithelial features and are highly polarized along their apical–basal axis, as is obvious from the organization of their plasma membrane[38,39] (FIG. 2a). Certain transmembrane proteins such as prominin-1 (CD133) are selectively found in the apical plasma membrane[40,41];

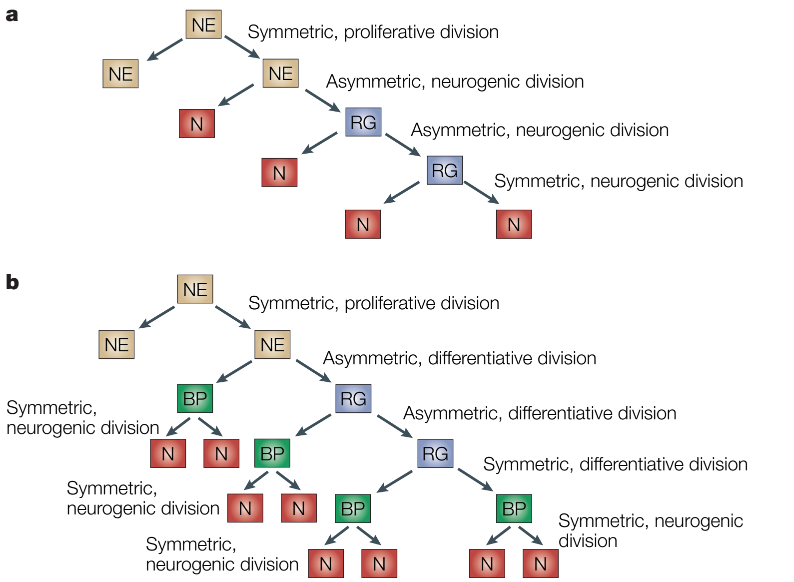

Figure 1 | **Lineage trees of neurogenesis.** The lineage trees shown provide a simplified view of the relationship between neuroepithelial cells (NE), radial glial cells (RG) and neurons (N), without (**a**) and with (**b**) basal progenitors (BP) as cellular intermediates in the generation of neurons. They also show the types of cell division involved.

TIGHT JUNCTIONS and ADHERENS JUNCTIONS are present at the most apical end of the lateral plasma membrane[42–44]; and receptors for basal lamina constituents such as integrin α_6 are concentrated in the basal plasma membrane, which contacts the basal lamina[39]. The apical–basal polarity of neuroepithelial cells seems to require the integrity of adherens junctions. Knocking out the adherens-junction-associated protein afadin, also known as AF6, perturbs the polarized organization of these cells[43].

Radial glial cells. With the generation of neurons, the neuroepithelium transforms into a tissue with numerous cell layers, and the layer that lines the ventricle (the most apical cell layer that contains most of the progenitor cell bodies) is referred to as the ventricular zone (FIG. 2b). With the switch to neurogenesis, neuroepithelial cells downregulate certain epithelial features, notably tight junctions (but not adherens junctions, nor ZO1 (zona occludens-1), which in the absence of tight junctions seems to associate with adherens junctions)[42] and the apical-versus-basal polarity of delivery of certain plasma-membrane proteins[45]. Concomitantly, ASTROGLIAL hallmarks appear. In essence, after the onset of neurogenesis, neuroepithelial cells give rise to a distinct, but related, cell type — radial glial cells — which exhibit residual neuroepithelial as well as astroglial properties[36,38,46,47]. Radial glial cells represent more fate-restricted progenitors than neuroepithelial cells[48,49] and successively replace the latter. As a consequence, most of the neurons in the brain are derived, either directly or indirectly, from radial glial cells[50,51].

The neuroepithelial properties that are maintained by radial glial cells include: the expression of neuroepithelial markers such as the intermediate-filament protein nestin[52]; the maintenance of an apical surface and important features of apical–basal polarity such as an apical localization of centrosomes[53] and prominin-1 (REF. 40); the presence, at the apical-most end of the lateral plasma membrane, of adherens junctions, proteins that associate with adherens junctions in the absence of tight junctions such as ZO1, and proteins that are associated with the apical cell cortex such as PAR3 (partitioning defective protein-3)/PAR6/aPKC (atypical protein kinase C)[39,42]; and the basal lamina contact[54] (TABLE 1). Like neuroepithelial cells, radial glial cells show interkinetic nuclear migration, with their nuclei undergoing mitosis at the apical surface of the ventricular zone and migrating basally for S phase of the cell cycle (FIG. 2b). However, whereas in neuroepithelial cells the nuclei migrate through the entire length of the cytoplasm (FIG. 2a), this is not the case in radial glial cells (FIG. 2b; see below).

In contrast to neuroepithelial cells, radial glial cells show several astroglial properties. An ultrastructural characteristic of astroglial cells, GLYCOGEN GRANULES[55], and various molecules that are characteristic of astrocytes — such as the astrocyte-specific glutamate transporter (GLAST), the Ca^{2+}-binding protein S100β, glial fibrillary acidic protein (GFAP), vimentin and brain-lipid-binding protein (BLBP) — start to appear in most ventricular zone cells during, but not before, neurogenesis[36,46,47] (T. Mori and M.G., unpublished observations). In mice, this transition occurs throughout most of the brain between embryonic day 10 (E10), when no astroglial markers can yet be detected, and E12, when most CNS regions are dominated by progenitor cells that are expressing several of these astroglial features[52,56] (FIG. 3).

Radial glial-cell appearance and cell fate restriction. In terms of potential, in contrast to early neuroepithelial cells, most radial glial cells are restricted to the generation of a single cell type, either astrocytes, oligodendrocytes or — as in most cases in neurogenesis — neurons[22,27–29,35,48–50,56–59]. This fate restriction is less often present in neuroepithelial cells and seems to correlate with the appearance of radial glial-cell properties. Therefore, transgenic mouse cell lines in which part of the nestin promoter or the regulatory element of the *Blbp* gene was used to drive the expression of the Cre-recombinase gene at early embryonic stages, such as E9/10 (REF. 60), mediated recombination before the appearance of radial glial features, and the recombined genes were found in all CNS cells[51]. In contrast, when the Cre-recombinase gene was under the control of the human *GFAP* promoter, recombination occurred at the time of radial glial-cell differentiation[50]. In this case, the progeny that inherited the recombination from radial glial cells was more restricted in terms of cell identity (for example, mostly glial cells were derived from radial glial cells in the ventral TELENCEPHALON[50]). Taken together, recombination-mediated fate mapping

OLIGODENDROCYTES
Glial cells of the central nervous system that form the myelin sheath.

PROLIFERATIVE DIVISION
A division of stem or progenitor cells that results in a doubling of their number, that is, one stem cell divides into two identical stem cells or one progenitor cell divides into two identical progenitor cells.

NON-STEM-CELL PROGENITORS
Cells that are able to generate differentiated cells such as neurons but that are unable to self-renew.

PROGENITOR CELLS
Collective term for stem cells and non-stem-cell progenitors.

CELL POLARITY
The polarized organization that is characteristic of many cells, notably epithelial cells, which have a basal and an apical side.

CLEAVAGE-PLANE ORIENTATION
The orientation of the cell-division plane, which in polarized cells can be orientated parallel to the axis of cell polarity, perpendicular to this axis or at any angle in between.

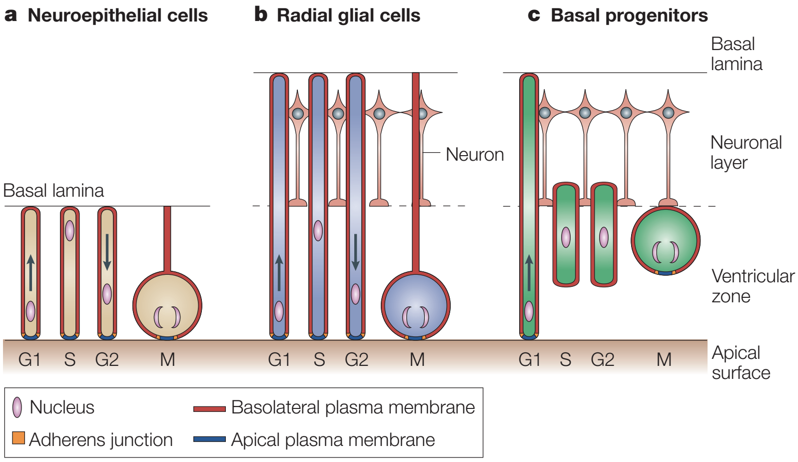

Figure 2 | **Polarized features of neuroepithelial cells, radial glial cells and basal progenitors.** The figure summarizes the polarized organization and interkinetic nuclear migration of neuroepithelial cells, radial glial cells and basal progenitors. **a** | In neuroepithelial cells, interkinetic nuclear migration spans the entire apical–basal axis of the cell, with the nucleus migrating to the basal side during G1 phase, being at the basal side during S phase, migrating back to the apical side during G2 phase, and mitosis occuring at the apical surface. **b** | In radial glial cells, the basally directed interkinetic nuclear migration does not extend all the way to the basal side (that is, through the neuronal layer to their pial end-feet), but is confined to the portion of the cell between the apical surface and the basal boundary of the ventricular zone or the subventricular zone (not shown). **c** | In basal progenitors, the nucleus migrates from the apical surface to the basal boundary of the ventricular zone (dashed line) or subventricular zone (not shown) for S phase and mitosis, and this is concomitant with the retraction of the cell from the apical surface[31]. Note the maintenance of basal processes by neuroepithelial and radial glial cells during mitosis[27,28].

INTERKINETIC NUCLEAR MIGRATION
The apical-to-basal and subsequent basal-to-apical migration of the cell nucleus during the cell cycle of epithelial, notably neuroepithelial, cells.

NEURAL PLATE
The neuroectodermal epithelium before the formation of the neural groove and neural tube.

NEURAL TUBE
The neuroectodermal epithelium after the closure of the neural groove.

TIGHT JUNCTIONS
Cell–cell junctions between epithelial cells at the apical-most end of the lateral membrane. These junctions prevent the lateral diffusion of integral membrane constituents between the apical and lateral plasma-membrane domains and the passage of extracellular compounds from the apical to the basal extracellular space and vice versa.

reveals a broad range of progeny from early neuroepithelial cells, but a more restricted progeny from radial glial cells. Similarly, a broader potential (including *in vivo* evidence for a tripotent progenitor that generated neurons, astrocytes and oligodendrocytes) was also observed in retrovirus-mediated cell-lineage experiments that were carried out at neuroepithelial-cell stages[58] compared to radial glial-cell stages. At the radial glial-cell stages most of the infected progenitors generated only a single cell type[22,59].

As summarized in FIG. 3, progenitors in the retina and spinal cord differ from those in the brain in that they mainly maintain neuroepithelial-cell properties or only partially develop radial glial-cell features during neurogenesis. Interestingly, retinal and spinal-cord progenitors have a broader developmental potential throughout neurogenesis than those in the brain[61–63]. So, there seems to be a link between the transition from a neuroepithelial cell to a radial glial cell and changes in fate restriction, which is consistent with the notion that radial glial cells represent a differentiated progeny of neuroepithelial cells.

Basal/subventricular-zone progenitors. Besides radial glial cells, another type of neuronal progenitor appears at the onset of neurogenesis — the so-called basal progenitor[29–31,64]. Basal progenitors are distinguished from neuroepithelial and radial glial cells, the nuclei of which undergo mitosis at the apical surface of the neuroepithelium/ventricular zone (FIG. 2a,b), by the fact that their nuclei undergo mitosis at the basal side of the ventricular zone[29–31] (FIG. 2c). Basal progenitors originate from the mitosis of neuroepithelial and radial glial cells at the apical surface of the neuroepithelium/ventricular zone. Concomitantly with the migration of their nucleus to the basal side of the neuroepithelium/ventricular zone for S phase, they subsequently retract their extension to the apical surface[31] (FIG. 2c). It remains to be seen to what extent basal progenitors retain apical–basal polarity. During later stages of neurogenesis, basal progenitors form the subventricular zone , a mitotic cell layer that is basal to the ventricular zone and that exists in certain regions of the mammalian brain, notably, in the telencephalon where basal progenitors are most abundant[30]. Basal/subventricular-zone progenitors differ from neuroepithelial and radial glial cells in terms of the genes they express — for example, they specifically express the non-coding RNA *SVET1* (REF. 65) and the genes that encode the transcription factors TBR2 (REF. 66), CUX1 and CUX2 (REFS 67,68). Basal/subventricular-zone progenitors have recently been found to contribute to neurogenesis by undergoing symmetric cell divisions that generate two neuronal daughter cells[29,30] (FIG. 1b). Therefore, basal/subventricular-zone progenitors might function to increase the number of neurons that are generated from a given number of apical/ventricular-zone progenitors by allowing a further round of cell division to occur that is distant from the apical surface[30]. This concept, originally proposed by Smart *et al.*, is also supported by the correlation between the increase in the size of the subventricular zone and the increase in the number of neurons in the cerebral cortex during phylogeny[69].

Cell biology of stem-cell division

The apical–basal polarity of neuroepithelial and radial glial cells is an important basis for their symmetric versus asymmetric division, as defined by an equal versus unequal distribution, respectively, of cellular constituents to the daughter cells (rather than an equal versus unequal cell fate)[38,39]. By analogy to the proliferative versus NEUROGENIC DIVISIONS in *Drosophila melanogaster*[39,70,71], it has been proposed that cleavage planes that are orientated in the radial dimension of the ventricular zone (vertical cleavages) result in symmetric, proliferative divisions of neuroepithelial and radial glial cells, because crucial apical and basal constituents will be distributed equally to the daughter cells (FIG. 4a). On the other hand, cleavage planes that are parallel to the apical surface of the ventricular zone (horizontal cleavages) result in asymmetric, neurogenic divisions, because the apical constituents will be inherited by one daughter cell and the basal constituents by the other[26] (FIG. 4b). However, horizontal cleavages are rare[64,72,73], so this concept has been modified to explain why vertical cleavages can also give rise to asymmetric, neurogenic divisions[38]. Importantly, the apical plasma membrane of neuroepithelial and radial glial cells represents

Table 1 | **Comparison of the properties of neuroepithelial and radial glial cells**

Property	Neuroepithelial cells	Radial glial cells
Interkinetic nuclear migration	Apical–basal	Apical–basal to the boundary of the ventricular or subventricular zone
Apical surface	Present	Present
Apical–basal polarity	Present	Present, but downregulated
Tight junctions	Present (early stages)	Absent
Adherens junctions	Present	Present
Basal lamina contact	Present	Present
Nestin expression	Present	Present
Astroglial markers	Absent	Present
Tis21 expression*	Confined to the neurogenic subpopulation	Present in the neurogenic subpopulation
Neurogenesis	First phase	Subsequent phases

*The antiproliferative gene *Tis21* is a molecular marker that is selectively expressed in virtually all neuroepithelial cells that are about to undergo a neurogenic division, but not in proliferating neuroepithelial cells[74].

only a tiny fraction (1–2%) of their total plasma membrane[38,73]. So, it was postulated[38], and recently shown[73], that vertical cleavage planes of neuroepithelial and radial glial cells can either bisect (FIG. 4a) or bypass (FIG. 4c) the apical plasma membrane and the junctional complexes that are found at the most apical end of the lateral plasma membrane. This results in their inheritance by either both or only one of the daughter cells and therefore in either symmetric (FIG. 4a) or asymmetric (FIG. 4c) division, respectively.

Are such symmetric divisions of neuroepithelial and radial glial cells proliferative (that is, do they expand the progenitor pool) and are such asymmetric divisions neurogenic? Given that proliferative and neurogenic divisions of neuroepithelial cells coexist in the same region of the ventricular zone, an answer to this question only became possible after the identification of the first molecular marker that is selectively expressed in essentially all neuroepithelial cells that are about to undergo a neurogenic division, but not in proliferating neuroepithelial cells[74]. This marker is an antiproliferative gene called *Tis21* (REF. 74). Analysis of knock-in mouse embryos that expressed green fluorescent protein (GFP) from the *Tis21* locus[30] showed that more than 80% of the mitotic neuroepithelial cells that were distributing apical plasma membrane to both daughter cells were not yet expressing *Tis21* and therefore underwent proliferative divisions. On the other hand, almost 90% of the mitotic neuroepithelial cells that were distributing the apical plasma membrane to only one daughter cell were expressing *Tis21* and underwent neurogenic divisions. More than 85% of these cells showed a vertical cleavage plane[73]. Furthermore, extending previous time-lapse video-microscopy studies, which showed that neurogenic divisions of radial glial cells at the ventricular surface are asymmetric — in that they generate one neuron and one radial glial cell[27,28] (FIG. 1a) — multiphoton imaging of the progeny of the *Tis21*-expressing neuroepithelial cells showed that their daughter cells behaved differently. This is consistent with one becoming a neuron and the other remaining a neuroepithelial cell[30]. Taken together, these observations show that vertical cleavages can give rise to asymmetric, neurogenic divisions of neuroepithelial cells, as was previously reported for the much less frequently occurring horizontal cleavages[26].

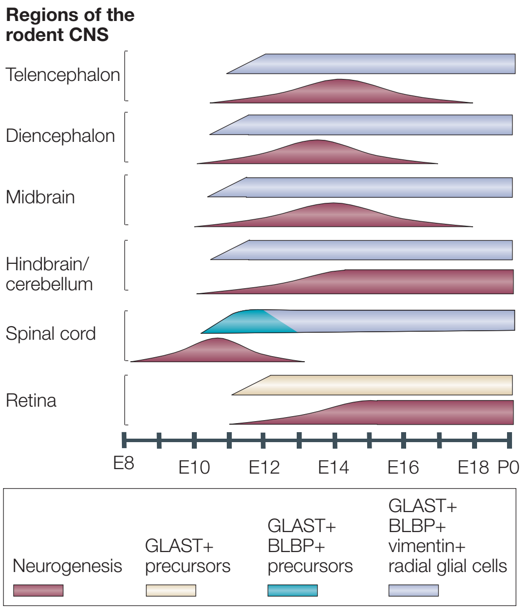

Figure 3 | **Neurogenesis and radial glial cells.** The figure summarizes the time course of neurogenesis and the appearance of radial glial cells in various regions of the rodent central nervous system (CNS). It should be noted that the appearance of astroglial features — the astrocyte-specific glutamate transporter (GLAST), brain-lipid-binding protein (BLBP) and vimentin — correlates with the onset of neurogenesis in almost all regions of the developing CNS. The two notable exceptions are the retina and the spinal cord, which maintain neuroepithelial features during neurogenesis. Interestingly, the appearance of astroglial features also correlates with a fate restriction of the progenitors. E, embryonic day; P0, postnatal day 0 (day of birth).

ADHERENS JUNCTIONS
Cell–cell junctions that exert an anchoring function and that in epithelial cells are found at the apical end of the lateral membrane just below tight junctions.

ASTROGLIAL CELLS
Term for cells that exhibit the properties of astrocytes.

GLYCOGEN GRANULES
Storage sites for glycogen in cells, notably, radial glial cells.

TELENCEPHALON
The most anterior, rostral part of the brain, which includes the cerebral cortex.

NEUROGENIC DIVISIONS
Divisions of stem or progenitor cells in which either one or both of the daughter cells are neurons.

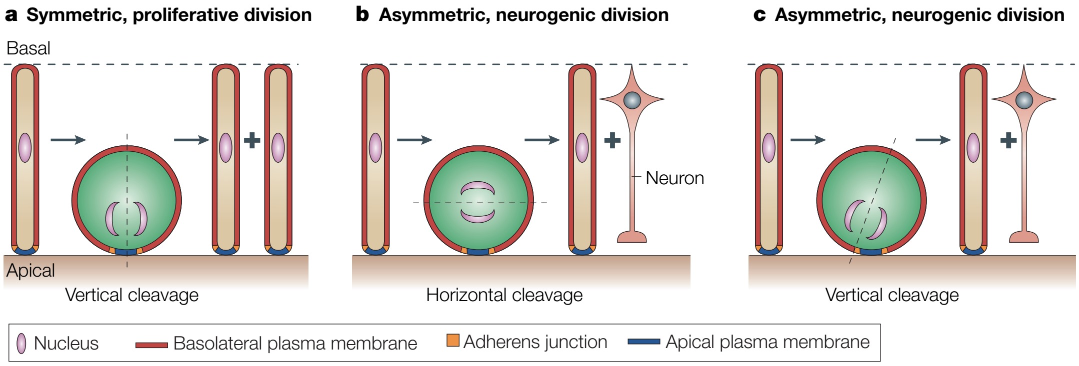

Figure 4 | **Symmetric versus asymmetric division of neuroepithelial and radial glial cells.** The figure summarizes the relationship between apical–basal polarity, cleavage-plane orientation and the symmetric, proliferative versus asymmetric, neurogenic division of neuroepithelial and radial glial cells. For the apical–basal polarity of the plasma membrane, please refer to the key. **a** | Vertical cleavage results in a symmetric, proliferative division. **b** | Horizontal cleavage results in an asymmetric, neurogenic division. **c** | Vertical cleavage results in an asymmetric, neurogenic division. It should be noted that the basal processes that are maintained during mitosis[27,28] (FIG. 2) have been omitted for clarity.

In light of the observation that the apical plasma membrane constitutes only a minute fraction of the total plasma membrane of neuroepithelial cells[73], the cellular machinery responsible for determining the orientation of the cleavage plane must operate with remarkable precision to ensure the bisection of the apical plasma membrane that seems to be required for a symmetric, proliferative division. The transcription factor EMX2 promotes not only a vertical cleavage-plane orientation, but also symmetric, proliferative cell divisions[75]. By contrast, the transcription factor PAX6 promotes asymmetric, neurogenic cell divisions[76]. These transcription factors therefore regulate cell fate and the appropriate mode of cell division in a coordinated manner, but the underlying mechanisms remain to be elucidated.

Extrapolating from other cell systems[77], the primary feature that determines neuroepithelial cleavage-plane orientation will probably be the positioning of the poles of the MITOTIC SPINDLE. As in other systems[77], the spindle poles in mitotic neuroepithelial and radial glial cells seem to oscillate around their final positions before anaphase[78], but little more is known about the mechanism that underlies spindle-pole positioning in mammalian neuroepithelial and radial glial cells. However, by analogy with other polarized cells[79], it seems probable that a spindle-pole position that is exactly perpendicular to the apical–basal axis of the neuroepithelial cell, and is required for the bisection of the apical plasma membrane and symmetric division, will be based, eventually, on the apical–basal polarity of the neuroepithelial-cell plasma membrane. It is therefore interesting to note that neuroepithelial-cell plasma-membrane polarity is downregulated before the onset of neurogenesis[45], which perhaps allows for a greater variability in spindle-pole positioning and thereby promotes the occurrence of asymmetric, neurogenic cell divisions.

Two further points should be made in this context. The first concerns the *ASPM* (abnormal spindle-like microcephaly-associated) gene, which is a crucial determinant of cerebral cortical size[80]. The evolution of the *ASPM* gene has been implicated in the expansion of the primate brain[81], and mutations in the human *ASPM* gene cause a reduction in the volume of the cerebral cortex, which is known as PRIMARY MICROCEPHALY[80,82]. Extrapolating from the role of the *D. melanogaster* ASPM orthologue in the organization of microtubules at the spindle poles, it has been proposed that subtle changes in mitotic spindle orientation, which reflect evolutionary changes in the ASPM protein, might alter the proportion of symmetric, proliferative versus asymmetric, neurogenic divisions of neuroepithelial and radial glial cells[80,81]. Remarkably, only a subtle change in the orientation of the mitotic spindle is required to shift the plane of cell division from bisecting the apical plasma membrane to bypassing it[73].

Second, the observation that the apical plasma membrane constitutes only a tiny fraction of the total plasma membrane of mitotic neuroepithelial cells[73] has an important implication with regards to the machinery that controls spindle-pole positioning. Specifically, a reduction in the precision of spindle-pole positioning relative to the apical–basal axis of neuroepithelial cells might be sufficient to result, by default, in the cleavage plane bypassing (rather than bisecting) the apical plasma membrane, and might therefore lead to asymmetric division.

Although the position of the mitotic spindle determines the overall orientation of the CLEAVAGE FURROW, it is the fusion of the plasma membrane on completion of CYTOKINESIS that finally determines whether both or only one of the daughter cells inherits the apical plasma membrane (FIG. 5). In neuroepithelial and radial glial cells, the formation of the cleavage furrow proceeds from the basal to the apical surface[73]. Cytokinesis that results in the inheritance of the apical plasma membrane by both daughter cells — that is, in a symmetric division — implies that there is

MITOTIC SPINDLE
A microtubule-based structure that originates from the two centrosomes and that segregates the chromosomes during mitosis.

PRIMARY MICROCEPHALY
A neurodevelopmental disorder that is anatomically characterized by a small but architecturally normal brain, with the cerebral cortex showing the greatest reduction in size.

CLEAVAGE FURROW
The invagination of the plasma membrane during cell division that ultimately leads to cell fission.

CYTOKINESIS
The division of the cytoplasm, which follows nuclear division (mitosis) and completes the process of cell division.

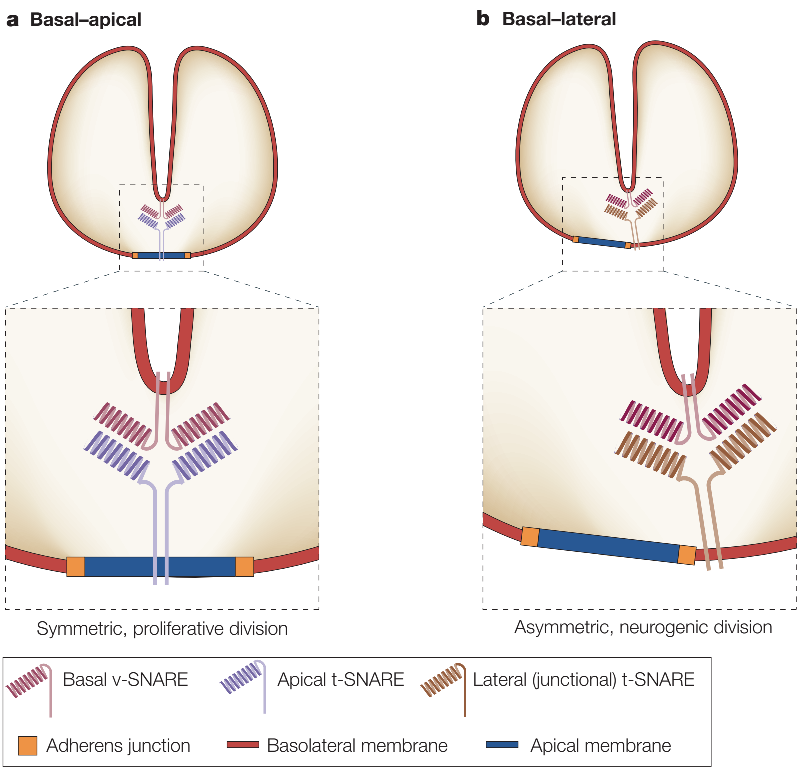

Figure 5 | **SNARE control of the symmetric versus asymmetric division of neuroepithelial and radial glial cells. a** | The symmetric, proliferative division of neuroepithelial and radial glial cells involves heterophilic, basal–apical SNARE-mediated plasma-membrane fusion to complete cytokinesis. **b** | By contrast, the asymmetric, neurogenic division of neuroepithelial and radial glial cells involves homophilic, basal–lateral SNARE-mediated plasma-membrane fusion. Please refer to the key for the plasma-membrane domains and v- and t-SNAREs involved. SNARE, soluble *N*-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptor; t, target membrane; v, vesicle membrane.

SNARE PROTEINS
(soluble *N*-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptor proteins). Integral membrane proteins in various cellular membranes that interact with one another during membrane fusion.

APICAL CELL CORTEX
The apical plasma membrane plus the cytoplasmic components that are associated with it.

BASAL PROCESS
A process of neuroepithelial and radial glial cells that extends from the perikaryon (the cell body that contains the nucleus and many organelles) to the basal lamina.

fusion of the basal with the apical plasma membrane (heterophilic fusion; FIG. 5a). By contrast, cytokinesis that results in the inheritance of the apical plasma membrane by only one daughter cell — that is, in an asymmetric division — implies that the basal membrane fuses with the lateral plasma membrane (near the junctional complexes in the case of a vertical cleavage), which can be considered homophilic fusion within the basolateral plasma-membrane domain (FIG. 5b). It is interesting to note that in polarized epithelial cells, SNARE PROTEINS, which mediate plasma-membrane fusion in cytokinesis[83–86], show a polarized distribution, with certain SNAREs being selectively found in either the apical or the basolateral plasma membrane, and within the basolateral plasma-membrane domain they are often concentrated in the junctional region[87,88]. In light of the specificity of SNARE-mediated membrane fusion[89,90], it is reasonable to suggest the hypothesis that the symmetric versus asymmetric division of neuroepithelial and radial glial cells involves the control of basal–apical versus basal–lateral SNARE-mediated plasma-membrane fusion, respectively (FIG. 5).

In this context, it is interesting to note that a member of the SNARE-mediated membrane-fusion machinery has recently been found to be involved in the control of cell fate determination in neuroepithelial cells[91]. In *hyh* (hydrocephalus with hop gait) mice, which carry a hypomorphic missense mutation in the gene encoding α-SNAP (α-soluble *N*-ethylmaleimide-sensitive fusion protein (NSF) attachment protein), neuronal progenitors apparently switch prematurely from proliferative to neurogenic divisions[91]. This was proposed to be due to impaired apical membrane traffic and impaired apical protein localization[91], which is in line with the general requirement for Golgi-derived membrane traffic for neuronal progenitor proliferation[92]. Perhaps, however, there is also impaired basal–apical membrane fusion during cytokinesis and therefore less proliferative divisions of *hyh* neuroepithelial and radial glial cells.

Apical and adherens-junction proteins

Given the equal versus unequal distribution of the apical plasma membrane for the symmetric, proliferative versus the asymmetric, neurogenic division of neuroepithelial and radial glial cells[73], it is reasonable to postulate that the inheritance of the apical plasma membrane (including the associated APICAL CELL CORTEX), and, presumably, the apical-most junctional complexes, contributes to the daughter cell remaining in the cell cycle, whereas the lack of this inheritance contributes to the daughter cell becoming a neuron. Below, we focus on candidate apical/junctional cell constituents that are crucial for neuroepithelial-cell and radial glial-cell proliferation. However, it should be emphasized that inheritance of the BASAL PROCESSES of neuroepithelial and radial glial cells that extend towards the basal lamina (FIG. 2) is also considered important in determining daughter-cell fate[28,37,39,93]. Another key player in this context is the protein Numb, a paradigm of an asymmetrically localized cell fate determinant in the asymmetric division of *D. melanogaster* neuroblasts[39,94,95]. However, it remains to be elucidated how the equal versus unequal distribution of Numb on division of mammalian neuroepithelial and radial glial cells is related to its role in neurogenesis[96], and discussing this complex issue is outside the scope of this review.

Apical plasma membrane. A conceivable scenario is that a signal for proliferation is present in the lumen of the neural tube and is transduced into neuroepithelial and radial glial cells through their apical membrane (FIGS 2,4). Two transmembrane proteins of the neuroepithelial apical plasma membrane deserve comment in this context and, interestingly, both show a link to cholesterol.

The first is megalin, a low-density-lipoprotein-receptor-related protein that is localized to the intermicrovillar space of the apical surface, where endocytosis occurs[97–99]. The neuroepithelium of megalin-deficient mouse embryos shows an abnormal phenotype that is consistent with impaired proliferation, which might result from insufficient cholesterol uptake and from the perturbed transduction of signals from cholesterol-containing ligands such as SONIC HEDGEHOG[98–100,144].

The second apical transmembrane protein is prominin-1, which, in contrast to megalin, is specifically concentrated on plasma-membrane protrusions[40,41]. Prominin-1 is expressed on various somatic stem cells, including neuroepithelial and radial glial cells, which is consistent with a role for it in their proliferation[40,41,73,101]. It is intriguing that prominin-1 specifically interacts with membrane cholesterol and is associated with a specific cholesterol-based membrane microdomain[41,102]. Perhaps the proliferation of neuroepithelial and radial glial cells is based on a specific, presently poorly understood, cholesterol-dependent organization of the apical plasma membrane.

Adherens junctions. In neuroepithelial and radial glial cells, proteins that are associated with adherens junctions are concentrated just beneath the apical plasma membrane[42–44]. So, similar to constituents of the apical plasma membrane, adherens-junction proteins might be subject to an equal versus unequal distribution on vertical cleavage (FIG. 4), and might therefore determine proliferative versus neurogenic cell division. Indeed, PAR3 — a protein that is localized to the apical cortex of mammalian neuroepithelial cells in the vicinity of adherens junctions[44,73,103] and has been implicated in cell polarity and asymmetric division[39,104,105] — seems to be inherited equally and unequally on the proliferative and neurogenic divisions of neuroepithelial cells, respectively[73]. However, the most intriguing protein in this context is β-catenin, which is involved in the Wingless signalling pathway and in linking the cytoplasmic domains of cadherins that are clustered at adherens junctions to the cytoskeleton. Various transgenic mouse models indicate that β-catenin-mediated signal transduction controls neuroepithelial-cell and radial glial-cell proliferation and the size of the pool of neuronal progenitors[106–108]. Apical β-catenin is markedly reduced in *hyh* neuroepithelial and radial glial cells, which switch prematurely from proliferative to neurogenic divisions[91]. Moreover, a similar phenotype is observed in conditional β-catenin mutants[108,109]. Understanding what determines the distribution of adherens-junction-associated β-catenin to the respective daughter cells on symmetric, proliferative and asymmetric, neurogenic divisions of neuroepithelial and radial glial cells therefore seems to be an important aspect of future research.

SONIC HEDGEHOG
A morphogen that is involved in the patterning of the central nervous system. It carries covalently bound cholesterol at its C terminus.

LISSENCEPHALY
A malformation of the human brain in which the normal convolution of the cerebral cortex is absent, which results in a smooth cortical surface.

Interkinetic nuclear migration

A hallmark of neuroepithelial cells, radial glial cells and, to a limited extent, basal progenitors is the migration of the nucleus during the cell cycle — a process that is referred to as interkinetic nuclear migration[110,111]. In neuroepithelial cells before the onset of neurogenesis, this interkinetic nuclear migration spans the entire apical–basal axis of the cell, with the nucleus migrating to the basal side during the G1 phase of the cell cycle, staying at the basal side during S phase, migrating back to the apical side during the G2 phase and undergoing mitosis at the apical side[110,111] (FIG. 2a). In radial glial cells, the same interkinetic nuclear migration occurs, except that it does not span the entire apical–basal axis of the cell but is confined to the portion of the cell in the ventricular zone (FIG. 2b).

In contrast to neuroepithelial and radial glial cells, basal progenitors show little, if any, nuclear migration between S phase and M phase; when mitosis occurs, the nucleus is in the same region as it was during S phase — that is, in the basal region of the ventricular zone (FIG. 2c) or in the subventricular zone. It has also been observed that after S phase the nuclei of basal progenitors migrate first in the apical direction (as is typical during G2 phase for neuroepithelial and radial glial cells), then change direction, migrating back in the basal direction, and then undergo mitosis in the basal ventricular zone or subventricular zone[30]. Together with the apparent loss of apical plasma membrane and adherens junctions[31], the lack of apically directed nuclear migration in G2, or the reversal of apical migration by subsequent basally directed migration, might causally contribute to the formation of basal progenitors[30] (FIG. 2c).

Little is known about the mechanisms that underlie interkinetic nuclear migration in neuroepithelial and radial glial cells[112]. The nucleus adopts an elongated shape along the apical–basal axis when migration starts and rounds up when migration stops[30], which is consistent with it being pulled by some cytoskeletal machinery. Nuclear migration in the apical direction (G2) is faster than in the basal direction (G1)[30], which points to differences in the components of the underlying machinery. Early work on interkinetic nuclear migration indicated the involvement of microtubules[113,114], an idea that is supported by the fact that nuclear migration and positioning is a microtubule-dependent process in many cells[115,116].

Recent studies of LIS1 are consistent with this idea. Mutations in the human *LIS1* gene[117,118] are responsible for the type I form of LISSENCEPHALY (‘smooth brain’), which is a severe malformation of the brain[119]. The LIS1 protein can be found in a complex with cytoplasmic dynein and dynactin, which binds to microtubules and affects microtubule dynamics. Mice with reduced LIS1 levels show abnormal neuronal migration, as well as defects in the interkinetic nuclear migration of neuroepithelial cells[120].

In addition to microtubules, actin filaments might be involved in the interkinetic nuclear migration of neuroepithelial cells. Cytochalasin B, a drug that interferes with actin polymerization[121], blocks this process[122,123], and the ablation of non-muscle myosin heavy chain II-B results in disordered nuclear migration in neuroepithelial cells[124].

Considering that interkinetic nuclear migration is a long-known hallmark of neuroepithelial cells[110] and how much is known about other cytoskeleton-based processes in eukaryotic cells, it is amazing how sparse our knowledge is about the mechanism involved and, even more so, about the function of interkinetic nuclear migration[112]. Important issues in this regard include the significance of the coupling between the nuclear position relative to the apical–basal axis of the cell and the cell-cycle phase, and the consequences, for neurogenesis, of uncoupling interkinetic nuclear migration and the cell cycle. This coupling requires the transcription factor PAX6 (REFS 125,126). Inhibition of interkinetic nuclear migration by cytochalasin B does not block cell-cycle progression, which results in mitosis occurring when the nucleus is positioned anywhere in the ventricular zone, rather than apically[123,127]. Conversely, the inhibition of S-phase progression by hydroxyurea does not block interkinetic nuclear migration, which results in DNA replication occurring in the apical as well as the basal region of the ventricular zone[127]. So, interkinetic nuclear migration and the cell cycle of neuroepithelial cells, although coordinated with one another during physiological development, can be uncoupled by pharmacological means, which reflects the differences in the underlying machineries.

Interestingly, such uncoupling leads to an apparent increase in neurogenesis[127], but why this is so remains to be determined. One possibility is that there are spatial clues for the regulation of neurogenesis along the apical–basal axis of neuroepithelial and radial glial cells[127], and that disturbing the coordination between the position of the nucleus along this axis and the appropriate phase of the cell cycle can promote neurogenesis. Another is that the pharmacological manipulations that are used to transiently inhibit cell-cycle progression and to block interkinetic nuclear migration[127] slow cell-cycle progression, which can be sufficient to promote neurogenesis[128].

The presence of the neuroepithelial-cell and radial glial-cell nucleus in a specific region of these highly polarized cells in certain phases of the cell cycle probably has implications for signal transduction. Specifically, the daughter-cell nuclei that result from mitosis being initiated when the parent nucleus is at the apical surface of the neuroepithelium are initially — that is, early in G1 — exposed to signalling pathways that originate from the apical plasma membrane and the apical junctional complexes. It is interesting to note that, after an asymmetric division of neuroepithelial and radial glial cells that is initiated when the nucleus is at the apical surface and that produces a neuron and a progenitor cell, the progenitor cell nucleus remains in the apical region of the ventricular zone longer than the neuronal nucleus, which is the first to migrate basally[26,30]. Perhaps this contributes to the different fate of these two cells.

Cell-cycle length and neural-stem-cell fate

The transition of neuroepithelial to radial glial cells and their progression from proliferative to neurogenic divisions during embryonic development is associated with an increase in the length of their cell cycle[129]. Specifically, an increase in the proportion of neurogenic neuroepithelial and radial glial cells in any particular area of the neural tube correlates with an increase in the average cell-cycle length of neuroepithelial/radial glial cells[129]. Remarkably, this increase in cell-cycle length for neuroepithelial and radial glial cells is predominantly, if not exclusively, due to a lengthening of the G1 phase; the length of the other phases remains largely constant[129]. These results, which are distinct from those showing that cell-cycle arrest in G1 can potentiate neural cell fate determination[130], raise three questions.

First, does the lengthening of the cell cycle occur similarly in both proliferating and neurogenic neuroepithelial cells, or does it occur preferentially in the neurogenic subpopulation? The finding that *Tis21* is selectively expressed in virtually all neurogenic, but not in proliferating, neuroepithelial cells[30,74] opened the way to distinguish between these two subpopulations and to determine cell-cycle length separately for proliferating and neurogenic cells. Indeed, the *Tis21*-expressing — that is, neurogenic — progenitors in the embryonic telencephalon show a significantly longer cell cycle than the proliferating neuroepithelial cells, which lack *Tis21* expression[145].

This leads to the second question, which is whether the lengthening of the neuroepithelial cell cycle that is associated with their switch to neurogenesis is a cause or a consequence of this switch. It has long been known that cell fate determinants can influence cell-cycle progression. Conversely, cell-cycle regulators such as p27 have also been shown to affect the cell fate of neuronal progenitors[131–134], although it has been unclear whether this reflects an effect on cell-cycle progression *per se* or another activity of the protein. Recently, olomoucine, a cyclin-dependent kinase inhibitor, was used at a concentration that lengthened, but did not block, the neuroepithelial cell cycle, and was shown to be sufficient to trigger premature neurogenesis in mouse embryos that were developing in whole-embryo culture[128]. Similarly, overexpression of *PC3* — the rat orthologue of *Tis21*, which inhibits G1-to-S-phase progression[135,136] — is sufficient to increase neurogenesis, and it inhibits the extent of neuroepithelial-cell proliferation at the same time[137,138]. Together with the observation that neuroepithelial cells apparently begin to express *Tis21* in the G1 phase of the cell cycle that precedes the first neurogenic mitoses[30,74], and consistent with the effects of growth factors on cell-cycle regulators and the cell-cycle kinetics of neuroepithelial and radial glial cells *in vitro*[139], these data indicate that lengthening the G1 phase of the neuroepithelial cell cycle can trigger neurogenesis *in vivo*[128].

The third question that then arises is how does lengthening the neuroepithelial cell cycle, and specifically the G1 phase, promote the switch to neurogenesis? A possible answer is provided by the 'cell-cycle length hypothesis', which is supported by *in vitro*[139] and *in vivo*[128] data on neuroepithelial and radial glial cells. In essence, this hypothesis says that time is a

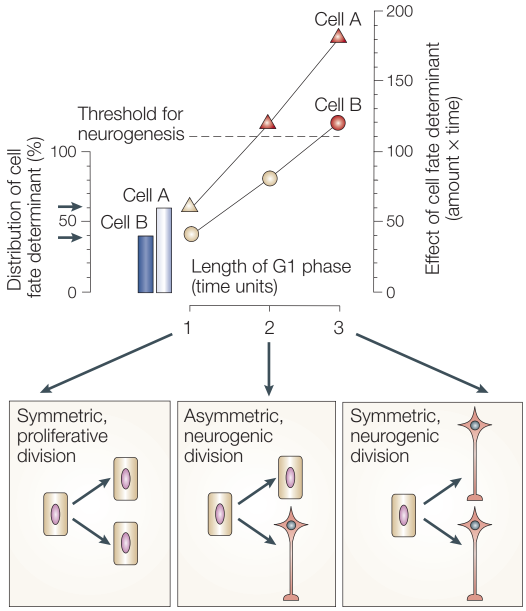

Figure 6 | **The cell-cycle length hypothesis.** A neurogenic cell fate determinant that, following cell division, is distributed unequally to daughter cells A and B (60% and 40%, respectively) can induce one or both of the daughter cells to become a neuron depending on whether G1 phase is sufficiently long for the cell fate determinant to achieve its neurogenic effect. So, neither cell A nor cell B will become a neuron after one unit of time. Cell A, but not cell B, will become a neuron after two units of time. Both cell A and cell B will become a neuron after three units of time. The upper panel of the figure is modified, with permission, from REF. 128 © The Company Of Biologists (2003).

EPENDYMAL CELLS
Epithelial cells that line the brain ventricles and the central canal of the spinal cord.

crucial factor. Therefore, an extrinsic or intrinsic cell fate determinant might or might not induce a cell fate change depending on whether it is allowed to function for a sufficient length of time[128]. Moreover, after a cell division that results in a cell fate determinant — for example, a differentiation factor — being present at different levels either outside or inside the two daughter cells, the cell-cycle length hypothesis makes specific predictions with regard to their symmetric versus asymmetric fate[128]. If the relevant phase of the cell cycle is too short for the cell fate determinant to induce differentiation, both daughter cells will adopt a symmetric fate and continue to proliferate (FIG. 6). If the cell cycle is longer, such that the cell fate determinant is able to induce differentiation in one but not the other daughter cell, the cells will adopt an asymmetric fate, with one daughter continuing to proliferate and the other differentiating (FIG. 6). If the cell cycle is even longer, such that the cell fate determinant is able to induce differentiation in both daughter cells, they will adopt a symmetric fate, with both daughter cells differentiating (FIG. 6). It is interesting to note that, consistent with the cell-cycle length hypothesis[128] and concomitant with a progressive lengthening of their cell cycle, neuroepithelial and radial glial cells switch from symmetric, proliferative divisions to asymmetric, neurogenic divisions and, eventually, to symmetric, neurogenic divisions[18,129,140] (FIG. 1a).

Conclusions and perspectives

Over the past few years, the dissection of the cell-biological basis of proliferative versus neurogenic divisions of neural stem and progenitor cells during the development of the mammalian CNS has given us our first insights into the spatial and temporal control mechanisms that are involved in these processes. In particular, the polarized organization of neural stem and progenitor cells and the length of their cell cycle have emerged as important determinants. It will be important to elucidate how such spatial and temporal control mechanisms are coordinated as potential molecular links — for example, HES1 and HES5 (REF. 141) and the lethal giant larvae gene *Lgl1* (REF. 142) — emerge between the two.

At the level of spatial organization, the apical plasma membrane and the adjacent adherens junctions seem to be crucial for the self-renewal of neural stem cells, and the lack of these apical cell constituents seems to be associated with neuronal differentiation. Important challenges for future research therefore include the identification and characterization of the signal-transduction processes that originate in the ventricular lumen and are transmitted into the interior of the neural stem cell through the apical plasma membrane and the adherens junctions.

These findings might also have implications for adult neurogenesis. Recent evidence shows that the adult mammalian brain (including the human brain) contains cells with reconstitutive potential[1–4], even though they are present in small numbers and are restricted to two small regions of the mammalian telencephalon[3,5,8] (it should be noted that the evidence for EPENDYMAL CELLS as stem cells[9] has not been reproduced so far[10,11]). Specifically, a subset of astrocytes has been identified as the source of neurons in these regions. Despite some decrease in old age, these cells can undergo neurogenesis throughout the lifespan of an organism, that is, for an apparently unlimited number of cell divisions. Moreover, these astrocytes have the capacity to restore adult neurogenesis after all the rapidly proliferating cells have been eliminated[1,2,12]. So, one key question is why cannot all astrocytes in the adult mammalian brain maintain this neurogenic potential from their ancestors, the radial glial cells? It is interesting to note that the astrocytes that can undergo adult neurogenesis have access to the ventricle through their apical membrane[1,2,143]. Most other astrocytes that do not generate neurons do not have such access, and only contact the basement membrane surrounding the blood vessels. So, the perspective for future research into adult neural stem cells might well become similar to the one outlined above for the stem and progenitor cells of the developing mammalian CNS.

1. Doetsch, F., Garcia-Verdugo, J. M. & Alvarez-Buylla, A. Regeneration of a germinal layer in the adult mammalian brain. *Proc. Natl Acad. Sci. USA* **96**, 11619–11624 (1999).
2. Doetsch, F., Caille, I., Lim, D. A., Garcia-Verdugo, J. M. & Alvarez-Buylla, A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* **97**, 703–716 (1999).
Identified astroglial cells as the source of adult neurogenesis and as adult neural stem cells. This paper has revolutionized our thinking about astroglial cells.
3. Bedard, A. & Parent, A. Evidence of newly generated neurons in the human olfactory bulb. *Brain Res. Dev. Brain Res.* **151**, 159–168 (2004).
4. Sanai, N. *et al.* Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature* **427**, 740–744 (2004).
5. Alvarez-Buylla, A., Garcia-Verdugo, J. M. & Tramontin, A. D. A unified hypothesis on the lineage of neural stem cells. *Nature Rev. Neurosci.* **2**, 287–293 (2001).
6. Gabay, L., Lowell, S., Rubin, L. L. & Anderson, D. J. Deregulation of dorsoventral patterning by FGF confers trilineage differentiation capacity on CNS stem cells *in vitro*. *Neuron* **40**, 485–499 (2003).
7. Hack, M. A., Sugimori, M., Lundberg, C., Nakafuku, M. & Götz, M. Regionalization and fate specification in neurospheres: the role of Olig2 and Pax6. *Mol. Cell. Neurosci.* **25**, 664–678 (2004).
8. Garcia, A. D., Doan, N. B., Imura, T., Bush, T. G. & Sofroniew, M. V. GFAP-expressing progenitors are the principal source of constitutive neurogenesis in adult mouse forebrain. *Nature Neurosci.* **7**, 1233–1241 (2004).
9. Johansson, C. B. *et al.* Identification of a neural stem cell in the adult mammalian central nervous system. *Cell* **96**, 25–34 (1999).
10. Capela, A. & Temple, S. LeX/ssea-1 is expressed by adult mouse CNS stem cells, identifying them as nonependymal. *Neuron* **35**, 865–875 (2002).
11. Seaberg, R. M. & van der Kooy, D. Adult rodent neurogenic regions: the ventricular subependyma contains neural stem cells, but the dentate gyrus contains restricted progenitors. *J. Neurosci.* **22**, 1784–1793 (2002).
12. Seri, B., Garcia-Verdugo, J. M., McEwen, B. S. & Alvarez-Buylla, A. Astrocytes give rise to new neurons in the adult mammalian hippocampus. *J. Neurosci.* **21**, 7153–7160 (2001).
13. Niemann, C. & Watt, F. M. Designer skin: lineage commitment in postnatal epidermis. *Trends Cell Biol.* **12**, 185–192 (2002).
14. Arvidsson, A., Collin, T., Kirik, D., Kokaia, Z. & Lindvall, O. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nature Med.* **8**, 963–970 (2002).
15. Lachapelle, F., Avellana-Adalid, V., Nait-Oumesmar, B. & Baron-Van Evercooren, A. Fibroblast growth factor-2 (FGF-2) and platelet-derived growth factor AB (PDGF AB) promote adult SVZ-derived oligodendrogenesis *in vivo*. *Mol. Cell. Neurosci.* **20**, 390–403 (2002).
16. Reynolds, B. A. & Weiss, S. Clonal and population analyses demonstrate that an EGF-responsive mammalian embryonic CNS precursor is a stem cell. *Dev. Biol.* **175**, 1–13 (1996).
17. Rakic, P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. *Trends Neurosci.* **18**, 383–388 (1995).
18. McConnell, S. K. Constructing the cerebral cortex: neurogenesis and fate determination. *Neuron* **15**, 761–768 (1995).
19. Gray, G. E., Glover, J. C., Majors, J. & Sanes, J. R. Radial arrangement of clonally related cells in the chicken optic tectum: lineage analysis with a recombinant retrovirus. *Proc. Natl Acad. Sci. USA* **85**, 7356–7360 (1988).
20. Price, J. & Thurlow, L. Cell lineage in the rat cerebral cortex: a study using retroviral-mediated gene transfer. *Development* **104**, 473–482 (1988).
21. Luskin, M. B., Pearlman, A. L. & Sanes, J. R. Cell lineage in the cerebral cortex of the mouse studied *in-vivo* and *in-vitro* with a recombinant retrovirus. *Neuron* **1**, 635–647 (1988).
22. Grove, E. A., Williams, B. P., Li, D.-Q., Hajihosseini, M., Friedrich, A. & Price, J. Multiple restricted lineages in the embryonic rat cerebral cortex. *Development* **117**, 553–561 (1993).
23. Kornack, D. R. & Rakic, P. Radial and horizontal deployment of clonally related cells in the primate neocortex: relationship to distinct mitotic lineages. *Neuron* **15**, 311–321 (1995).
24. Mione, M. C., Cavanagh, J. F., Harris, B. & Parnavelas, J. G. Cell fate specification and symmetrical/asymmetrical divisions in the developing cerebral cortex. *J. Neurosci.* **17**, 2018–2029 (1997).
25. Reid, C. B., Tavazoie, S. F. & Walsh, C. A. Clonal dispersion and evidence for asymmetric cell division in ferret cortex. *Development* **124**, 2441–2450 (1997).
26. Chenn, A. & McConnell, S. K. Cleavage orientation and the asymmetric inheritance of Notch1 immunoreactivity in mammalian neurogenesis. *Cell* **82**, 631–641 (1995).
Examined the cell division of neural progenitors live in slice cultures of the developing cerebral cortex. Led to the proposal that the orientation of cell division is correlated with, and predicts, the fate of daugther cells.
27. Noctor, S. C., Flint, A. C., Weissman, T. A., Dammerman, R. S. & Kriegstein, A. R. Neurons derived from radial glial cells establish radial units in neocortex. *Nature* **409**, 714–720 (2001).
Observed the generation of neurons from GFP-labelled radial glial cells using live time-lapse video microscopy in slice cultures from the developing cerebral cortex.
28. Miyata, T., Kawaguchi, A., Okano, H. & Ogawa, M. Asymmetric inheritance of radial glial fibers by cortical neurons. *Neuron* **31**, 727–741 (2001).
Revised the dogma that dividing precursors round up and retract their processes. Time-lapse video microscopy of labelled radial glial cells in cortical slice cultures showed that the radial process is maintained during cell division and is inherited by only one daughter cell.
29. Noctor, S. C., Martinez-Cerdeno, V., Ivic, L. & Kriegstein, A. R. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. *Nat. Neurosci.* **7**, 136–144 (2004).
30. Haubensak, W., Attardo, A., Denk, W. & Huttner, W. B. Neurons arise in the basal neuroepithelium of the early mammalian telencephalon: a major site of neurogenesis. *Proc. Natl Acad. Sci. USA* **101**, 3196–3201 (2004).
31. Miyata, T. *et al.* Asymmetric production of surface-dividing and non-surface-dividing cortical progenitor cells. *Development* **131**, 3133–3145 (2004).
References 29–31 used time-lapse imaging to describe basal/subventricular zone progenitors, which divide symmetrically to generate two neurons each.
32. Qian, X., Goderie, S. K., Shen, Q., Stern, J. H. & Temple, S. Intrinsic programs of patterned cell lineages in isolated vertebrate CNS ventricular zone cells. *Development* **125**, 3143–3152 (1998).
33. Qian, X. *et al.* Timing of CNS cell generation: a programmed sequence of neuron and glial cell production from isolated murine cortical stem cells. *Neuron* **28**, 69–80 (2000).
34. Shen, Q., Zhong, W., Jan, Y. N. & Temple, S. Asymmetric Numb distribution is critical for asymmetric cell division of mouse cerebral cortical stem cells and neuroblasts. *Development* **129**, 4843–4853 (2002).
35. Götz, M., Hartfuss, E. & Malatesta, P. Radial glial cells as neuronal precursors: a new perspective on the correlation of morphology and lineage restriction in the developing cerebral cortex of mice. *Brain Res. Bull.* **57**, 777–788 (2002).
36. Kriegstein, A. R. & Götz, M. Radial glia diversity: a matter of cell fate. *Glia* **43**, 37–43 (2003).
37. Fishell, G. & Kriegstein, A. R. Neurons from radial glia: the consequences of asymmetric inheritance. *Curr. Opin. Neurobiol.* **13**, 34–41 (2003).
38. Huttner, W. B. & Brand, M. Asymmetric division and polarity of neuroepithelial cells. *Curr. Opin. Neurobiol.* **7**, 29–39 (1997).
Presents the hypothesis that vertical cleavage planes can result in symmetric and asymmetric divisions of neuroepithelial cells, as such cleavages can either bisect or bypass the apical plasma membrane.
39. Wodarz, A. & Huttner, W. B. Asymmetric cell division during neurogenesis in *Drosophila* and vertebrates. *Mech. Dev.* **120**, 1297–1309 (2003).
40. Weigmann, A., Corbeil, D., Hellwig, A. & Huttner, W. B. Prominin, a novel microvilli-specific polytopic membrane protein of the apical surface of epithelial cells, is targeted to plasmalemmal protrusions of non-epithelial cells. *Proc. Natl Acad. Sci. USA* **94**, 12425–12430 (1997).
41. Corbeil, D., Röper, K., Fargeas, C. A., Joester, A. & Huttner, W. B. Prominin: a story of cholesterol, plasma membrane protrusions and human pathology. *Traffic* **2**, 82–91 (2001).
42. Aaku-Saraste, E., Hellwig, A. & Huttner, W. B. Loss of occludin and functional tight junctions, but not ZO-1, during neural tube closure — remodeling of the neuroepithelium prior to neurogenesis. *Dev. Biol.* **180**, 664–679 (1996).
43. Zhadanov, A. B. *et al.* Absence of the tight junctional protein AF-6 disrupts epithelial cell–cell junctions and cell polarity during mouse development. *Curr. Biol.* **9**, 880–888 (1999).
44. Manabe, N. *et al.* Association of ASIP/mPAR-3 with adherens junctions of mouse neuroepithelial cells. *Dev. Dyn.* **225**, 61–69 (2002).
45. Aaku-Saraste, E., Oback, B., Hellwig, A. & Huttner, W. B. Neuroepithelial cells downregulate their plasma membrane polarity prior to neural tube closure and neurogenesis. *Mech. Dev.* **69**, 71–81 (1997).
46. Campbell, K. & Götz, M. Radial glia: multi-purpose cells for vertebrate brain development. *Trends Neurosci.* **25**, 235–238 (2002).
47. Götz, M. Glial cells generate neurons — master control within CNS regions: developmental perspectives on neural stem cells. *Neuroscientist* **9**, 379–397 (2003).
48. Williams, B. P. & Price, J. Evidence for multiple precursor cell types in the embryonic rat cerebral cortex. *Neuron* **14**, 1181–1188 (1995).
49. Malatesta, P., Hartfuss, E. & Götz, M. Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. *Development* **127**, 5253–5263 (2000).
The first direct evidence for a role for radial glial cells as neuronal progenitors.
50. Malatesta, P. *et al.* Neuronal or glial progeny: regional differences in radial glia fate. *Neuron* **37**, 751–764 (2003).
Showed that there are regional differences in radial glial-cell fate. Radial glial cells from the dorsal telencephalon generate the bulk of neurons in this region, whereas those from the ventral telencephalon generate only a few neurons.
51. Anthony, T. E., Klein, C., Fishell, G. & Heintz, N. Radial glia serve as neuronal progenitors in all regions of the central nervous system. *Neuron* **41**, 881–890 (2004).
This work contradicts the results of reference 50, and indicates that radial glial cells function as neuronal progenitors in all regions of the CNS.
52. Hartfuss, E., Galli, R., Heins, N. & Gotz, M. Characterization of CNS precursor subtypes and radial glia. *Dev. Biol.* **229**, 15–30 (2001).
53. Chenn, A., Zhang, Y. A., Chang, B. T. & McConnell, S. K. Intrinsic polarity of mammalian neuroepithelial cells. *Mol. Cell. Neurosci.* **11**, 183–193 (1998).
54. Halfter, W., Dong, S., Yip, Y. P., Willem, M. & Mayer, U. A critical function of the pial basement membrane in cortical histogenesis. *J. Neurosci.* **22**, 6029–6040 (2002).
55. Gadisseux, J. F. & Evrard, P. Glial-neuronal relationship in the developing central nervous system. A histochemical-electron microscope study of radial glial cell particulate glycogen in normal and reeler mice and the human fetus. *Dev. Neurosci.* **7**, 12–32 (1985).
56. Noctor, S. C. *et al.* Dividing precursor cells of the embryonic cortical ventricular zone have morphological and molecular characteristics of radial glia. *J. Neurosci.* **22**, 3161–3173 (2002).
57. Williams, B. P. *et al.* A PDGF-regulated immediate early gene response initiates neuronal differentiation in ventricular zone progenitor cells. *Neuron* **18**, 553–562 (1997).
58. McCarthy, M., Turnbull, D. H., Walsh, C. A. & Fishell, G. Telencephalic neural progenitors appear to be restricted to regional and glial fates before the onset of neurogenesis. *J. Neurosci.* **21**, 6772–6781 (2001).
59. Reid, C. B., Liang, I. & Walsh, C. Systematic widespread clonal organization in cerebral cortex. *Neuron* **15**, 299–310 (1995).
60. Graus-Porta, D. *et al.* β1-class integrins regulate the development of laminae and folia in the cerebral and cerebellar cortex. *Neuron* **31**, 367–379 (2001).
61. Turner, D. L. & Cepko, C. A common progenitor for neurons and glia persists in rat retina late in development. *Nature* **328**, 131–136 (1987).
62. Turner, D. L., Snyder, E. Y. & Cepko, C. L. Lineage-independent determination of cell type in the embryonic mouse retina. *Neuron* **4**, 833–845 (1990).

63. Leber, S. M. & Sanes, J. R. Migratory paths of neurons and glia in the embryonic chick spinal cord. *J. Neurosci.* **15**, 1236–1248 (1995).
64. Smart, I. H. M. Proliferative characteristics of the ependymal layer during the early development of the mouse neocortex: a pilot study based on recording the number, location and plane of cleavage of mitotic figures. *J. Anat.* **116**, 67–91 (1973).
A classic pioneering study of neuronal progenitor cell division.
65. Tarabykin, V., Stoykova, A., Usman, N. & Gruss, P. Cortical upper layer neurons derive from the subventricular zone as indicated by *Svet1* gene expression. *Development* **128**, 1983–1993 (2001).
66. Englund, C. *et al.* Pax6, Tbr2, and Tbr1 are expressed sequentially by radial glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. *J. Neurosci.* **25**, 247–251 (2005).
67. Nieto, M. *et al.* Expression of Cux-1 and Cux-2 in the subventricular zone and upper layers II–IV of the cerebral cortex. *J. Comp. Neurol.* **479**, 168–180 (2004).
68. Zimmer, C., Tiveron, M. C., Bodmer, R. & Cremer, H. Dynamics of Cux2 expression suggests that an early pool of SVZ precursors is fated to become upper cortical layer neurons. *Cereb. Cortex* **14**, 1408–1420 (2004).
69. Smart, I. H., Dehay, C., Giroud, P., Berland, M. & Kennedy, H. Unique morphological features of the proliferative zones and postmitotic compartments of the neural epithelium giving rise to striate and extrastriate cortex in the monkey. *Cereb. Cortex* **12**, 37–53 (2002).
70. Jan, Y. N. & Jan, L. Y. Asymmetric cell division in the *Drosophila* nervous system. *Nature Rev. Neurosci.* **2**, 772–779 (2001).
71. Knoblich, J. A. Asymmetric cell division during animal development. *Nature Rev. Mol. Cell Biol.* **2**, 11–20 (2001).
72. Landrieu, P. & Goffinet, A. Mitotic spindle fiber orientation in relation to cell migration in the neo-cortex of normal and reeler mouse. *Neurosci. Lett.* **13**, 69–72 (1979).
73. Kosodo, Y. *et al.* Asymmetric distribution of the apical plasma membrane during neurogenic divisions of mammalian neuroepithelial cells. *EMBO J.* **23**, 2314–2324 (2004).
This study confirmed the hypothesis proposed in reference 38 that vertical cleavage planes can result in symmetric and asymmetric divisions of neuroepithelial cells.
74. Iacopetti, P. *et al.* Expression of the antiproliferative gene *TIS21* at the onset of neurogenesis identifies single neuroepithelial cells that switch from proliferative to neuron-generating division. *Proc. Natl Acad. Sci. USA* **96**, 4639–4644 (1999).
This paper describes the first pan-neurogenic marker, *Tis21*, which is expressed in progenitors that undergo neurogenic divisions, but not in progenitors that undergo proliferative divisions.
75. Heins, N. *et al.* Emx2 promotes symmetric cell divisions and a multipotential fate in precursors from the cerebral cortex. *Mol. Cell. Neurosci.* **18**, 485–502 (2001).
76. Heins, N. *et al.* Glial cells generate neurons: the role of the transcription factor Pax6. *Nature Neurosci.* **5**, 308–315 (2002).
This work shows that PAX6 is important for the neurogenesis of radial glial cells in the developing cerebral cortex, and is also sufficient to instruct the neurogenesis of postnatal astrocytes *in vitro*.
77. Gönczy, P., Grill, S., Stelzer, E. H., Kirkham, M. & Hyman, A. A. Spindle positioning during the asymmetric first cell division of *Caenorhabditis elegans* embryos. *Novartis Found. Symp.* **237**, 164–175 (2001).
78. Haydar, T. F., Ang, E. Jr. & Rakic, P. Mitotic spindle rotation and mode of cell division in the developing telencephalon. *Proc. Natl Acad. Sci. USA* **100**, 2890–2895 (2003).
79. Reinsch, S. & Karsenti, E. Orientation of spindle axis and distribution of plasma membrane proteins during cell division in polarized MDCKII cells. *J. Cell Biol.* **126**, 1509–1526 (1994).
80. Bond, J. *et al.* ASPM is a major determinant of cerebral cortical size. *Nature Genet.* **32**, 316–320 (2002).
81. Kouprina, N. *et al.* Accelerated evolution of the *ASPM* gene controlling brain size begins prior to human brain expansion. *PLoS Biol.* **2**, 653–663 (2004).
82. Bond, J. *et al.* Protein-truncating mutations in ASPM cause variable reduction in brain size. *Am. J. Hum. Genet.* **73**, 1170–1177 (2003).
83. Burgess, R. W., Deitcher, D. L. & Schwarz, T. L. The synaptic protein syntaxin1 is required for cellularization of *Drosophila* embryos. *J. Cell Biol.* **138**, 861–875 (1997).
84. Nacry, P., Mayer, U. & Jurgens, G. Genetic dissection of cytokinesis. *Plant Mol. Biol.* **43**, 719–733 (2000).
85. Glotzer, M. Animal cell cytokinesis. *Annu. Rev. Cell Dev. Biol.* **17**, 351–386 (2001).
86. Low, S. H. *et al.* Syntaxin 2 and endobrevin are required for the terminal step of cytokinesis in mammalian cells. *Dev. Cell* **4**, 753–759 (2003).
87. Mostov, K. E., Verges, M. & Altschuler, Y. Membrane traffic in polarized epithelial cells. *Curr. Opin. Cell Biol.* **12**, 483–490 (2000).
88. Low, S. H. *et al.* Retinal pigment epithelial cells exhibit unique expression and localization of plasma membrane syntaxins which may contribute to their trafficking phenotype. *J. Cell Sci.* **115**, 4545–4553 (2002).
89. Rothman, J. E. Mechanisms of intracellular protein transport. *Nature* **372**, 55–63 (1994).
90. Jahn, R. & Südhof, T. C. Membrane fusion and exocytosis. *Annu. Rev. Biochem.* **68**, 863–911 (1999).
91. Chae, T. H., Kim, S., Marz, K. E., Hanson, P. I. & Walsh, C. A. The HYH mutation uncovers roles for α-SNAP in apical protein localization and control of neural cell fate. *Nature Genet.* **36**, 264–270 (2004).
92. Sheen, V. L. *et al.* Mutations in *ARFGEF2* implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Nature Genet.* **36**, 69–76 (2004).
93. Saito, K. *et al.* Morphological asymmetry in dividing retinal progenitor cells. *Dev. Growth Differ.* **45**, 219–229 (2003).
94. Roegiers, F. & Jan, Y. N. Asymmetric cell division. *Curr. Opin. Cell Biol.* **16**, 195–205 (2004).
95. Schweisguth, F. Regulation of Notch signaling activity. *Curr. Biol.* **14**, R129–R138 (2004).
96. Zhong, W. Diversifying neural cells through order of birth and asymmetry of division. *Neuron* **37**, 11–14 (2003).
97. Kerjaschki, D., Noronha-Blob, L., Sacktor, B. & Farquhar, M. G. Microdomains of distinctive glycoprotein composition in the kidney proximal tubule brush border. *J. Cell Biol.* **98**, 1505–1513 (1984).
98. Herz, J. & Bock, H. H. Lipoprotein receptors in the nervous system. *Annu. Rev. Biochem.* **71**, 405–434 (2002).
99. May, P. & Herz, J. LDL receptor-related proteins in neurodevelopment. *Traffic* **4**, 291–301 (2003).
100. Machold, R. *et al.* Sonic hedgehog is required for progenitor cell maintenance in telencephalic stem cell niches. *Neuron* **39**, 937–950 (2003).
101. Fargeas, C. A., Corbeil, D. & Huttner, W. B. AC133 antigen, CD133, prominin-1, prominin-2, etc. : prominin family gene products in need of a rational nomenclature. *Stem Cells* **21**, 506–508 (2003).
102. Röper, K., Corbeil, D. & Huttner, W. B. Retention of prominin in microvilli reveals distinct cholesterol-based lipid microdomains in the apical plasma membrane. *Nature Cell Biol.* **2**, 582–592 (2000).
103. Takekuni, K. *et al.* Direct binding of cell polarity protein PAR-3 to cell–cell adhesion molecule nectin at neuroepithelial cells of developing mouse. *J. Biol. Chem.* **278**, 5497–500 (2003).
104. Lin, D. *et al.* A mammalian PAR-3–PAR-6 complex implicated in Cdc42/Rac1 and aPKC signalling and cell polarity. *Nature Cell Biol.* **2**, 540–547 (2000).
105. Ohno, S. Intercellular junctions and cellular polarity: the PAR–aPKC complex, a conserved core cassette playing fundamental roles in cell polarity. *Curr. Opin. Cell Biol.* **13**, 641–648 (2001).
106. Chenn, A. & Walsh, C. A. Increased neuronal production, enlarged forebrains and cytoarchitectural distortions in β-catenin overexpressing transgenic mice. *Cereb. Cortex* **13**, 599–606 (2003).
107. Chenn, A. & Walsh, C. A. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* **297**, 365–369 (2002).
108. Zechner, D. *et al.* β-Catenin signals regulate cell growth and the balance between progenitor cell expansion and differentiation in the nervous system. *Dev. Biol.* **258**, 406–418 (2003).
109. Machon, O., van den Bout, C. J., Backman, M., Kemler, R. & Krauss, S. Role of β-catenin in the developing cortical and hippocampal neuroepithelium. *Neuroscience* **122**, 129–143 (2003).
110. Sauer, F. C. Mitosis in the neural tube. *J. Comp. Neurol.* **62**, 377–405 (1935).
111. Takahashi, T., Nowakowski, R. S. & Caviness, V. S. Cell cycle parameters and patterns of nuclear movement in the neocortical proliferative zone of the fetal mouse. *J. Neurosci.* **13**, 820–833 (1993).
112. Frade, J. M. Interkinetic nuclear movement in the vertebrate neuroepithelium: encounters with an old acquaintance. *Prog. Brain Res.* **136**, 67–71 (2002).
113. Messier, P.-E. & Auclair, C. Inhibition of nuclear migration in the absence of microtubules in the chick embryo. *J. Embryol. Exp. Morph.* **30**, 661–671 (1973).
114. Messier, P. E. Microtubules, interkinetic nuclear migration and neurulation. *Experientia* **34**, 289–296 (1978).
115. Reinsch, S. & Gönczy, P. Mechanisms of nuclear positioning. *J. Cell Sci.* **111**, 2283–2295 (1998).
116. Morris, N. R. Nuclear positioning: the means is at the ends. *Curr. Opin. Cell Biol.* **15**, 54–59 (2003).
117. Faulkner, N. E. *et al.* A role for the lissencephaly gene *lis1* in mitosis and cytoplasmic dynein function. *Nature Cell Biol.* **2**, 784–791 (2000).
118. Sapir, T., Elbaum, M. & Reiner, O. Reduction of microtubule catastrophe events by LIS1, platelet-activating factor acetylhydrolase subunit. *EMBO J.* **16**, 6977–6984 (1997).
119. Olson, E. C. & Walsh, C. A. Smooth, rough and upside-down neocortical development. *Curr. Opin. Genet. Dev.* **12**, 320–327 (2002).
120. Gambello, M. J. *et al.* Multiple dose-dependent effects of Lis1 on cerebral cortical development. *J. Neurosci.* **23**, 1719–1729 (2003).
121. MacLean-Fletcher, S. & Pollard, T. D. Mechanism of action of cytochalasin B on actin. *Cell* **20**, 329–341 (1980).
122. Karfunkel, P. The activity of microtubules and microfilaments in neurulation in the chick. *J. Exp. Zool.* **181**, 289–301 (1972).
123. Messier, P.-E. & Auclair, C. Effect of cytochalasin B on interkinetic nuclear migration in the chick embryo. *Dev. Biol.* **36**, 218–223 (1974).
124. Tullio, A. N. *et al.* Structural abnormalities develop in the brain after ablation of the gene encoding nonmuscle myosin II-B heavy chain. *J. Comp. Neurol.* **433**, 62–74 (2001).
125. Götz, M., Stoykova, A. & Gruss, P. Pax6 controls radial glia differentiation in the cerebral cortex. *Neuron* **21**, 1031–1044 (1998).
126. Estivill-Torrus, G., Pearson, H., van Heyningen, V., Price, D. J. & Rashbass, P. Pax6 is required to regulate the cell cycle and the rate of progression from symmetrical to asymmetrical division in mammalian cortical progenitors. *Development* **129**, 455–466 (2002).
127. Murciano, A., Zamora, J., Lopez-Sanchez, J. & Frade, J. M. Interkinetic nuclear movement may provide spatial clues to the regulation of neurogenesis. *Mol. Cell. Neurosci.* **21**, 285–300 (2002).
128. Calegari, F. & Huttner, W. B. An inhibition of cyclin-dependent kinases that lengthens, but does not arrest, neuroepithelial cell cycle induces premature neurogenesis. *J. Cell Sci.* **116**, 4947–4955 (2003).
This study formulates the cell-cycle length hypothesis, which is supported by the finding that lengthening the cell cycle of neuroepithelial cells can be sufficient to switch neuroepithelial cells from proliferative to neurogenic divisions.
129. Takahashi, T., Nowakowski, R. S. & Caviness, V. S. The cell cycle of the pseudostratified ventricular epithelium of the embryonic murine cerebral wall. *J. Neurosci.* **15**, 6046–6057 (1995).
A seminal study showing that the cell cycle of ventricular zone cells lengthens concomitant with the onset and progression of neurogenesis.
130. Durand, B. & Raff, M. A cell-intrinsic timer that operates during oligodendrocyte development. *Bioessays* **22**, 64–71 (2000).
131. Ohnuma, S., Philpott, A. & Harris, W. A. Cell cycle and cell fate in the nervous system. *Curr. Opin. Neurobiol.* **11**, 66–73 (2001).
132. Cremisi, F., Philpott, A. & Ohnuma, S. Cell cycle and cell fate interactions in neural development. *Curr. Opin. Neurobiol.* **13**, 26–33 (2003).
133. Bally-Cuif, L. & Hammerschmidt, M. Induction and patterning of neuronal development, and its connection to cell cycle control. *Curr. Opin. Neurobiol.* **13**, 16–25 (2003).
134. Ohnuma, S. & Harris, W. A. Neurogenesis and the cell cycle. *Neuron* **40**, 199–208 (2003).
135. Matsuda, S., Rouault, J., Magaud, J. & Berthet, C. In search of a function for the TIS21/PC3/BTG1/TOB family. *FEBS Lett.* **497**, 67–72 (2001).
136. Tirone, F. The gene $PC3^{TIS21/BTG2}$, prototype member of the PC3/BTG/TOB family: regulator in control of cell growth, differentiation, and DNA repair? *J. Cell Physiol.* **187**, 155–165 (2001).
137. Malatesta, P. *et al.* PC3 overexpression affects the pattern of cell division of rat cortical precursors. *Mech. Dev.* **90**, 17–28 (2000).

138. Canzoniere, D. *et al.* Dual control of neurogenesis by PC3 through cell cycle inhibition and induction of Math1. *J. Neurosci.* **24**, 3355–3369 (2004).
139. Lukaszewicz, A., Savatier, P., Cortay, V., Kennedy, H. & Dehay, C. Contrasting effects of basic fibroblast growth factor and neurotrophin 3 on cell cycle kinetics of mouse cortical stem cells. *J. Neurosci.* **22**, 6610–6622 (2002).
140. Takahashi, T., Nowakowski, R. S. & Caviness, V. S. The leaving or Q fraction of the murine cerebral proliferative epithelium: a general model of neocortical neuronogenesis. *J. Neurosci.* **16**, 6183–6196 (1996).
141. Hatakeyama, J. *et al.* Hes genes regulate size, shape and histogenesis of the nervous system by control of the timing of neural stem cell differentiation. *Development* **131**, 5539–5550 (2004).
142. Klezovitch, O., Fernandez, T. E., Tapscott, S. J. & Vasioukhin, V. Loss of cell polarity causes severe brain dysplasia in Lgl1 knockout mice. *Genes Dev.* **18**, 559–571 (2004).
143. Doetsch, F., Petreanu, L., Caille, I., Garcia-Verdugo, J. M. & Alvarez-Buylla, A. EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. *Neuron* **36**, 1021–1034 (2002).
144. Spoelgen, R. *et al.* LRP2/megalin is required for patterning of the ventral telencephalon. *Development* **132**, 405–414 (2005).
145. Calegari, F., Haubensak, W., Haffner, C. & Huttner, W. B. Selective lengthening of the cell cycle in the neurogenic subpopulation of neural progenitor cells during mouse brain development. *J. Neurosci.* **25**, 6533–6538 (2005).

Competing interests statement
The authors declare no competing financial interests.

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