

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};

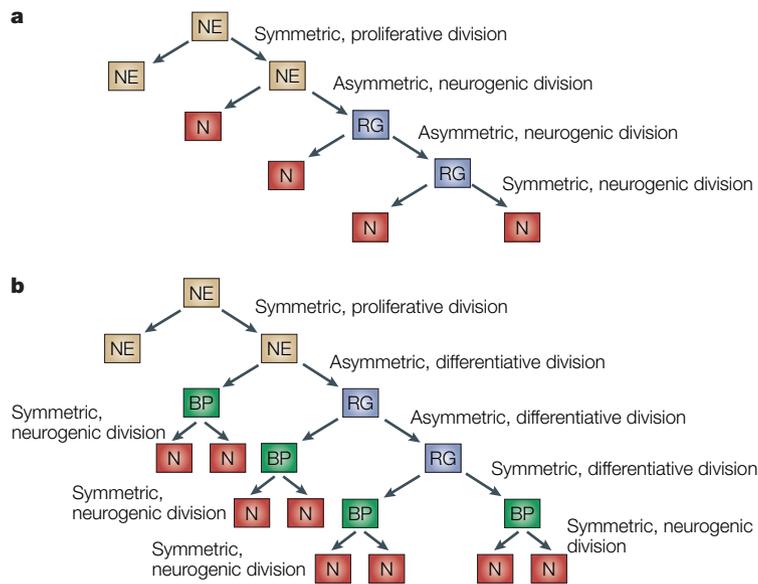


Figure 1 | Lineage trees of neurogenesis. The lineage trees shown provide a simplified view of the relationship between neuroepithelial cells (NE), radial glial cells (RG) and neurons (N), without (a) and with (b) basal progenitors (BP) as cellular intermediates in the generation of neurons. They also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

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 oriented parallel to the axis of cell polarity, perpendicular to this axis or at any angle in between.

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 lamina³⁹. 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 cells⁴³.

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 proteins⁴⁵. 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 nestin⁵²; the maintenance of an apical surface and important features of apical–basal polarity such as an apical localization of centrosomes⁵³ 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 contact⁵⁴ (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 GRANULES⁵⁵, and various molecules that are characteristic of astrocytes — such as the astrocyte-specific glutamate transporter (GLAST), the Ca^{2+} -binding protein S100 β , 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 *Bbbp* 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 cells⁵¹. 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 differentiation⁵⁰. 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 TELENCEPHALON⁵⁰). Taken together, recombination-mediated fate mapping

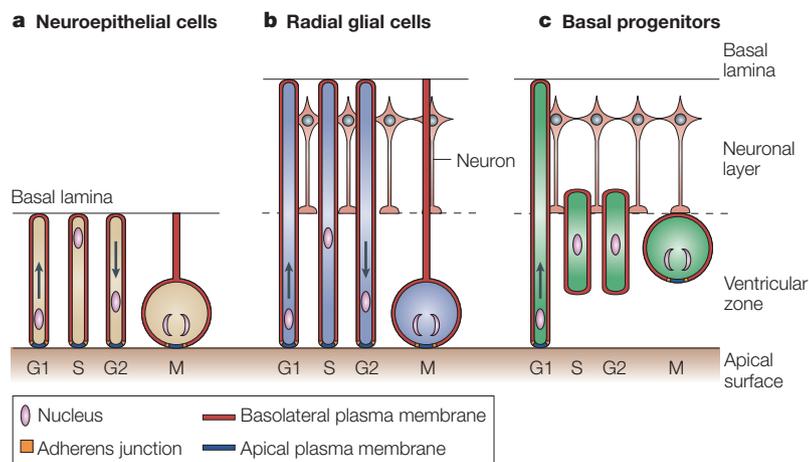


Figure 2 | Polarized features of neuroepithelial cells, radial glial cells and basal progenitors. The figure summarizes the polarized organization and interkinetic nuclear migration of neuroepithelial cells, radial glial cells and basal progenitors. **a** | In neuroepithelial cells, interkinetic nuclear 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 occurring 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 surface³¹. 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 stages⁵⁸ 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 surface³¹ (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 abundant³⁰. 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 surface³⁰. 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 phylogeny⁶⁹.

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 other²⁶ (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 divisions³⁸. 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
<i>Tis21</i> 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 cells⁷⁴.

only a tiny fraction (1–2%) of their total plasma membrane^{38,73}. So, it was postulated³⁸, and recently shown⁷³, 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 cells⁷⁴. 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* locus³⁰ 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 plane⁷³. Furthermore, extending previous time-lapse videomicroscopy 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 cell³⁰. 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 cleavages²⁶.

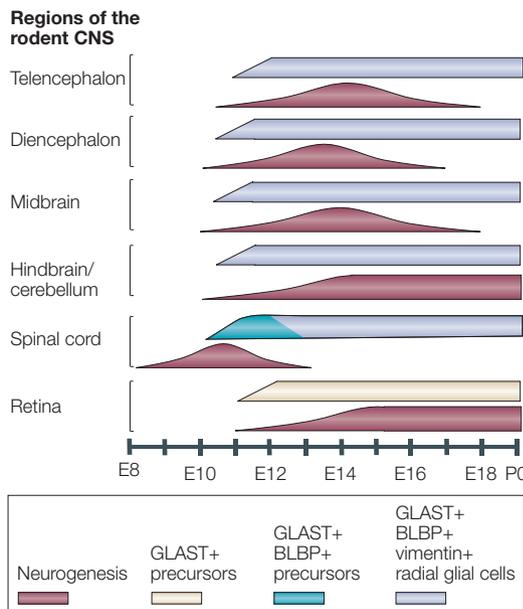


Figure 3 | Neurogenesis and radial glial cells. The figure summarizes the time course of neurogenesis and the appearance of radial glial cells in various regions of the rodent central nervous system (CNS). It should be noted that the appearance of astroglial features — the astrocyte-specific glutamate 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.

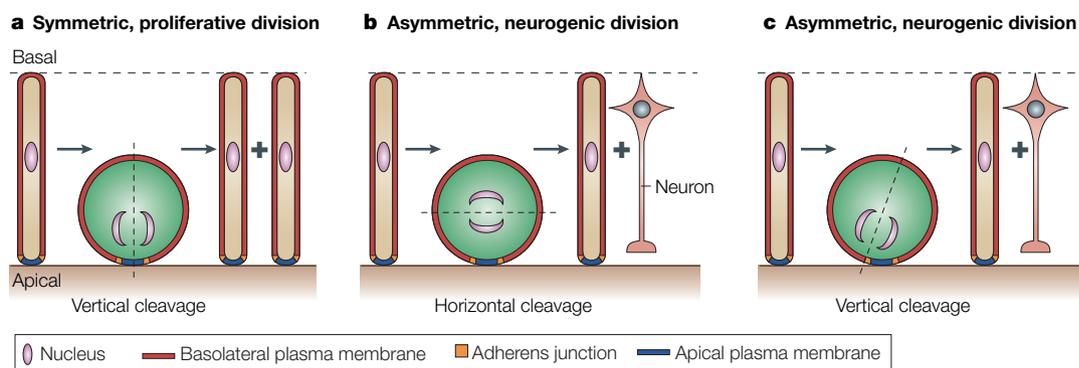


Figure 4 | Symmetric versus asymmetric division of neuroepithelial and radial glial cells. The figure summarizes the relationship between apical–basal polarity, cleavage-plane orientation and the symmetric, proliferative versus asymmetric, neurogenic division of neuroepithelial and radial glial cells. 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 cells⁷³, 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 divisions⁷⁵. By contrast, the transcription factor **PAX6** promotes asymmetric, neurogenic cell divisions⁷⁶. 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 systems⁷⁷, the primary feature that determines neuroepithelial cleavage-plane orientation will probably be the positioning of the poles of the **MITOTIC SPINDLE**. As in other systems⁷⁷, the spindle poles in mitotic neuroepithelial and radial glial cells seem to oscillate around their final positions before anaphase⁷⁸, 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 cells⁷⁹, 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 neurogenesis⁴⁵, 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 size⁸⁰. The evolution of the **ASPM** gene has been implicated in the expansion of the primate brain⁸¹, 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 it⁷³.

Second, the observation that the apical plasma membrane constitutes only a tiny fraction of the total plasma membrane of mitotic neuroepithelial cells⁷³ 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 surface⁷³. 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.

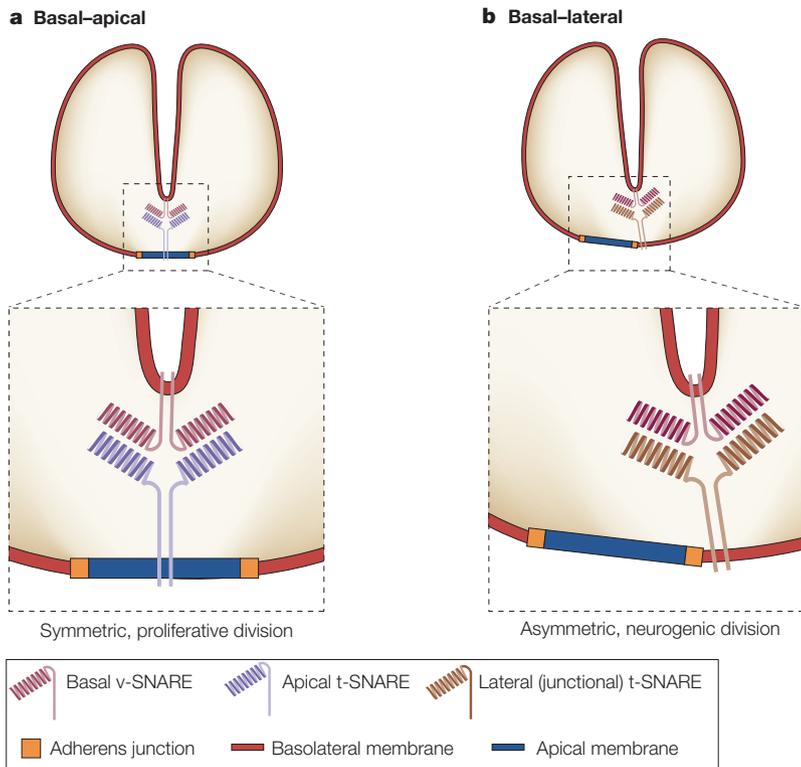


Figure 5 | SNARE control of the symmetric versus asymmetric division of neuroepithelial and radial glial cells. **a** | The symmetric, proliferative division of neuroepithelial and radial glial cells involves heterophilic, basal–apical SNARE-mediated plasma-membrane fusion to complete cytokinesis. **b** | 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 cells⁹¹. 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 divisions⁹¹. This was proposed to be due to impaired apical membrane traffic and impaired apical protein localization⁹¹, which is in line with the general requirement for Golgi-derived membrane traffic for neuronal progenitor proliferation⁹². 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 cells⁷³, 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 neurogenesis⁹⁶, 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, respectively⁷³. However, the most intriguing protein in this context is β -catenin, which is involved in the Wnt signaling 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 divisions⁹¹. 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.

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 zone³⁰. Together with the apparent loss of apical plasma membrane and adherens junctions³¹, 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 progenitors³⁰ (FIG. 2c).

Little is known about the mechanisms that underlie interkinetic nuclear migration in neuroepithelial and radial glial cells¹¹². The nucleus adopts an elongated shape along the apical–basal axis when migration starts and rounds up when migration stops³⁰, 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 brain¹¹⁹. 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 cells¹²⁰.

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 polymerization¹²¹, blocks this process^{122,123}, and the ablation of non-muscle myosin heavy chain II-B results in disordered nuclear migration in neuroepithelial cells¹²⁴.

Considering that interkinetic nuclear migration is a long-known hallmark of neuroepithelial cells¹¹⁰ and

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.

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 migration¹¹². 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 zone¹²⁷. 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 neurogenesis¹²⁷, 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 cells¹²⁷, 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 migration¹²⁷ slow cell-cycle progression, which can be sufficient to promote neurogenesis¹²⁸.

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 cycle¹²⁹. 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 cells¹²⁹. 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 constant¹²⁹. These results, which are distinct from those showing that cell-cycle arrest in G1 can potentiate neural cell fate determination¹³⁰, 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* expression¹⁴⁵.

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 culture¹²⁸. 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

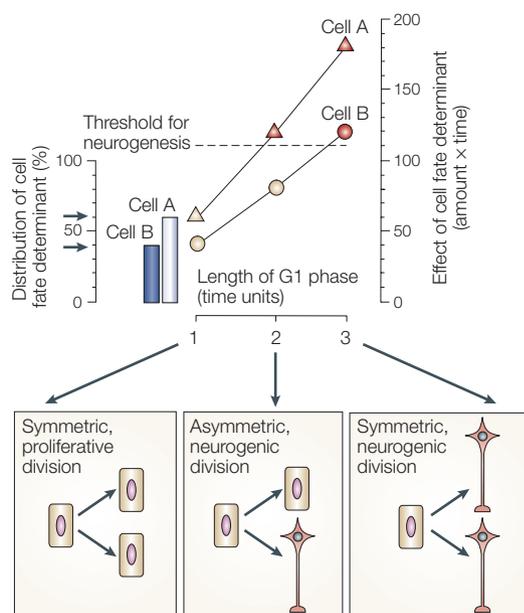


Figure 6 | **The cell-cycle length hypothesis.**

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).

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 time¹²⁸. 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 fate¹²⁸. 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 hypothesis¹²⁸ 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 cells⁹ 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.

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Competing interests statement
The authors declare no competing financial interests.

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