

The cell biology of neural stem and progenitor cells and its significance for their proliferation versus differentiation during mammalian brain development

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The switch of neural stem and progenitor cells from proliferation to differentiation during development is a crucial determinant of brain size. This switch is intimately linked to the architecture of the two principal classes of neural stem and progenitor cells, the apical (neuroepithelial, radial glial) and basal (intermediate) progenitors, which in turn is crucial for their symmetric versus asymmetric divisions. Focusing on the developing rodent neocortex, we discuss here recent advances in understanding the cell biology of apical and basal progenitors, place key regulatory molecules into subcellular context, and highlight their roles in the control of proliferation versus differentiation.

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Introduction

The fundamental issue of cell proliferation versus differentiation has been investigated from various angles, including those of cell-to-cell signaling, cell polarity, and the symmetry of cell division. These areas of investigation differ in the extent to which a mechanistic, cell biological approach prevails. This holds true also for cell proliferation versus differentiation during the development of the mammalian brain, the focus of this review. Specifically, we will concentrate on the divisions of neural stem and progenitor cells and how these result in (i) the expansion of stem/progenitor cells, (ii) the self-renewal of stem/progenitor cells, (iii) the generation of downstream progenitors in the lineage to neurons, and (iv) the generation of neurons.

The conceptual guideline for highlighting the recent advances in the field will be the subcellular architecture

of the specific neural stem/progenitor cell under discussion. In other words, the starting points of our dissection will be specific cellular organelles and key molecules associated with them, and we will address their roles for (i) cell-to-cell signaling, (ii) cell polarity, and (iii) the symmetry of cell division even if a link to the control of proliferation versus differentiation remains to be established or is controversial. We do so because of the simple conviction that molecular interactions constitute the core of cellular control processes, and that understanding these interactions and their dynamics requires consideration of the underlying subcellular architecture.

Before addressing these issues, we will briefly introduce the major classes of neural stem and progenitor cells in the mammalian brain, concentrating on rodents, the neocortex, and stem/progenitor cells that generate neurons (rather than astrocytes and oligodendrocytes). For space limitations, we will confine our discussion to embryonic brain development and will not address adult neurogenesis [1]. For the same reason, we will not comment on the parallels and discrepancies between vertebrate and invertebrate neural stem and progenitor cells, notably the *Drosophila* neuroblast paradigm [2].

Neural stem and progenitor cells in the rodent neocortex

All neurons of the mammalian neocortex derive, directly or indirectly, from the neuroepithelium, a specialized epithelium lining the lumen of the lateral ventricle. During the course of development, neuroepithelial cells, the primary neural stem/progenitor cells, undergo both symmetric and asymmetric types of division. Before the onset of neurogenesis, neuroepithelial cells expand via symmetric divisions. With the onset of neurogenesis, neuroepithelial cells switch to an asymmetric mode of division, generating distinct types of secondary neural stem and progenitor cells (radial glial cells, basal progenitors), and neurons. The secondary neural stem and progenitor cells also undergo both symmetric and asymmetric types of division [2–7].

Neuroepithelial cells

The highly polarized neuroepithelial cells undergo mitosis exclusively at the ventricular (apical) surface. Their nuclei perform a characteristic cell cycle-dependent apical-to-basal (G1) and basal-to-apical (G2) movement, called interkinetic nuclear migration (INM), which leads to pseudostratification of the neuroepithelium (nuclei are

Table 1**Comparison of apical and basal progenitors in the embryonic rodent neocortex.**

	Apical progenitors	Basal progenitors
Molecular markers	Transcriptional regulators: Pax6, Hes5 Membrane protein: prominin-1 (CD133) Radial glia markers: BLBP, GLAST	Transcriptional regulator: Tbr2 Non-coding RNA: Svet1
Cell biology—interphase		
Typical morphology	Radial	Multipolar
Apical–basal polarity	Present	Downregulated
Apical process contacting ventricle	Present	Retracted
Adherens junctions	Present	Absent
Basal process contacting the basal lamina	Present	Absent
Interkinetic nuclear migration	Present (VZ)	Absent (only delamination)
Cell biology—mitosis		
Typical location of cell body	Apical	Basal
Apical–basal polarity	Present	Absent
Adherens junctions	Present	Absent
Basal process contacting the basal lamina	Present	Absent
Cleavage plane orientation	Vertical (parallel to apical–basal axis)	Random
Cleavage furrow ingression	Unidirectional (basal-to-apical)	Bidirectional
Types of cell division		
Symmetric proliferative	Two APs (Tis21–)	Two BPs (Tis21–, Insm1+)
Asymmetric differentiative	AP + BP or neuron (Tis21+)	Virtually absent
Symmetric differentiative	Two BPs or neurons (Tis21+)	Two neurons (Tis21+, Insm1+)

BLBP, brain lipid binding protein; GLAST, astrocyte-specific glutamate transporter.

positioned in several layers, but all cells extend from the basal lamina to the ventricle). Before the onset of neurogenesis, the entire neuroepithelium consists of a single germinal layer, the ventricular zone (VZ).

Radial glial cells

After closure of the neural tube, and in particular with the onset of neurogenesis, neuroepithelial cells start to express glial markers and transform into the related radial glial cells (RGCs) (Table 1) [6,8]. Like neuroepithelial cells, RGCs exhibit apical–basal polarity and span the entire cortical wall, with an apical end-foot (apical process) at the ventricular surface and a basal end-foot (basal process) at the pial surface. RGCs also perform INM (their nuclei migrate only within the VZ). Elegant imaging studies have shown that RGCs undergo self-renewing stem cell-like asymmetric divisions, producing either a neuron or a further type of neural progenitor, and do so through several consecutive division cycles at the ventricular, apical surface [9–11]. Therefore, RGCs can be regarded as neural stem cells.

Basal (intermediate) progenitors

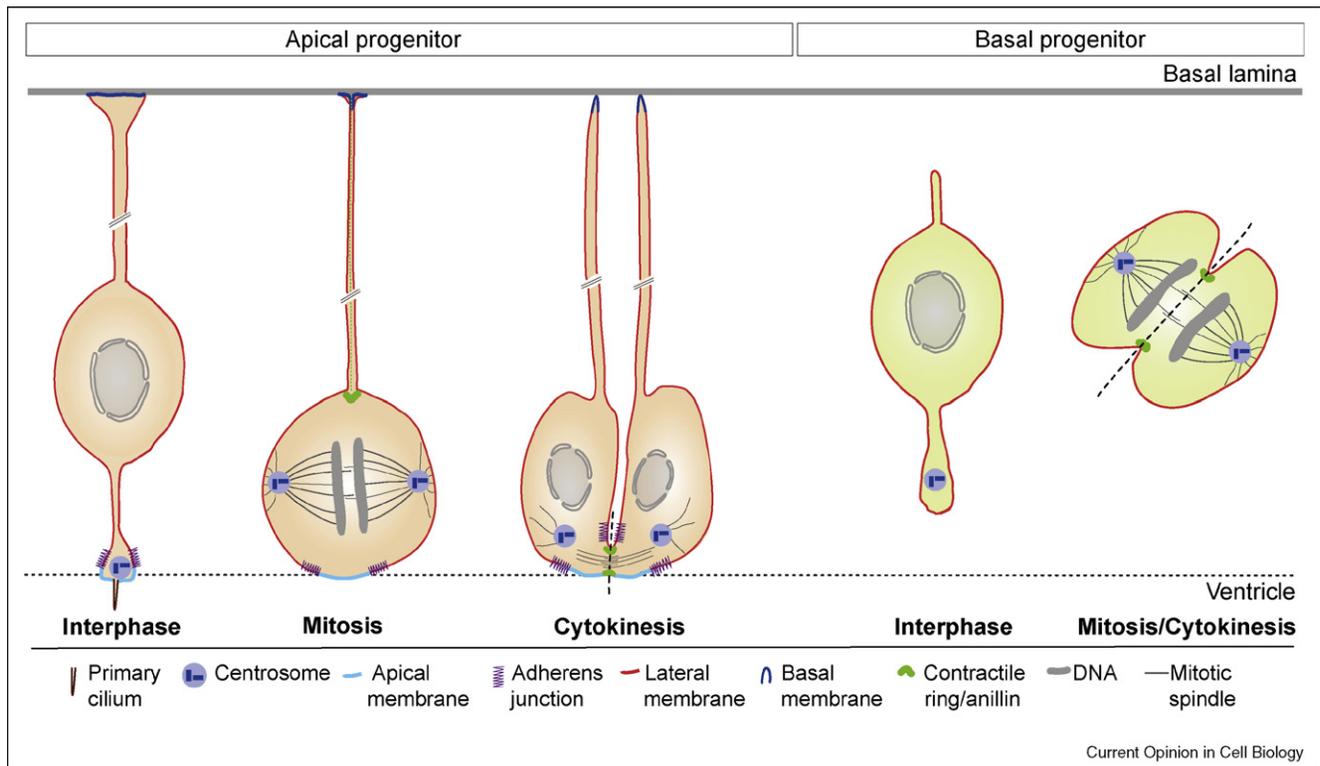
A further type of neural progenitor appearing at the onset of neurogenesis in rodents is the basal or intermediate progenitor (BP, also called non-surface progenitor) (Table 1) [10,12,13]. BPs delaminate from the apical surface of the neuroepithelium, translocate their nucleus to the basal region of the VZ to form the second germinal layer, the subventricular zone (SVZ), and retract both their apical and basal process before mitosis. Accordingly,

BP divisions are typically located in the basal VZ and SVZ (Figure 1). Most BP divisions are symmetric self-consuming, producing two neurons. However, it has been suggested that a small fraction of rodent BPs are capable of proliferative symmetric divisions, thereby expanding the BP pool in the SVZ [9,10,14].

Classification of neural stem and progenitor cells

From a cell biological perspective, a hallmark of the neuroepithelium, and later in development of the cortical wall, is its apical–basal polarity. In light of this, and irrespective of their morphological and functional diversity and marker expression, neural stem and progenitor cells fall into two principal groups. The first comprises those neural stem and progenitor cells that undergo mitosis at (or very near to) the apical, ventricular surface and that, during M-phase, are connected to each other by adherens junctions at the apical-most end of their lateral plasma membrane. These are the neuroepithelial cells and RGCs, which will therefore be collectively referred to as apical progenitors (APs). The second group comprises those neural progenitors that undergo mitosis in an abventricular location, typically in the basal VZ and SVZ (though mitosis just beneath the adherens junctions may, in principle, be possible) and that, during M-phase, are no longer part of the adherens junction-connected AP assembly. These are the basal or intermediate progenitors, and we shall use the former term (BPs) to stress their cell biological difference to APs. Table 1 summarizes key aspects of APs and BPs, and Figure 1 illustrates some of the cell biological features of interphase and mitotic APs and BPs discussed below.

Figure 1



Cell biological features of APs and BPs in interphase and during mitosis and cytokinesis. For details, see text and key.

Architecture of apical progenitors and its role in proliferation versus differentiation

Apical progenitors in interphase

Basal lamina and basal plasma membrane

It was previously reported that in knockout mice lacking certain basal lamina constituents or integrin receptors, in which attachment of radial glial end-feet to the basal lamina was disrupted, AP proliferation and peak neurogenesis were seemingly unaffected [15]. These observations are consistent with the general notion [6,16] that key factors for the control of polarized neural progenitor proliferation versus differentiation reside in the apical rather than basal portion of APs. Nonetheless, the study of Haubst *et al.* [15] is one of several examples (see also below) showing that disturbing a major cell biological feature of polarized neural progenitors may have surprisingly little effect. Such findings raise at least two principal, general questions. First, are there compensatory mechanisms that we are unaware of? Second, do we underestimate the robustness of cell-intrinsic programs of neural progenitors? The impressive studies showing that distinct lineage trees can be observed for single dissociated neural progenitors [17], that is, in the absence of any tissue context, provide compelling evidence for such robustness.

Lateral plasma membrane and adherens junctions

The lateral plasma membrane constitutes by far the greatest proportion of the AP cell surface. Yet, for most of its extension, this membrane has not been the subject of functional studies, as primarily the apical-most domain of the lateral membrane, which harbors the adherens junctions, has been in the focus of investigation. Several lines of evidence suggest that adherens junctions and their molecular constituents function as key determinant of cell polarity and cell proliferation.

Cadherins and associated proteins Dlg5, a member of the disc-large (Dlg) protein family, has been found to be involved in plasma membrane delivery of cadherins by linking cadherin-containing transport vesicles with the t-SNARE targeting complex [18]. Loss of Dlg5 leads to loss of cell polarity and of apical junctional proteins in neuronal progenitors at later stages of neurogenesis. Regarding the cadherins themselves, conditional loss of N-cadherin in the developing telencephalon provoked a complete loss of apical-basal polarity of the neuroepithelium and loss of adherens junctions [19]. In an attempt to clarify the role of cell adhesion in regulating symmetric versus asymmetric divisions, both loss-of-function and gain-of-function experiments using N-cadherin were performed *in vitro* [20]. The bottom line of these studies is

that adherens junction integrity is crucial for apical–basal polarity, but altered β -catenin signaling rather than cadherin-mediated cell adhesion represents the primary mechanism regulating the choice between proliferation and differentiation of neural progenitors.

Numb and adherens junctions Previous studies from several laboratories on the Notch inhibitor Numb, specifically, on its subcellular localization, inheritance upon symmetric versus asymmetric division, and its effects on daughter cell fate, had not yet provided a coherent picture [21]. A major contradiction between Numb function and subcellular localization has now been resolved using immunoelectron microscopy [22^{••}]. Specifically, the previously reported apparent apical crescent of m-Numb during mitosis actually represents the end-feet of interphase RGCs surrounding the mitotic cell, and m-Numb in the mitotic cell is in fact distributed throughout the basolateral cortex. Here, Numb is found on endosomal vesicles concentrated near adherens junctions and regulates cadherin trafficking. Importantly, Numb emerges as a major regulator of adherens junction maintenance and AP cell polarity, and this novel function of Numb appears to be distinct from its canonical role as a Notch inhibitor [22^{••}].

Apical plasma membrane and primary cilium

By analogy with other epithelial cells, the apical plasma membrane of APs can be divided into at least three subdomains, (i) the planar portion constituting the ventricular surface, (ii) the subapical domain between the ventricular apical membrane and the lateral adherens junctions, and (iii) the membrane protrusions emerging from the ventricular apical membrane, such as microvilli and, in particular, the primary cilium. Progress has been made regarding the role of proteins associated with the cell cortex underneath the apical plasma membrane, and with respect to the primary cilium.

Apical cell cortex The cell cortex underneath the apical plasmalemma contains protein complexes crucial for cell polarity and fate. The proteins Par-3 (ASIP), Par-6, and aPKC (PKC λ and PKC ζ) localize to the apical cell cortex (including the adherens junctions) [23]. Previous work had established a crucial role of PKC λ [24] and the small Rho-GTPase Cdc42 [25], a Par complex regulator, for the integrity of adherens junctions and neuroepithelial cell polarity. Using both loss-of-function and gain-of-function experiments in the mouse telencephalon, a recent study now demonstrates a crucial role of the Par protein complex in the maintenance of symmetrically dividing APs [26[•]]. Par protein manipulation had similar effects in undissociated tissue and dissociated progenitor cells, indicating a cell-intrinsic effect of the Par protein [26[•]]. It remains to be studied to which extent this is affected by the shuttling of Par proteins between the cell cortex and the nucleus [27].

The primary cilium The three subdomains of the apical plasma membrane mentioned above not only differ in their morphology but also exhibit distinct molecular composition. Here, membrane lipids are moving into the focus of investigation. For example, the cholesterol-interacting pentaspan membrane protein prominin-1 (CD133) is highly enriched in microvilli and, when these disappear with the onset of neurogenesis, in the primary cilium [28,29^{••}]. By analogy with other epithelial systems [30], it is likely that specific lipids such as certain gangliosides will also be enriched in apical plasma membrane protrusions of APs.

Besides serving as an anchor site for the centrosome in interphase (see below), the primary cilium has been shown to serve as an antenna for extracellular signals (for recent reviews see [31,32]). Two major signaling pathways regulating proliferation versus differentiation have been linked to ciliary function: the sonic hedgehog (shh) and the wnt pathways [33,34]. Thus, shh signaling via the primary cilium has a crucial role for the expansion of neural progenitors during adult neurogenesis in the dentate gyrus of the hippocampus [35] and during neurogenesis in the developing cerebellum [36]. Extrapolating from these observations to embryonic neurogenesis in the neocortex, the intriguing possibility arises that the expansion of APs also involves signal transduction via their primary cilium. If so, the previously postulated importance of the apical plasma membrane [16] may lie, at least partly, in the fact that it contributes to the primary ciliary membrane. Given that the primary cilium is disassembled before M-phase and re-established thereafter, an important question arising in this context is whether the microdomains of the primary ciliary plasma membrane that contain the relevant signal transducing molecules remain in the apical plasma membrane during M-phase, or are endocytosed before it, as this may be important for their distribution to the daughter cells during cytokinesis (see below).

In this context, another unresolved question concerns the route that any ligand, signaling to APs via the primary cilium, would take to reach the receptor in the primary ciliary membrane. It has been proposed that transforming growth factor (TGF)- β 1 is released from the choroid plexus and reaches APs via the cerebrospinal fluid [37]. In the early neural tube, green fluorescent protein (GFP)-tagged shh was found in small vesicles enriched, within the apical cell cortex, at the basal body, but its ventricular localization still remains an enigma [38]. It should be noted that the mouse neuroepithelium loses tight junctions between E8 and E9 [6], and so a ligand present in the cerebrospinal fluid may reach its receptor even when the latter is present in the lateral (rather than apical) plasma membrane. On a general note, understanding the interplay between factors promoting expansion of APs (e.g. shh, FGF, wnt, EGF) and those inhibiting expansion

and promoting differentiation (e.g. TGF- β) at the cell biological level will require further information on the extracellular trafficking routes of these factors and the subcellular localization of their receptors.

Finally, the primary cilium of APs appears to be a novel site for the budding of extracellular membrane vesicles carrying the somatic stem cell marker prominin-1 (CD133) into the ventricular fluid [29^{••}]. It remains to be determined whether this membrane budding is relevant for the life cycle of the primary cilium during the cell cycle, for example, its disassembly before AP mitosis, or for the signal transduction that occurs across the ciliary plasma membrane.

Golgi complex and endosomes

Golgi complex A recent study suggests a Golgi-based mechanism for regulating Numb function that operates differentially in mitotic and post-mitotic cells [39[•]]. After Golgi fragmentation in AP mitosis, a novel Numb-binding protein called ACBD3 is released from Golgi membranes into the cytosol. By contrast, in newborn post-mitotic neurons, ACBD3 associates with the reformed Golgi and is unable to bind Numb. It is proposed that ACBD3 binding to Numb during AP mitosis affects its inhibition of Notch signaling [39[•]]. Thus, a cell cycle-dependent, Golgi-based sequestration and release of molecules appears to indirectly affect progenitor versus neuronal cell fate.

Endosomes Notch signaling is known to promote RGC identity, and RGCs express Notch target genes, indicative of Notch activation. Extending earlier observations in *Drosophila* and zebrafish, Notch activation in the signal-receiving cell (the AP) is now shown to require endocytosis-dependent activation of Notch ligands in the signal-sending cell, specifically Mindbomb1 (Mib1), a ubiquitin ligase involved in endocytosis. Its conditional disruption abolishes Notch activation in APs, which results in these cells now undergoing symmetric differentiative divisions producing either two BPs or two neurons, and hence premature consumption of RGCs [40[•]]. In line with the classical lateral inhibition model, BPs and newborn neurons are proposed to be the signal-sending cells that ensure RGC maintenance.

Nucleus—interkinetic nuclear migration

A hallmark of APs is the apical–basal–apical migration of the nucleus during the cell cycle. Centrosomes and microtubule-associated proteins play a major role not only in moving the nucleus during neuronal migration but also in maintaining the neuronal progenitor pool during neurogenesis. A recent study has identified two centrosome-associated proteins, Cep120 (Ccdc100) and its binding partner Tacc3, as crucial players in INM and in maintaining the AP pool, establishing a link between the centrosome and INM in neurogenesis [41[•]]. Upon loss-

of-function for either Cep120 or Tacc3, the AP pool was found to be markedly depleted as a specific result of reduced INM. Notably, neuronal migration was not impaired. As no change was observed with regard to (i) cleavage plane orientation, (ii) cell cycle length, and (iii) apical polarity, these findings imply a crucial function of INM in AP pool maintenance.

Apical progenitors in M-phase

Basal process and cleavage furrow

Elegant live imaging studies on telencephalic slice cultures have reported that the basal process of APs is maintained during mitosis and inherited by one of the daughter cells [42]. Recent observations have advanced this notion in an unexpected direction. Specifically, for both mouse and zebrafish APs, it has been found that the basal process can be split during M-phase, and the split basal processes can be inherited either asymmetrically by one, or symmetrically by both, daughter cells [43]. It appears that in these cells, cytokinesis is initiated before anaphase onset and proceeds in the basal-to-apical direction along the entire length of the basal process during prometaphase [43]. These observations offer an explanation as to why in AP divisions, the cleavage furrow ingresses strictly from the basal pole of the cell body toward the apical, ventricular surface, and why this ingression occurs parallel (rather than perpendicular) to the long, apical–basal axis of the cell. Importantly, such asymmetric, basal-to-apical, furrow ingression may facilitate the maintenance of adherens junctions during AP divisions, and thus the integrity of the neuroepithelium.

Mitotic spindle

Cleavage furrow ingression is known to occur perpendicular to the axis of the mitotic spindle. Consistent with the cleavage furrow ingression occurring parallel to the apical–basal axis of APs, it is now generally accepted that the mitotic spindle is oriented perpendicular to this axis in the vast majority of APs [16,44], a notion confirmed in several recent studies [9,45^{••},46,47].

Cell cortex—lgn As to the machinery that regulates the orientation of the mitotic spindle in APs [2], two recent studies have provided evidence that interfering with the function of the G-protein regulator LGN (Gpsm2) results in random spindle positioning, both in mouse telencephalon and in chick spinal cord [45^{••},48^{••}]. Remarkably, despite this perturbation in a major cell biological feature of AP division, overall neuron production was not significantly affected. This raises, again, the issues of the robustness of cell-intrinsic programs of neural progenitors, and whether unknown compensatory mechanisms exist.

Microtubules—lis1 However, perturbation of the mitotic spindle in APs via other target proteins can have dramatic consequences for brain development. Using hypomorphic *Lis1* mutant mice, it was shown that mitotic

spindles have no astral microtubules owing to reduced attachment at the cell cortex, mediated via dynein and Ndel1, leading to randomized cleavages and metaphase arrest in neuroepithelial cells without disruption of apical polarity or epithelial integrity [49^{••},50]. Notably, the mutant progenitors were eliminated by apoptosis, resulting in extreme cases in the complete loss of the affected brain area. By contrast, loss of Lis1 in RGC induced less severe phenotypes, suggesting that symmetrically dividing neuroepithelial cells are more dependent on Lis1 function than the asymmetrically dividing RGCs.

Centrosomes—*aspm* and *pericentrin* It has been known that mutations in genes encoding centrosomal proteins (ASPM, CENPJ, CDK5RAP2) can cause primary microcephaly in humans [51]. Recent studies add the centrosomal protein pericentrin (PCNT) to the list, loss-of-function mutations in which also result in microcephaly [52,53]. However, the underlying cell biological mechanism remains to be elucidated.

A proper ingression of the cleavage furrow parallel to the apical–basal axis of APs requires not only that the mitotic spindle is correctly positioned before anaphase onset but also that its orientation is maintained through anaphase and telephase until the ingressing cleavage furrow has reached the apical plasma membrane for abscission. Interestingly, *Aspm*, mutations in which are a major cause of primary microcephaly in humans [54] and that is associated with mitotic spindle poles in APs [55], is emerging as a protein that exerts the latter function [56]. Given the small size of the apical plasma membrane [16], *Aspm* thus maintains symmetric proliferative divisions of APs [55] by functioning as a ‘cleavage precision protein’ [56]. An important question arising is whether this crucial role of *Aspm* is exerted at the poles of the mitotic spindle and/or the midbody (see below), where *Aspm* has also been found [57].

Midbody

The midbody is a thin cytoplasmic bridge connecting the nascent daughter cells that is formed at the late stage of cytokinesis as a result of cleavage furrow ingression and that contains the remnants of the central spindle and the contractile ring (midbody ring) [58]. Typically, a single cut through the midbody on one side of the midbody ring leads to abscission (the separation of the daughter cells). Remarkably, the relatively large (0.5–1 μm) membrane particles carrying prominin-1 (CD133) that were previously found to be released into the ventricular fluid just before the switch of APs to neurogenic divisions [28] have now been shown to represent midbodies released from symmetrically dividing neuroepithelial cells [29^{••}]. This raises the exciting possibility that midbody release, which is a means of reducing, in APs, the apical plasma membrane and membrane microdomains enriched in the somatic stem cell marker prominin-1 (CD133), contrib-

utes to the switch of APs from symmetric, proliferative to asymmetric, neurogenic division.

Architecture of basal progenitors and its role in proliferation versus differentiation

Basal progenitors in interphase

Generation of basal progenitors

There are two routes to generate BPs in rodents, (i) a primary route in which an AP, presumably by asymmetric division, produces a BP that translocates its nucleus and cell body basally, and (ii) a secondary route in which a BP self-amplifies by symmetric division [4,5,10,13,14,46]. Only a small proportion of BPs (≈10%) appear to be capable of self-amplification [10], which presumably correspond to the minor subpopulation of BPs that do not yet express the neurogenic marker Tis21 [12] and that may well originate from the minor subpopulation of asymmetrically dividing APs that are Tis21-negative [16,46]. By contrast, the vast majority of rodent BPs (90%) divide symmetrically into two neurons and, accordingly, are Tis21-positive on mitosis [12,46].

Although BPs lack INM, the apical-to-basal translocation of their nucleus and cell body to the basal VZ and SVZ may well involve components of the machinery that mediates the G1-INM of APs. However, differences may also exist, as the apical-to-basal translocation of BPs represents a delamination process that is accompanied, eventually, by the loss of adherens junctions and the retraction of their apical process [13,46], whereas this is not the case for the G1-INM of APs.

What is the molecular machinery that underlies the generation of BPs? BPs are known to specifically express the transcription factor Tbr2 [14,59], and it might be anticipated that Tbr2 promotes BP biogenesis. Interestingly, using both loss-of-function and gain-of-function analyses, the transcriptional repressor Insulinoma-associated 1 (*Insm1*) has been identified not only as a pan-neurogenic factor but, in the neocortex, as a master regulator of BP biogenesis [60^{••}]. Loss of *Insm1* results in a substantial lateral expansion of the ventricular zone at the expense of BP and neuron production. Conversely, forced expression of *Insm1* increases the level of BPs at the expense of APs and, interestingly, promotes self-expansion of BPs at the expense of neuron production. Thus, a set of transcription factors is emerging that control the conversion of APs into BPs [13,60^{••},61], and it will be interesting to dissect the downstream molecular machinery that mediates the relevant cell biological changes, notably the delamination and process retraction.

Cell polarity, interaction with other cells

Arising from APs, which exhibit apical–basal polarity through mitosis, newborn BPs will not be devoid of polarity cues in interphase, but have been shown to lack

apical–basal polarity by the time they undergo mitosis [46] (see below). Nonetheless, candidates for cell-to-cell interactions with BPs exist, such as (i) newborn neurons, (ii) endothelial cells of invading blood vessels, and (iii) importantly, RGC. RGCs and their progeny are electrically coupled, raising the possibility that BPs are also directly coupled to RGCs through gap junctions [62]. Another form of cell-to-cell interaction between BPs and RGCs is the one occurring in the context of Delta-Notch signaling [40•] (see above). It will be important to determine the consequences of these interactions for BP proliferation versus differentiation.

Basal progenitors in M-phase

Lack of apicobasal polarity and processes

BPs in mitosis lack apical–basal polarity and adherens junctions, as revealed by immunostaining for established markers such as prominin-1 (CD133), megalin, aPKC, and ZO-1 [46], and exhibit, if at all, very short (one cell body diameter in length) processes [9,46]. This lack of apical–basal polarity has implications for the role of cleavage plane orientation in symmetric versus asymmetric division of BPs (see below).

Mitotic spindle and cleavage plane

Rodent BPs divide with a nearly randomized cleavage plane orientation [9,46]. This is compatible with most, if not all, BP divisions being cell biologically symmetric because mitotic BPs lack apical–basal polarity. Indeed, the vast majority of rodent BP divisions are symmetric also in terms of the fate of the progeny, producing either two neurons or, much less frequently, two BPs [9,46]. A key issue of future research will be to identify the molecular determinants that govern whether the symmetric divisions of BPs are proliferative (two BPs) or differentiative (two neurons). Cell cycle length may well be a candidate, as the small proportion of BPs undergoing self-amplification [10] almost certainly correspond to that lacking Tis21 expression (an inhibitor of cell cycle progression) [12], and the self-expanding BPs observed upon forced *Insm1* expression are Tis21-negative [60••].

Conclusions and perspectives

During the past few years, there has been a remarkable increase in the number of studies that aim to understand the proliferation versus differentiation of mammalian neural stem and progenitor cells at the mechanistic, cell biological level. Relevant specific features of the architecture of these cells have been unravelled in the developing rodent brain, and molecules that act as master regulators have been put into subcellular context. It is a safe prediction that this approach to neural stem cell biology will even be expanded in the future. However, perhaps the most exciting vision is that a dissection of the cell biology of neural stem and progenitor cells in species other than the canonical rodent model, notably in primates, is within reach. This holds the promise to

understand the evolution of the primate neocortex at the cellular level.

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