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Cortical progenitor expansion, self-renewal and neurogenesis—a polarized perspective

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Neural stem and progenitor cells giving rise to neurons in developing mammalian neocortex fall into two principal classes with regard to location of mitosis—apical and basal, and into three principal classes in terms of cell polarity during mitosis—bipolar, monopolar, and nonpolar. Insight has been gained into how inheritance of polarized, apical and basal, cell constituents is related to symmetric versus asymmetric divisions of these progenitors, and how this inheritance is linked to their expansion, self-renewal, and neurogenesis. Retention and inheritance of the basal process emerge as key for self-renewal, notably for the monopolar progenitors of prospective gyrencephalic neocortex that undergo asymmetric mitoses at basal locations. The resulting expansion of the neocortex during evolution is proposed to be associated with an increased cone-shape of radial units.

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Introduction—a cell polarity-based classification of cortical stem and progenitor cells

The expansion of the neocortex during evolution is primarily due to the increase in the number of neurons and glial cells generated during development by divisions of cortical stem and progenitor cells [1–3]. With regard to the increase in neurogenesis, which is the focus of the present review, cortical stem and progenitor cells have been studied with growing emphasis on their mode of cell division and the role of cell polarity in this mode [1,4]. In terms of polarized morphology at M-phase, three classes of cortical stem and progenitor cells can be distinguished: bipolar, monopolar and nonpolar cells (Figure 1). We will therefore first delineate a cell polarity-based classification of cortical stem and progenitor cells, and then discuss recent studies showing how cell polarity impacts on their expansion/self-renewal and on neurogenesis.

Bipolar progenitors

Neuroepithelial and radial glial cells

Cortical stem and progenitor cells with bipolar morphology at M-phase are the neuroepithelial (NE) cells and the radial glial (RG) cells they transform into with the onset of neurogenesis (Figure 1). Their bipolar nature reflects their apical–basal polarity, with an apical plasma membrane corresponding to the ventricular surface, adherens junctions (AJs) at the apical-most end of the lateral plasma membrane, and a basal process contacting the basal lamina, all being present throughout the cell cycle. NE and RG cell bodies reside in the ventricular zone (VZ), and their nuclei undergo interkinetic nuclear migration (INM), with mitosis occurring at the apical surface [1,4–6]. These cells will be referred to collectively as apical progenitors (APs). The defining criteria for this term are the presence of an apical plasma membrane and their integration into the apical AJ belt as the cell undergoes mitosis apically, rather than the absence or presence of certain markers. APs generate the progenitors described below and some cortical neurons.

Monopolar progenitors

Outer-subventricular-zone progenitors

Cortical stem and progenitor cells with monopolar morphology at M-phase are the outer-subventricular-zone (OSVZ) progenitors [7] recently characterized in human and ferret [8••,9••] (Figure 1). OSVZ-progenitors are thought to originate from APs and to delaminate from the apical AJ belt, and translocate their nucleus to the subventricular zone (SVZ), predominantly the OSVZ, for mitosis. Their monopolar nature at M-phase reflects the retention of a basal process but lack of an apical plasma membrane [8••,9••]. Lack of apical contact, mitosis in the SVZ and basal process retention during M-phase are the defining criteria of OSVZ-progenitors.

Short neural precursors

The recently characterized short neural precursors (SNPs) [10,11] can be regarded as another type of monopolar cortical progenitor (Figure 1). SNPs are APs according to the above definition [11], exhibit apical polarity and apical AJs but have been reported to retract, in contrast to NE and RG cells, their basal process for M-phase [10,11], hence their classification as monopolar.

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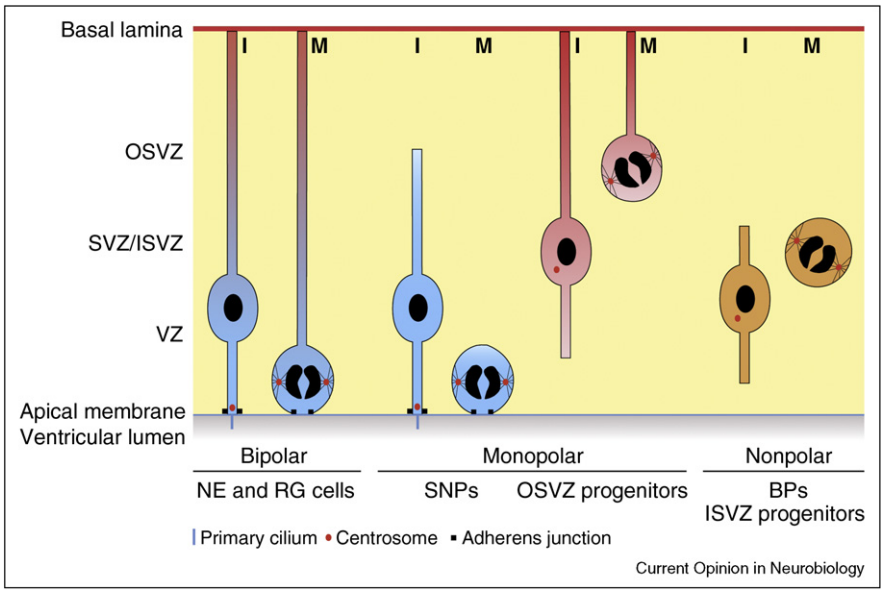
Figure 1



Neural stem and progenitor cells classified according to the absence or presence of polarized morphology at M-phase. I, interphase; M, M-phase. For details, see text.

Nonpolar progenitors

Basal/intermediate progenitors, inner subventricular zone progenitors

Cortical progenitor cells with nonpolar morphology at M-phase are the basal progenitors (BPs), also called intermediate progenitors, that have been studied in rodents [5,6,12–15], and the inner-SVZ (ISVZ) progenitors recently characterized in human and ferret [8••,9••] (Figure 1). Rodent BPs originate from APs. Human ISVZ-progenitors originate from OSVZ-progenitors [8••] but presumably also from APs, as ISVZ-progenitors appear abundantly before OSVZ-progenitors [9••].

BPs delaminate from the apical AJ belt and translocate their nucleus to an abventricular location for mitosis, typically in the SVZ or basal VZ [4–6,12]. The fundamental cell biological difference between a mitotic AP and BP is the presence versus absence of apical plasma membrane, and integration versus lack of integration into the apical AJ belt. Thus, irrespective of the presence or absence of certain markers, a progenitor that undergoes mitosis in a slightly abventricular location, for example one nuclear layer away from the ventricle, is an AP if it has apical plasma membrane and is integrated into the apical AJ belt, but a BP if this is no longer the case.

BPs retract their apical and basal processes before M-phase, with any remaining processes during mitosis being typically less than one cell body diameter long, and lack apical–basal polarity [5,6,12–14]. For these reasons, we classify BPs as having nonpolar morphology at M-phase, although the BP cell body may exhibit polarity. For example, if a BP establishes junctions with a radial glial fiber or an endothelial cell [16,17], these macromolecular assemblies may constitute a polarized cue to the cell body even if this is not translated into an overt polarized morphology. Taken together, the defining criteria of BPs are mitosis in an abventricular location and lack of apical features (apical plasma membrane, junctions and process) and a basal process at M-phase.

ISVZ-progenitors appear to be very similar to BPs in that they exhibit a nonpolar morphology at M-phase [7,8••,9••]. This classification is not contradicted by the observations that some ISVZ-progenitors exhibit a short apical process at telophase [8••,9••], which may reflect the early establishment of an interphase property.

In a wider sense, ISVZ-progenitors and OSVZ-progenitors can be regarded as 'basal' progenitors, as they divide basally. However, given the existence of 'basal' progenitor subclasses with regard to polarized morphology at M-phase, we shall use the original terminology (ISVZ-, OSVZ-progenitor) and restrict the term BP to progenitors as defined above.

Occurrence of progenitor classes in lissencephalic versus gyrencephalic cortex

APs constitute the canonical progenitors in the mammalian VZ (Figure 2); however, an open issue is the relative abundance of bipolar APs (NE and RG cells) to

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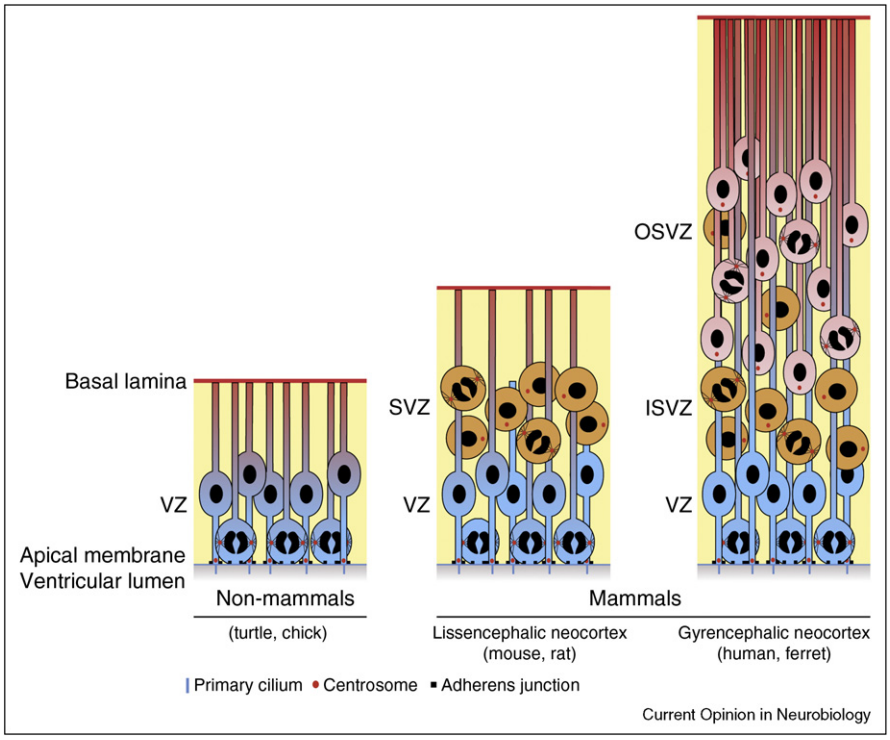
Figure 2



Comparison of progenitor layers in non-mammalian vertebrates (left), mammals developing a lissencephalic neocortex (middle) and mammals developing a gyrencephalic neocortex (right). See also Figure 1. For details, see text.

monopolar APs (SNPs) [10,11,13,15]. Nonpolar progenitors, too, are a conserved feature of the developing neocortex, with the majority of ISVZ-progenitors of gyrencephalic neocortex being the counterpart, at least in terms of cell polarity, of the BPs of lissencephalic neocortex [7,8••,9••] (Figure 2). The most striking difference between the developing lissencephalic and gyrencephalic neocortex seems to be the abundance of delaminated monopolar progenitors, the OSVZ-progenitors, in the latter [8••,9••] (Figure 2).

Differences in cell polarity between progenitor classes reflect a spectrum of alterations in subcellular organization, which is thought to impact on their mode of division and hence on the number of progenitors and neurons generated therefrom [1,4]. In discussing the recent insight into cortical progenitor biology, we focus on specific subcellular structures such as the apical cell cortex, primary cilium, centrosome and basal process, as well as processes linked to these structures such as cleavage plane orientation. The molecules and organelles discussed are summarized in Table 1. Owing to space limitations, we cannot address other recent advances in cortical progenitor biology such as those concerning the role of chromatin remodeling or of microRNAs, nor provide a comprehensive discussion of signaling pathways.

Bipolar progenitors in lissencephalic neocortex

Apical cell cortex including adherens junctions

It has previously been suggested that the apical domain (a term collectively referring to the apical plasma membrane, associated apical cell cortex and apical AJs, Figure 1) of APs harbors molecules that are crucial for cell polarity, promote AP self-renewal and influence daughter cell fate [4,18]. Substantial progress has been made regarding the identification of such molecules. Extending previous work on mouse cortical APs and Par3 [18,19], a constituent of an apical protein complex also containing Par6 and aPKC, the level of Par3 inheritance has now been shown to crucially influence daughter cell fate, with Par3 overexpression promoting progenitor fate and Par3 depletion neuronal fate [20•]. These effects are mediated by Notch signaling through Par3 interaction with the Notch inhibitors Numb and Numblike. In interphase APs, Par3 is concentrated just apical to AJs [20•,21] in the subapical domain. Thus, in mechanistic terms, Par3 may sequester Numb and Numblike, which are normally associated with AJs and the lateral plasma membrane [22], to the subapical cell cortex, thereby reducing the probability that these proteins inhibit Notch signaling.

Divergent observations have been reported regarding Par3 localization during cytokinesis of mouse APs, as

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Table 1

Molecules and organelles discussed in this review

Molecule/organelle	Implication	Reference
Apical cell cortex		
Par3	AP self-renewal/expansion	[18,19,20•,21]
Pals1	AP self-renewal/cell cycle reentry	[28]
Mals-1, Mals-2, Mals-3	AP self-renewal/cell cycle reentry	[29]
MARCKS	AP self-renewal	[30]
Primary cilium		
Sonic hedgehog	AP self-renewal/expansion	[31–33]
Centrosome	AP self-renewal	[39••]
Basal process		
Laminin α2 and α4, integrin β1	AP survival	[42]
Retinoic acid	AP differentiation/neurogenesis	[43•]
Notch	OSVZ progenitor maintenance	[8••]
RGD-sensitive integrins (e.g. αvβ3)	AP/OSVZ population size	[9••]
Mitotic spindle and cleavage plane orientation		
Lfc	AP differentiation/neurogenesis	[47•]
Lis1/DCX	AP survival/expansion	[49,50]
Cdk5rap2	AP survival/expansion	[52,53]
Aspm	AP expansion	[51,54••]
Magoh	BP population size	[57]
Transcription factors		
Insm1	BP genesis/expansion	[59]
Tbr2	BP genesis/expansion	[60,61]
AP2γ	BP genesis	[63•]
Fezf1 and Fezf2	BP genesis	[64]
Ngn2	BP genesis	[65]
Cux2	BP differentiation/neurogenesis	[67]
Cell cycle regulators		
Cdk4/cyclin D1, cyclin E and D2	BP expansion	[70••,71••,72]

Par3 has been found to largely remain localized at the subapical cell cortex [18,21] or to become concentrated at the cleavage furrow [20•]. Be this as it may, in either case an asymmetric Par3 inheritance by the daughter cells has been inferred, which is thought to result in their asymmetric fate, with the daughter cell inheriting more Par3 proposed to remain an AP [18,20•,21].

An unexpected turn as to the effects of asymmetric Par3 inheritance on AP daughter cell fate has come from an elegant imaging study of Par3-GFP–expressing APs in the zebrafish neural tube [23•]. This study revealed that symmetric versus asymmetric Par3 inheritance is largely correlated with symmetric versus asymmetric daughter cell fate, respectively. Remarkably, on asymmetric Par3 inheritance, the daughter inheriting the apical Par3 domain adopted neuronal fate, whereas the other daughter re-established an apical domain and thus remained an AP [23•]. Hence, concerning the effect of apical domain inheritance on daughter cell fate (progenitor versus neuron), these findings [23•] are opposite to the *Drosophila* neuroblast paradigm [24] and to what has been originally proposed [4,18,25] and recently shown [19,20•] for mammalian cortical APs. These apparently contradictory observations can be reconciled if inheritance of the basal process is taken into account, as will be discussed below.

Pals1 (Protein associated with Lin7), the mammalian homologue of *Drosophila* stardust, is a component of another apical protein complex [26]. In line with the interaction of stardust with the subapical transmembrane protein crumbs [27], the Pals1 complex is a constituent of the subapical cell cortex in mouse cortical APs and physically interacts with the Par3/Par6/aPKC complex [28]. Using conditional ablation and RNAi as well as overexpression approaches in mouse cortical APs, Pals1 has been shown to promote progenitor fate, notably cell cycle reentry [28]. Pals1 function thus appears to be similar to that of Par3. Moreover, the notion that proteins of the subapical cell cortex promote AP fate and cell cycle reentry is further supported by the phenotype of developing mouse cortex lacking the three Mals (Lin7) proteins, which are additional components of the subapical cell cortex interacting with the Pals1 complex [29]. A similar conclusion can be drawn from the phenotype of developing mouse cortex lacking the PKC substrate MARCKS (myristoylated alanine-rich C-kinase substrate), which is also enriched in the apical domain of APs [30].

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Primary cilium and centrosomes

Why may the inheritance of the apical domain be a determinant for AP daughter cell fate? Significantly, it is the apical domain that harbors the single primary cilium of APs [5]. Two aspects of the primary cilium of APs are crucial in this regard, (i) the fact that it forms an apical plasma membrane protrusion into the ventricular lumen, and (ii) that its basal body constitutes one of the centrioles of the centrosome (Figure 1).

Ciliary plasma membrane

The primary cilium has been shown to serve as a sensory organelle that transduces, via transmembrane receptors, extracellular signals from the ventricular fluid that regulate brain patterning, and the proliferation and specification of neural progenitors (for recent reviews, see [31,32]). In line with the notion that the apical primary cilium transduces signals present in the embryonic ventricular fluid that promote the expansion of cortical APs [5], sonic hedgehog, a morphogen known to mediate neural progenitor expansion and to signal via the primary cilium [31,32], has recently been detected in the mouse embryonic cerebrospinal fluid (CSF) [33]. In this context, it may be significant that the embryonic CSF is rich in lipoproteins [34], as many morphogens, notably those of the hedgehog and wingless families, are associated with lipoproteins [35]. Moreover, mouse embryonic CSF contains membrane particles derived from AP midbodies, cilia and microvilli that carry molecules characteristic of somatic stem cells, such as prominin-1/CD133 [36]. Thus, embryonic CSF may contain a variety of soluble and particulate molecules that could promote AP fate via primary cilium-based signal transduction.

Basal body/centrosomes

Since one centriole of the centrosome forms the basal body of the AP primary cilium, the centrosomes of APs are localized to the apical plasma membrane during interphase [5]. As in any cycling cell, the two centrioles in the centrosome of a mother AP before centrosome duplication were synthesized in the two previous cell cycles, that is in the grandmother and grand-grandmother AP, but following centrosome duplication end-up in two separate daughter cells [37]. In other words, any AP division (as any cell division) is asymmetric with regard to the age of the centrioles in the centrosomes inherited by the daughter cells.

Consistent with previous studies in invertebrates showing that asymmetric centrosome inheritance plays a crucial role in maintaining self-renewing divisions [38], an elegant imaging study [39••] has recently uncovered an intriguing relationship between asymmetric centrosome inheritance and asymmetric AP daughter cell fate. Specifically, the centrosome with the older centriole is inherited by the AP daughter, whereas that with the younger centriole is inherited by the differentiating cell leaving the VZ (presumably a BP) and is eventually found in neurons [39••]. Moreover, this asymmetric centrosome inheritance was shown to be essential for AP maintenance. These findings are proposed to reflect the differential timing of ciliogenesis in the daughter cells, with the AP daughter being able to re-establish its primary cilium, and hence to respond to ventricular signals, earlier than the non-AP daughter [39••]. While this is an intriguing concept, an important question to be resolved is how asymmetric centrosome inheritance can be reconciled with symmetric, proliferative divisions of APs, which give rise to two AP daughters.

The apically localized centrosomes of APs are also a determinant for their mitoses occurring apically and for the preceding basal-to-apical leg of INM. Substantial progress has been made in unraveling the INM machinery. However, owing to space limitation, these studies will not be discussed here, but the reader is referred to a recent review [40].

Basal process

One of the major conceptual advances that has emerged recently is that bipolar AP identity, self-renewal and expansion requires inheritance not only of the apical domain, but also of the basal process [41] (Figure 1). Consistent with this, basal lamina attachment mediated by the basal process, specifically involving laminin $\alpha 2$ and $\alpha 4$ and integrin $\beta 1$, has been found to be important for the maintenance of the AP pool during neurogenesis and the development of the cerebral cortex to normal size [42]. In this context, not only the basal lamina but also the overlying meningeal cells appear to influence APs as retinoic acid released from menigeal cells has been implicated in the switch of APs from symmetric proliferative to asymmetric BP-genic/neurogenic divisions [43•]. Although in the case of retinoic acid it is unclear whether its effects actually involved its entry into the basal process followed by intracellular transport to the AP nucleus (where it acts), as opposed to paracellular diffusion to the AP cell body, the proximity of the basal process endfeet to the meninges could be significant for sensing extracellular signals of basal origin, in particular if this involves cell surface receptors.

Previous studies of asymmetric AP divisions in developing rodent cortex had shown that the AP daughter inherits the basal process [44]. A recent imaging study has extended this notion to asymmetric AP divisions in zebrafish, showing that the basal process is inherited by the AP daughter [23•].

If AP fate is linked to inheritance of the basal process, which has been thought to be inheritable by only one of the daughter cells [41,44], how do APs ever achieve symmetric proliferative division? Studies on mouse and zebrafish NE cells have led to the remarkable observation

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that their basal process can be split during M-phase, specifically during prometaphase [23•,45]. Splitting occurred in the basal-to-apical direction and was followed by inheritance of the split basal processes by one daughter cell (AP daughter, asymmetric inheritance) or inheritance of one basal process each by both daughter cells (symmetric inheritance) [23•,45]. Thus, basal process splitting, together with the splitting of the apical domain, would allow for symmetric proliferative divisions of NE cells.

Not only NE cells, but also rodent RG cells undergo symmetric proliferative divisions, resulting in two RG cells [13,46]. However, the basal process of RG cells is substantially longer than that of NE cells, and thus may be less likely to undergo splitting. In fact, imaging studies showed that on symmetric division of RG cells, the basal process was inherited by only one of the daughters, whereas the other daughter apparently re-grew its basal process [46]. These observations raise the issue whether basal process inheritance is an absolute requirement for AP daughters to adopt an AP fate, or can be compensated by other means.

Mitotic spindle orientation and cleavage furrow ingression

The distribution of polarized, apical and basal, cell fate determinants to the daughters arising from AP divisions is ultimately determined by the orientation of the cleavage furrow, which ingresses perpendicular to the axis of the mitotic spindle (Figure 1). An equal distribution of apical and basal cell constituents to AP daughters requires that ingression of the cleavage furrow, which proceeds in the basal-to-apical direction [45], occurs precisely along the apical–basal cell axis, leading to bisection of the apical plasma membrane [1] (vertical cleavage plane). This requires that the axis of the mitotic spindle is positioned precisely perpendicular to the apical–basal axis of APs (horizontal spindle). Consequently, the machinery involved in the control of mitotic spindle and cleavage furrow orientation has a crucial role in ensuring correct AP daughter fate. Significant insight into key molecules of this machinery has been obtained during the past few years.

The first set of molecules are associated with the mitotic spindle and affect its positioning, presumably via effects on the cell cortex. Lfc, a guanine nucleotide exchange factor activating the small GTPase RhoA, promotes oblique mitotic spindle orientation and neurogenesis [47•]. Conversely, inhibition of Lfc-mediated RhoA activation by the LFC-sequestering protein Tctex-1 promotes horizontal spindle orientation and AP self-renewal/expansion [47•]. These findings are consistent with the concept that cleavage furrow ingression precisely along the apical–basal axis is required for AP self-renewal and expansion, and that deviation from this orientation promotes neurogenesis [1,4]. However, how can they be reconciled with previous observations showing that inducing randomization of mitotic spindle orientation of APs had little, if any, effect on neuronal output [41,48]? Perhaps a key difference between the various approaches is whether or not they also perturb the retention of the basal process of APs through M-phase. One may speculate that RhoA activation [47] also affected the basal process of APs whereas this was not the case upon manipulation of LGN function [41,48].

Perturbation of proper, horizontal mitotic spindle orientation in mouse APs is also caused by ablation of two proteins of the microtubule system, mutations of which cause lissencephaly type I in humans, Lis1 [49] and the functionally interacting protein doublecortin (Dcx) [50]. The resulting spindle alterations are accompanied by depletion of the AP pool and an increase in progenitors dividing in an abventricular location, with the phenotype being most severe in the *Lis1*/*Dcx* double mutant [50].

The second set of molecules are associated with the centrosome and cause primary microcephaly in humans when mutated. Previous work using acute knockdown had shown that the mitotic spindle pole-associated protein Aspm is involved in maintaining the horizontal spindle orientation required for symmetric proliferative AP divisions and thus functions as a cleavage precision protein [1,51]. Two recent studies have similarly explored the function of another microcephaly protein, the centrosomal protein Cdk5rap2 [52,53]. Both, mouse embryos subjected to acute Cdk5rap2 knockdown [52] and mutant mouse embryos expressing a truncated form of Cdk5rap2 defective in γ-tubulin association [53], show a reduction in APs and premature neurogenesis, which in the case of the latter is shown to be associated with a decrease in vertical cleavage plane orientation. However, the lack of Cdk5rap2 function also causes additional mitotic defects, such as abnormal spindle pole number and delay in mitotic progression, which ultimately lead to increased apoptosis and probably contribute to the microcephaly phenotype observed in the mutant mouse embryos [53].

A more general role in cell division also emerges for Aspm. Specifically, mutant mice expressing truncated forms of Aspm exhibit mild microcephaly [54••]. However, in contrast to acute Aspm knockdown [51], APs in the *Aspm* mutant embryos show no perturbation of cleavage plane orientation, presumably because the truncated Aspm proteins retain the microtubule-binding domain [54••]. Thus, the microcephaly phenotype of Aspm loss-of-function mice is not necessarily a result of impaired cleavage precision, but may have additional causes. Remarkably, *Aspm* mutant mice exhibit major germline defects in addition to microcephaly, and both phenotypes are rescued by human ASPM [54••]. Therefore, the positive selection of *ASPM* during primate evolution might reflect its function in the germline [54••] rather than in brain development (for a recent review, see [55]).

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Moreover, the *Cdk5rap2* mutant mice [53] also show defects in germ cells [56]. This points to a general role of these centrosome-/spindle pole-associated proteins in cell proliferation during development. Perhaps, other tissues are able to compensate, at least partly, fetal growth defects postnatally, whereas this may be impossible for the neocortex where neurogenesis stops prenatally.

Consistent with this scenario, mice lacking Magoh, a protein of the RNA-binding exon junction complex, develop microcephaly, presumably due to a reduction in vertical cleavage planes of APs and in BP levels caused by reduced Lis1 expression [57]. However, these mice also show an overall reduction in body size [57], suggesting progenitors in other tissues being affected as well.

Monopolar progenitors in lissencephalic neocortex

Short neural precursors

Extending previous work on SNPs [10], a recent study provides further insight into the characteristics of SNPs that distinguish them from RG cells [11] (Figure 1). Specifically, SNPs, identified by GFP expression driven by the tubulin α1 promoter, differ from bipolar APs, identified by GFP expression driven by the GLAST promoter, in that they exhibit a longer cell cycle and produce neurons rather than BPs. Like bipolar APs, mitotic SNPs express the AP marker Pax6 but very rarely the BP marker Tbr2 [11], hence resembling a distinct population of APs rather than a subset of BPs as previously suggested [13,15]. This heterogeneity in APs is implicated in neuronal fate diversity [10,11].

Basally dividing cells with OSVZ-progenitor-like morphology in rodents?

Whereas most investigators have not observed an overt polarized morphology of rodent neurogenic BPs in M-phase [13–15] (Figure 1), a previous study did report that basally dividing progenitors in mouse neocortex may inherit the basal process from the AP mother and retain it through M-phase [46]. In light of the recent demonstration, discussed below, that the OSVZ-progenitors in developing gyrencephalic neocortex retain their basal process through M-phase, it will be important to identify the reason for these discrepant observations and to determine which proportion of basally dividing progenitors in rodents retain a basal process contacting the basal lamina.

Irrespective of the outcome of this, two crucial differences between basally dividing progenitors in rodents and OSVZ-progenitors in developing gyrencephalic cortex need to be emphasized. First, the transcription factor Tbr2 [12] is expressed in virtually all basal mitoses in rodents, but not mitotic OSVZ-progenitors [8••,9••] (see below). Second, the vast majority of basally dividing progenitors in rodents (nonpolar or not) undergo symmetric neurogenic divisions, [4,12–14,58], whereas the monopolar OSVZ-progenitors in developing gyrencephalic cortex undergo repeated asymmetric self-renewing division [8••], with significant implications for neuronal output [9••].

Basally dividing progenitors that retain a basal process contacting the basal lamina have been observed at late stages of rodent embryonic cortical neurogenesis [13]. However, these progenitors are thought to be gliogenic rather than neurogenic [13] and hence will not be discussed here.

Nonpolar progenitors in lissencephalic neocortex

Biogenesis of BPs

Previous work had identified several transcription factors, including Insulinoma-associated 1 (Insm1) [59] and Tbr2 [60,61], that promote the generation of BPs from APs [62]. Recent studies add AP2γ [63•] as well as Fezf1 and Fezf2 [64] to this list. In contrast to Insm1 and Tbr2 which are expressed in BPs [59–61], AP2γ is expressed in BP-generating APs and drives Tbr2 expression [63•], and Fezf1/2 expression in APs represses Hes5 and derepresses Ngn2 [64] which then drives Insm1 [59] and Tbr2 [65] expression.

BP biogenesis involves their delamination from the apical AJ belt and the apical-to-basal translocation of their nucleus (Figure 1). This nuclear translocation utilizes the same cytoskeletal machinery, that is actomyosin contraction, as APs do for the abventricular leg of INM [66•]; this may have facilitated the evolution of SVZ progenitors [66•].

Expansion of BPs

Rodent BPs divide with a near-random to preferentially horizontal cleavage plane orientation [13,14,59] and lack apical–basal cell polarity [14], which implies that their divisions are largely symmetric in cell biological terms. The vast majority of rodent BP divide symmetrically also in terms of daughter cell fate, producing either two neurons or, much less frequently, two BPs [4,12–14,58]. What, then, determines whether BP divisions are symmetric proliferative or symmetric neurogenic? At least two classes of regulators have emerged recently.

First, transcription factors. Forced premature expression of Insm1 was found to induce BP expansion [59], with nearly all additional BPs showing a horizontal cleavage plane orientation [59]. One may speculate that expanding BPs form junctions with the basal process of APs, in which case a horizontal cleavage plane orientation may allow symmetric inheritance of these junctional complexes by both daughter BPs.

The transcription factor Cux2 negatively regulates BP expansion by limiting the number of symmetric

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proliferative BP divisions [67]. Although BPs generate neurons for all layers of the cerebral cortex [15], Cux2 ablation specifically increased the number of upper-layer neurons, which presumably reflects the physiological timing of Cux2 expression in BPs [67].

Second, cell cycle regulators. In line with the cell cycle length hypothesis [68,69] according to which shortening the cell cycle of progenitors may lead to their expansion, forced expression of Cdk4/cyclin D1 or cyclin E1 was found to shorten G1 of mouse VZ progenitors, to promote their proliferative over differentiative divisions, and to increase BP number and SVZ thickness, eventually resulting in increased numbers of upper-layer neurons [70••,71••]. The crucial role of cell cycle regulators for BP population size and proliferation is further supported by analysis of cyclin D2 knockout mouse, which showed a significant reduction in these parameters along with G1 lengthening of VZ progenitors [72].

Together, these recent insights into the machinery controlling the expansion of rodent BPs are likely to provide clues as to SVZ expansion during cortex evolution. The recent description of a 'niche' for BPs in the developing mouse cortex [16,17] is potentially relevant in this context. Specifically, the preferential localization of BPs in the vicinity of blood vessels raises the interesting possibility that blood vessel-derived signals, be it circulating factors or structural components such as the basal lamina, crucially affect BP proliferation and differentiation during cortical development [16,17].

From lissencephalic to gyrencephalic neocortex

SVZ expansion during neocortex evolution

Given that the expansion of the AP pool is eventually constrained by the necessity of their mitoses occurring apically, a further increase in neural progenitors for cortical expansion requires progenitors dividing in a location basal to the VZ, that is, SVZ progenitors. Consequently, it has been suggested that the increase in the SVZ is key to cortical expansion during evolution [1,2,58,73•] (Figure 2).

Comparative studies have shown that the dorsal telencephalon of non-mammalian vertebrates including turtle and chick lacks an organized SVZ, suggesting that the appearance of a cortical SVZ is linked to the occurrence of the 6-layered mammalian cortex [2,74] (Figure 2). Although in contrast to another study [75], a recent report [73•] provides evidence that abventricular mitoses in the dorsal telencephalon of marsupials, such as tammar wallaby and opossum, align along a distinct zone adjacent to the VZ, which is consistent with the existence of a cortical SVZ in these species. This indicates that the cortical SVZ emerged before the eutherian–metatherian split during evolution [73•].

A crucial finding has been the observation that within the SVZ of primates two morphologically distinct zones can be distinguished, that is ISVZ and OSVZ [7] (Figure 2). This reflects the fact that ISVZ-progenitors prevail in the ISVZ and OSVZ-progenitors in the OSVZ [8••,9••]. The abundance of OSVZ-progenitors in the developing primate [7], notably human [8••,9••], neocortex is consistent with the notion that the evolutionary expansion of the neocortex is specifically linked to this type of progenitor. In light of the occurrence of OSVZ-progenitors in the developing neocortex of the ferret, a gyrencephalic non-primate, this type of progenitor has recently been implicated in the evolution of gyrencephalic (rather than lissencephalic) neocortex in general [9••].

Bipolar progenitors in gyrencephalic neocortex

APs in the developing gyrencephalic neocortex appear to resemble those in the developing lissencephalic neocortex in terms of molecular and cellular features (Figure 2) [8••,9••,76–78].

Nonpolar progenitors in gyrencephalic neocortex

Similar to rodent BPs, ISVZ-progenitors in developing gyrencephalic neocortex express Tbr2 and downregulate Par3 and aPKC [8••,9••]. Their cleavage plane shows a near-random orientation, with slight preference for horizontal planes [9••], as has been reported for rat (but not mouse) BPs [13].

Monopolar progenitors in gyrencephalic neocortex

Short neural precursors

Whereas SNPs, which by definition lack a basal process at M-phase, have been reported to constitute a substantial proportion of APs in rodents [10,11], this does not appear to be the case for developing gyrencephalic neocortex, as ≈90% of all mitotic APs in human and ferret extend a phosphovimentin-positive basal process [9••].

OSVZ-progenitors

A key difference of OSVZ-progenitors in developing human and ferret neocortex as compared to rodent BPs is that they retain characteristics of RG cells (Figure 2). Thus, human and ferret OSVZ-progenitors maintain expression of Pax6 [8••,9••,79,80], nestin, GLAST, BLBP and GFAP (human, not ferret) [8••,9••,78,79]. Importantly, like APs, OSVZ-progenitors retain a basal process contacting the basal lamina throughout the cell cycle [8••,9••] (Figure 2). Hence, given their delamination from the apical AJ belt, OSVZ-progenitors can be regarded as delaminated RG cells that however downregulate apical polarity markers and lack an apical process in mitosis [8••,9••].

Similar to rodent BPs, the cleavage planes of OSVZ-progenitors show a near-random orientation when

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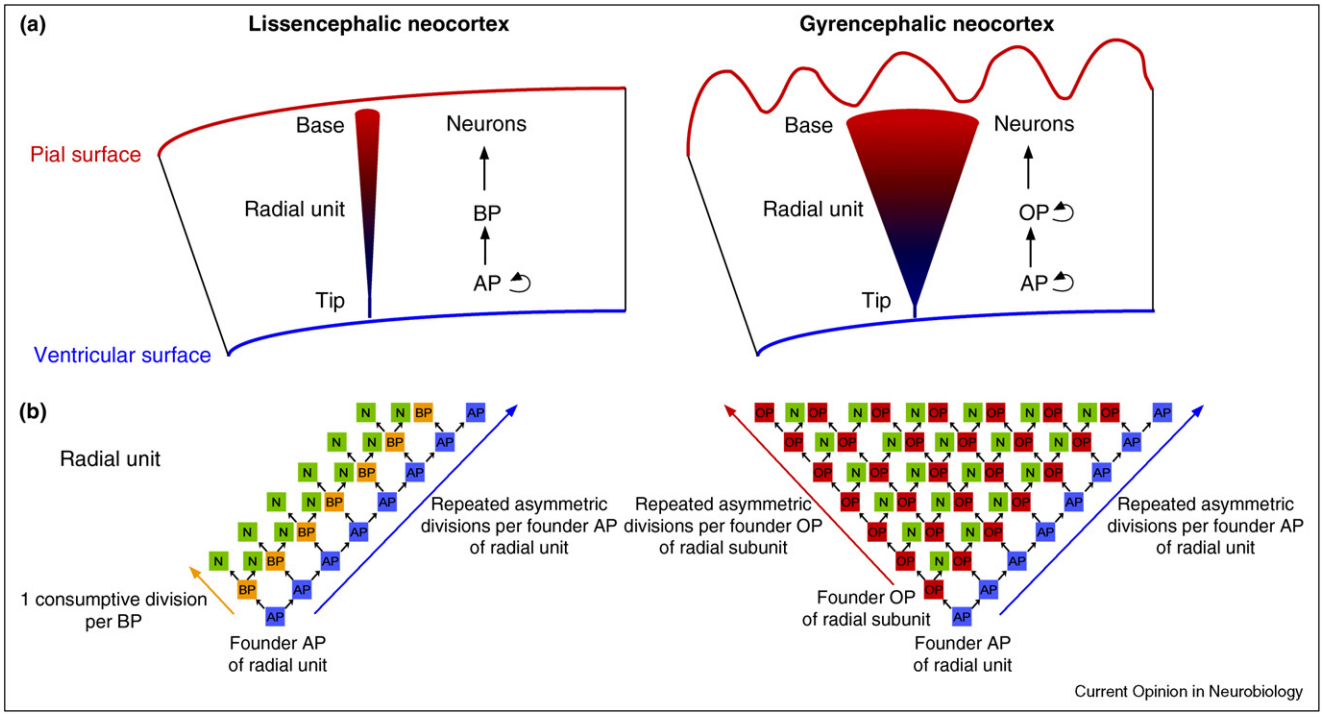
deduced from sister chromatid position at anaphase/early telophase [9••] and a predominantly horizontal orientation when deduced from the shape of the nascent daughter cell bodies [8••]. These observations are not necessarily contradictory but can be reconciled if there is re-orientation of daughter cell nuclei at telophase before cleavage furrow ingression. Importantly, given these cleavage plane orientations, the fact that a basal process extends from the cell body at M-phase implies that OSVZ-progenitor divisions, in contrast to rodent BP divisions [4,12–14,58], are asymmetric in cell biological terms [9••]. Indeed, also with regard to daughter cell fate, most OSVZ-progenitor divisions appear to be asymmetric, with the 'basal' daughter cell, that is the one inheriting the basal process, remaining an OSVZ-progenitor and the 'apical' daughter cell becoming an ISVZ-progenitor or a neuron [8••].

Importantly, in line with their relationship to APs, OSVZ-progenitors probably undergo multiple rounds of self-renewing divisions [8••], which may be linked to basal process inheritance [9••]. What, then, are the signaling pathways that endow OSVZ-progenitors with this property? One candidate is Notch signaling, which is required for maintaining OSVZ-progenitor fate [8••]. Another is integrin signaling, which is thought to be linked to basal process retention and basal lamina contact [9••]. Specifically, interference with integrin signaling, including that of β3-integrins localized at varicosities of the basal process, selectively decreases the population size of OSVZ-progenitors [9••].

Radial units—from cylindrical to conical shape

Compared to lissencephalic neocortex, gyrencephalic neocortex is characterized by an increase in pial surface area relative to ventricular surface area (Figure 3). This implies that the three-dimensional shape of radial units [3] changes from near-cylindrical in lissencephalic neocortex to conical in gyrencephalic neocortex, with the founding AP corresponding to the tip of the cone and the pial surface to its base (Figure 3). In fact, the more gyrencephalic a neocortex, the broader is the base of the radial unit cone relative to its apical tip. With regard to the expansion of the SVZ, notably the OSVZ, these geometrical considerations imply that there are more progenitors per nuclear layer of SVZ in a radial unit of gyrencephalic as compared to lissencephalic neocortex. Furthermore, given that OSVZ-progenitors are attached to the pial surface via their basal process, each OSVZ-progenitor in a radial unit can be regarded as the founder cell of a radial subunit (Figure 3). Thus, the increase in the basal-over-apical ratio of a cone-shaped radial unit in gyrencephalic neocortex may reflect (i) the increase in the number of OSVZ-progenitors per founder AP (i.e. the number of asymmetric differentiative divisions per single

Figure 3



Comparison of the shape of a radial unit in lissencephalic and gyrencephalic neocortex **(a)** and the consequences, for neuron number, of repeated asymmetric AP divisions followed by symmetric neurogenic BP division in lissencephalic neocortex (left) versus repeated asymmetric AP divisions followed by repeated asymmetric OSVZ-progenitor divisions in gyrencephalic cortex (right) **(b)**. N, neuron; OP, OSVZ-progenitor. For details, see text.

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AP), (ii) the increase in the number of neurons generated per single OSVZ-progenitor-based radial subunit (i.e. the number of asymmetric neurogenic divisions per single OSVZ-progenitor), or (iii) both (Figure 3).

Conclusions

Summing-up, the following principles emerge. For bipolar APs to expand and self-renew, the daughter cell(s) must possess both apical domain and basal process constituents. Self-renewal of monopolar OSVZ-progenitors requires that the daughter progenitor possesses basal process constituents. In both cell types, this is typically achieved via inheritance and continued expression of the relevant polarized constituents. Key questions of future investigations include the following. Which intracellular signaling pathways maintain bipolar AP and monopolar OSVZ-progenitor identity? How are these pathways linked to the apical domain and basal process constituents? Which extracellular signals that reach these progenitors via their apical and basal surfaces trigger the relevant intracellular signaling pathways?

Another major topic of future investigations concerns the lineage(s) from APs to neurons in developing gyrencephalic neocortex. Rodent models have revealed that an *AP* either *repeatedly generates neurons by asymmetric divisions*, or *repeatedly generates a BP by asymmetric divisions which in turn generates two neurons by symmetric division*. Several possibilities exist in developing gyrencephalic neocortex. First, similar to rodents, an *AP repeatedly generates an ISVZ-progenitor by asymmetric divisions which in turn generates two neurons by symmetric division*. Second, an *AP repeatedly generates an OSVZ-progenitor by asymmetric divisions which in turn repeatedly generates a neuron by asymmetric divisions*; this lineage already results in a substantial increase in neuron number [9••]. Third, an *AP repeatedly generates an OSVZ-progenitor by asymmetric divisions which in turn repeatedly generates an ISVZ-progenitor by asymmetric divisions which in turn generates two neurons by symmetric division* [8••]; this lineage doubles neuronal output over the second lineage scenario. These hypothetical lineages, as well as others, probably co-exist. Ideally, one would like to know the number and mode of divisions for each type of progenitor in a given lineage.

The greatest challenge presumably lies in identifying the alterations in progenitor types, and number and modes of their divisions, that underlie the evolutionary expansion of the neocortex. Here, the recent characterization of OSVZ-progenitors in developing gyrencephalic neocortex [8••,9••] is a good start. It should be exciting and rewarding to identify the genomic differences that ultimately are responsible for these crucial alterations.

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