The Cell Biology of Neurogenesis: Toward an Understanding of the Development and Evolution of the Neocortex

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Annu. Rev. Cell Dev. Biol. 2014. 30:465–502

First published online as a Review in Advance on June 27, 2014

The *Annual Review of Cell and Developmental Biology* is online at cellbio.annualreviews.org

This article's doi: 10.1146/annurev-cellbio-101011-155801

Keywords

neural stem cells, neural progenitors, radial glia, cilium, neuroepithelial cells, apical and basal processes, cell biology, neocortex evolution, cell polarity, asymmetric cell division, interkinetic nuclear migration, INM, cell cycle, cell fate determination

Abstract

Neural stem and progenitor cells have a central role in the development and evolution of the mammalian neocortex. In this review, we first provide a set of criteria to classify the various types of cortical stem and progenitor cells. We then discuss the issue of cell polarity, as well as specific subcellular features of these cells that are relevant for their modes of division and daughter cell fate. In addition, cortical stem and progenitor cell behavior is placed into a tissue context, with consideration of extracellular signals and cell-cell interactions. Finally, the differences across species regarding cortical stem and progenitor cells are dissected to gain insight into key developmental and evolutionary mechanisms underlying neocortex expansion.

Contents

INTRODUCTION

Neural stem and progenitor cells generate neurons via a process called neurogenesis (Götz & Huttner 2005, Noctor et al. 2007, Sun & Hevner 2014). In the developing vertebrate central nervous system, neurogenesis occurs in all regions of the neural tube following specific

STEM AND PROGENITOR CELLS

Stem cells are generally defined by their—ideally life-long—self-renewal capacity and the potential to generate all cell types of a given tissue. In the central nervous system, stem cells give rise to neurons and various glial cell types (astrocytes, NG2 glia, oligodendrocytes, ependymal cells). Cells with more limited proliferation capacity and progeny are referred to as progenitor cells.

In the developing mammalian forebrain, only neuroepithelial cells and their direct progeny, the apical radial glial cells, self-renew for several rounds of cell division. [In some mammals (e.g., the macaque monkey, see Betizeau et al. 2013), basal radial glial cells are also endowed with this capacity.] Some of the apical radial glia may persist beyond development and, depending on their location, may function in adult neurogenesis. However, few of these apical radial glia generate cells other than neurons and are multipotent (Malatesta et al. 2000, Pinto & Götz 2007), with the remainder generating neurons only. This is the case even when apical radial glial cells are taken out of their environment and either cultured in conditions favoring multipotency or transplanted into an environment favoring specific lineages. Thus, both neuroepithelial cells and apical radial glia are a mixture of cells with a variable extent of fate restriction. Despite recent progress, these cell subpopulations are still ill-defined, and no clear markers exist to distinguish radial glial cells with neural stem cell versus progenitor identity. This is why we use the collective term neural/cortical stem and progenitor cells.

Importantly, the widespread concept that radial glial cells generate first neurons and later glial cells is correct at the population level, as neurogenesis typically precedes gliogenesis, but does not apply to most neuroepithelial and radial glial cells at the single cell level. Inducible genetic fate mapping analyses have shown that glial cells arising from radial glia at later stages of development often originate from radial glia subpopulations different from those generating neurons, thereby corroborating the concept that many radial glial cells are specified in their lineage, if not restricted.

temporal and spatial patterns along the caudal-rostral, ventral-dorsal, and lateral-medial body axes (Mora-Bermúdez et al. 2013). Neurogenesis is followed by neuronal migration, neuronal differentiation, dendrite and axon formation, synaptogenesis, and the establishment of neuronal connectivity (Komuro & Rakic 1998, Kriegstein & Noctor 2004). These processes are interwoven with nonneuronal processes, notably gliogenesis (i.e., the generation of astrocytes and oligodendrocytes), myelination, angiogenesis, and formation of the blood-brain barrier.

In this review, we focus on neurogenesis in the telencephalon, the rostral-most region of the neural tube, which contains the parts of the central nervous system that are most expanded in vertebrates, in particular, mammals (Rakic & Lombroso 1998). Specifically, we concentrate on the mammalian dorsolateral telencephalon, which forms the evolutionarily youngest part of the cerebral cortex, the neocortex. Typically, the mammalian neocortex is composed of six layers of neurons and supporting glial cells. This part of the brain shows the greater extent of phylogenetic expansion, which occurs during its ontogeny (Borrell & Reillo 2012, Kriegstein et al. 2006, Lui et al. 2011). Thus, cortical stem and progenitor cells and their role in neurogenesis during neocortex development are the central object of this review (see sidebar, Stem and Progenitor Cells, for a description of the typical features of neural stem and progenitor cells; we use the collective term stem and progenitor cells, as it is not always possible to unambiguously distinguish between these cell types). Neural stem and progenitor cells in other parts of the mammalian central nervous system, including the ventral telencephalon, and their role in processes other than ontogenic neurogenesis are discussed only if directly relevant for our understanding of neurogenesis in the developing neocortex. We discuss the basic principles of cortical neurogenesis and their cell biological basis

and then proceed to the stem and progenitor cell diversity involved in expanding the neocortex. Topics beyond the scope of this review include transcriptional regulation of neurogenesis in the developing neocortex, adult neurogenesis, neuronal migration and differentiation, and gliogenesis; here, the reader is referred to recent reviews (Cremisi 2013, Guerout et al. 2014, Hippenmeyer 2014, Ninkovic & Götz 2013, Paridaen & Huttner 2014, Rowitch & Kriegstein 2010, Tuoc et al. 2014).

We previously reviewed neurogenesis during cortical development with a focus on the cell biology of neural stem and progenitor cells (Götz & Huttner 2005). Since then, enormous progress has been made with regard to further dissecting key cell biological processes, such as cell polarity, mitotic spindle and cleavage plane orientation (Lancaster & Knoblich 2012), symmetric versus asymmetric cell division (Shitamukai & Matsuzaki 2012), cell cycle regulation and its role in neurogenesis (Arai et al. 2011, Salomoni & Calegari 2010), interkinetic nuclear migration (INM) (Lee & Norden 2013, Taverna & Huttner 2010), and progenitor cell delamination (Itoh et al. 2013b). The progress also concerns insight into the underlying molecular mechanisms and ranges from the characterization of key transcription factors to cell surface receptors and from the identification of signaling networks to epigenetic mechanisms. Moreover, at the cellular level, novel neural stem and progenitor cell types have been uncovered, and at the supracellular level, diverse stem and progenitor cell lineages have been revealed. This has contributed to substantial advances in our understanding of the cytoarchitecture of the developing neocortex.

Most significant, perhaps, is that the findings made have been increasingly placed in the context of the evolution of the brain and, notably, the neocortex (Borrell & Reillo 2012, Fietz & Huttner 2011, Lui et al. 2011). We are therefore now in a position to adopt a broader perspective of neocortical neurogenesis and neural stem and progenitor cells than previously possible. We can now move from the mechanistic dissection of the cellular mechanisms governing stem and progenitor cell behavior to the analysis of supracellular organization and evolution.

PRINCIPAL TYPES OF CORTICAL STEM AND PROGENITOR CELLS

With the onset of cortical neurogenesis, neuroepithelial cells, the primary neural stem cells in the central nervous system, transform into radial glial cells, which are highly related to neuroepithelial cells but possess glial hallmarks (Götz & Huttner 2005) and, like the neuroepithelial cells, exhibit apical-basal cell polarity but are even more elongated (Bentivoglio & Mazzarello 1999, Rakic 2003). Only slightly more than a decade ago, it was demonstrated that radial glial cells function as neural stem cells and that cortical projection neurons arise from these cells (Malatesta et al. 2000, Miyata et al. 2001, Noctor et al. 2001). Since then, the field has seen an explosion of research, and additional types of cortical stem and progenitor cells have been discovered (Betizeau et al. 2013, Fietz et al. 2010, Hansen et al. 2010, Haubensak et al. 2004, Miyata et al. 2004, Noctor et al. 2004, Pilz et al. 2013, Reillo & Borrell 2012, Shitamukai et al. 2011, Wang et al. 2011). We would like to propose a set of three criteria that provide a framework for a basic classification of cortical stem and progenitor cell types. These are (*a*) the location of mitosis, (*b*) the extent of cell polarity, and (*c*) their proliferative capacity (**Figure 1**). These three criteria allow, of course, only a rough classification of cortical stem and progenitor cells, as various subtypes of these cells will exist within each group.

We then discuss the four principal classes of cell division modes that the various cortical stem and progenitor cells can undergo. These are of relevance for the different stem and progenitor cell lineages operating during corticogenesis, as well as their diversity across mammalian species. This in turn has a major impact on the number and types of neurons generated in a given species during cortical development.

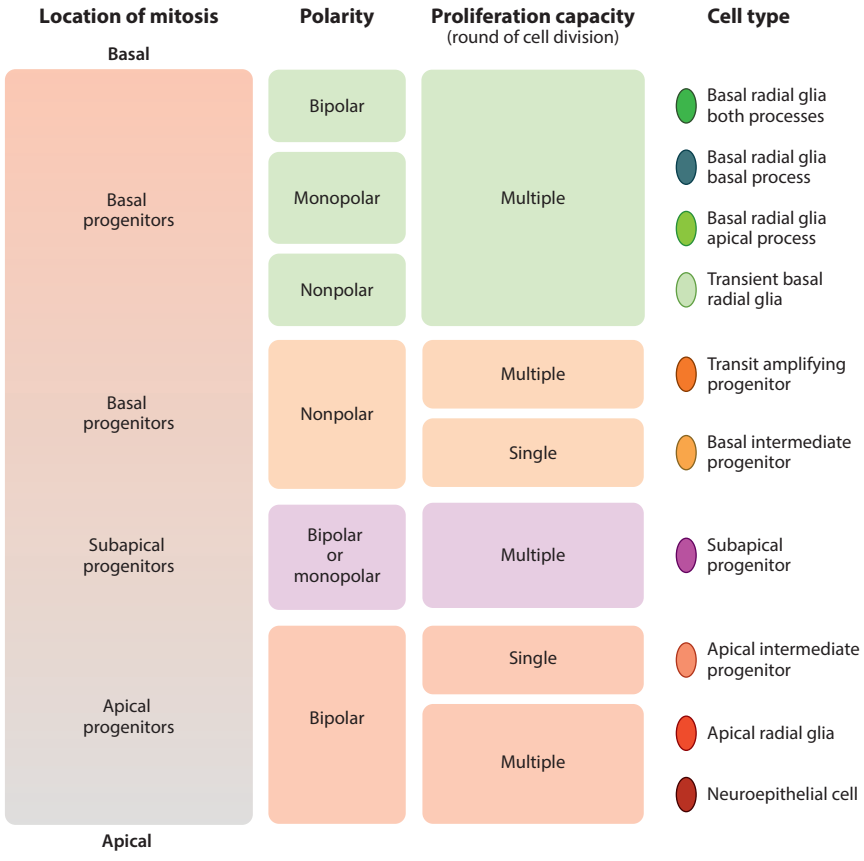

Figure 1

Neural stem and progenitor cell classification. A set of three different criteria (*left three columns*) is used to classify neural stem and progenitor cell types (*right column*). The three criteria are location of mitosis along the apical-basal axis of the cortical wall; cell polarity; and proliferation capacity, here expressed as the number of cell cycles a progenitor undergoes before its final consumptive cell division.

Location of Mitosis

The wall of the neural tube possesses an intrinsic tissue polarity: It contacts the lumen of the neural tube (i.e., the lateral ventricles in the case of the developing neocortex) on one side and the basal lamina on the other side. This tissue polarity allows us to classify stem and progenitor cells into at least two principal classes based on the location of mitosis (**Figures 1** and **2**): (*a*) apical progenitors (APs), which undergo mitosis at (or very near to) the lumenal surface of the ventricular zone (VZ) while being integrated into the apical adherens junction belt and exposing part of their plasma membrane to the ventricular lumen (i.e., the apical plasma membrane) (Götz & Huttner 2005, Kriegstein & Götz 2003), and (*b*) basal progenitors (BPs), which undergo mitosis at an abventricular location, typically in the subventricular zone (SVZ, see below), and which at mitosis are delaminated from the adherens junctional belt and lack apical plasma membrane (Betizeau et al. 2013, Fietz et al. 2010, Hansen et al. 2010, Haubensak et al. 2004, Miyata et al. 2004, Noctor et al. 2004, Reillo & Borrell 2012, Shitamukai et al. 2011, Wang et al. 2011).

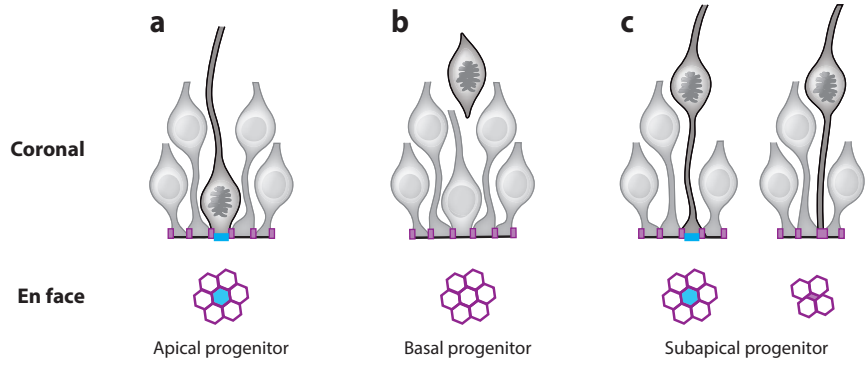

Figure 2

Apical progenitors, basal progenitors, and subapical progenitors: a cell biological perspective. Progenitors (*top*) in a standard, coronal view and (*bottom*) in an en face view. (*a*) In the apical progenitor, note the presence of an apical plasma membrane facing the ventricle (*top*, *blue line*) and integration into the apical adherens junctional belt (*bottom*, *blue hexagon*). (*b*) In the basal progenitor, the plasma membrane facing the ventricle is absent (*top*). As a consequence of delamination, basal progenitors are not integrated into the apical adherens junctional belt (*bottom*). (*c*) The newly discovered subapical progenitor (SAP) constitutes a third class of progenitor cells that extends a process to the ventricle and/or the apical junctional belt. Two main scenarios can be envisaged: The process reaches the ventricular lumen and the cell is integrated into the apical junctional belt (*left*), and the apically directed process forms apical adherens junctions without being exposed to the ventricular lumen (*right*).

Recently, a novel type of progenitor cell has been described, called a subapical progenitor (SAP), that is distinct from the AP as defined above because it undergoes mitosis at a subapical location, such as the basal VZ. SAPs are defined by the location of their mitosis but are heterogeneous in regard to their polarity, as discussed below (Pilz et al. 2013).

If BPs are sufficiently frequent in number, they give rise to an additional proliferative zone basal to the VZ, the SVZ. In many species, notably (but not only) those forming a gyrencephalic neocortex, the SVZ is further expanded to form an inner and outer SVZ (ISVZ and OSVZ, respectively) (Smart 1971, Smart et al. 2002; see below). Importantly, the relative abundance not only of APs, BPs, and SAPs in general but also of the various subtypes within each of these progenitor classes varies between different neocortical regions, developmental stages, and species (Borrell & Reillo 2012, Fietz & Huttner 2011, LaMonica et al. 2012, Lui et al. 2011).

Cell Polarity

We apply two distinct criteria to classify cortical stem and progenitor cells with regard to their cell polarity (**Figure 1**). One is the presence or absence of apical-basal cell polarity, reflected by the presence or absence of both apical-specific (e.g., prominin-1) and basolateral-specific (e.g., N-cadherin) plasma membrane constituents at mitosis. Another is a purely morphological criterion, that is, the presence or absence of polarized, apically directed and/or basally directed processes at mitosis, irrespective of whether the apically directed process exhibits apical plasma membrane identity. We choose mitosis as the defining stage of the cell cycle for two reasons. First, this is when distinct cell constituents are equally or differentially distributed to the daughter cells. Second, whether or not a progenitor extends processes may dynamically change during interphase (e.g., Betizeau et al. 2013). Thus, confining the analysis of cell polarity and morphological features to the mitotic stage avoids ambiguities in progenitor classification.

Applying these cell polarity and morphological criteria, the following types of cortical stem and progenitor cells can be distinguished: (*a*) for APs, neuroepithelial cells, apical radial glial cells, and short neural precursors, recently renamed apical intermediate progenitors (Gal et al. 2006, Tyler & Haydar 2013); (*b*) for BPs, basal radial glial cells (also called outer radial glial cells), basal intermediate progenitors, and the related transit amplifying progenitors (Betizeau et al. 2013, Fietz et al. 2010, Hansen et al. 2010, Haubensak et al. 2004, Miyata et al. 2004, Noctor et al. 2004, Reillo et al. 2011, Reillo & Borrell 2012, Shitamukai et al. 2011, Wang et al. 2011); (*c*) for SAPs, bipolar radial glia with an apical process contacting the ventricle and a basally directed process, which give rise to basal radial glial cells, and unipolar SAPs (Pilz et al. 2013) (**Figure 1**). [Note that basal radial glial cells have been shown to undergo transit amplification (Betizeau et al. 2013); however, here we restrict the term transit amplifying progenitor to nonpolar BPs (Hansen et al. 2010, Lui et al. 2011).] All three principal types of APs exhibit apical-basal cell polarity and extend apical and basal processes (**Figure 2**). However, whereas neuroepithelial and apical radial glial cells are highly bipolar cells, the basal process of which extends across the entire cortical wall toward the basal lamina, the basal process of apical intermediate progenitors tends to be confined to the VZ. For SAPs, it will be important to determine whether the apically directed process reaching the ventricular lumen (**Figure 2**) possesses both an apical plasma membrane and integration into the apical adherens junction belt at mitosis, or if the apically directed process forms apical adherens junctions without being exposed to the ventricular lumen.

Given that all principal types of BPs are delaminated from the adherens junctional belt at mitosis and lack an apical plasma membrane, none of them exhibits apical-basal cell polarity (Betizeau et al. 2013, Fietz et al. 2010, Hansen et al. 2010, Haubensak et al. 2004, Miyata et al. 2004, Noctor et al. 2004, Reillo & Borrell 2012, Reillo et al. 2011, Shitamukai et al. 2011). Nonetheless, basal radial glia are polarized cells that, at mitosis, are either bipolar, with a basal and an apical process, or monopolar, with either a basal or an apical process. In contrast, transit amplifying progenitors and basal intermediate progenitors may exhibit several short processes extending in any direction during interphase but typically are nonpolar at mitosis (Hansen et al. 2010, Haubensak et al. 2004, Miyata et al. 2004, Noctor et al. 2004, Pilz et al. 2013). Finally, SAPs can extend either both an apical and a basal process or only an apical process at mitosis (Pilz et al. 2013). These cell polarity features are thought to be relevant for certain cortical stem and progenitor cell properties, in particular for their proliferation capacity. In addition, it is important to consider these cell polarity features in the context of tissue polarity, as certain proliferative or differentiative signals may be conveyed via the ventricular fluid or the basal lamina (Johansson et al. 2010, Lehtinen & Walsh 2011, Lehtinen et al. 2011, Siegenthaler et al. 2009).

Proliferative Capacity

In terms of their proliferative capacity, the potential of neural stem cells to undergo multiple rounds of cell division is typically greater than that of neural progenitor cells. In addition, cell division of neural stem cells is invariably associated with self-renewal, whereas this is not necessarily the case for neural progenitor cells (see sidebar, Stem and Progenitor Cells, which also explains why we use the collective term stem and progenitor cells). Cortical stem and progenitor cells fall into two principal groups: those that undergo multiple rounds of cell division and those that divide just once (**Figure 1**). Apical and basal intermediate progenitors belong to the latter group, generating two neurons in a self-consuming division. All other types of APs (neuroepithelial cells, apical radial glial cells), BPs (basal radial glial cells, transit amplifying progenitors), and SAPs are capable of undergoing multiple rounds of cell division in which they either proliferate or self-renew (see below and sidebar, Stem and Progenitor Cells) before undergoing their terminal, self-consuming division.

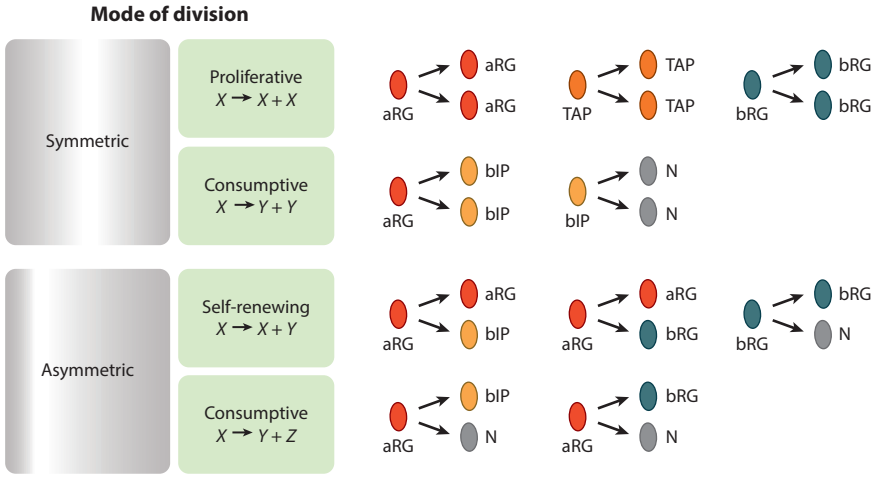

Figure 3

The various modes of cell division of neural stem and progenitor cells: symmetric or asymmetric. Symmetric divisions can be either proliferative or consumptive. Asymmetric divisions can be either self-renewing or consumptive. Some examples are given on the right. Abbreviations: aRG, apical radial glia; bIP, basal intermediate progenitor; bRG, basal radial glial cell; N, neuron; TAP, transit amplifying progenitor.

Modes of Cell Division

Cortical stem and progenitor cells can divide either symmetrically or asymmetrically, as judged by daughter cell identity (**Figure 3**). Either type of cell division can be associated with self-renewal or consumption of a given stem and progenitor cell type. Thus, there are four principal modes of cell division: (*a*) symmetric proliferative, (*b*) symmetric consumptive, (*c*) asymmetric self-renewing, and (*d*) asymmetric consumptive division (**Figure 3**).

In symmetric division, a cell generates two daughter cells with the same identity (**Figure 3**). This identity is not necessarily the same as that of the mother cell. If it is, this is a symmetric proliferative division. If it is not, this is a symmetric consumptive division. Examples of symmetric proliferative divisions include (*a*) one neuroepithelial cell generating two neuroepithelial cells, which is responsible for the early expansion of the founder stem cell pool prior to the onset of neurogenesis; (*b*) one apical radial glial cell generating two apical radial glial cells, which expands the stem cell pool during neurogenesis; and (*c*) one transit amplifying progenitor generating two transit amplifying progenitors, which is thought to contribute to the expansion of the SVZ and the neocortex (Hansen et al. 2010). The paradigm of a symmetric consumptive division is the symmetric neurogenic division of basal intermediate progenitors, which generates two neurons (Haubensak et al. 2004, Miyata et al. 2004, Noctor et al. 2004).

In asymmetric divisions, the two daughter cells have different identities (**Figure 3**). In an asymmetric, self-renewing division, one daughter cell has the same identity as the mother cell, and the other daughter cell has a different identity. [Note that we use the term self-renewal only when one of the daughter cells is identical to the mother cell and the term proliferation (rather than self-renewal) when both daughter cells are identical to the mother cell.] Typical examples of asymmetric self-renewing divisions are the self-renewing neurogenic apical radial glial cell division, which gives rise to an apical radial glial cell and a neuron, and the self-renewing differentiative apical radial glial cell division, which gives rise to an apical radial glial cell and a BP. By contrast, in an asymmetric consumptive division, the daughter cells differ in identity from one another, as well as from the

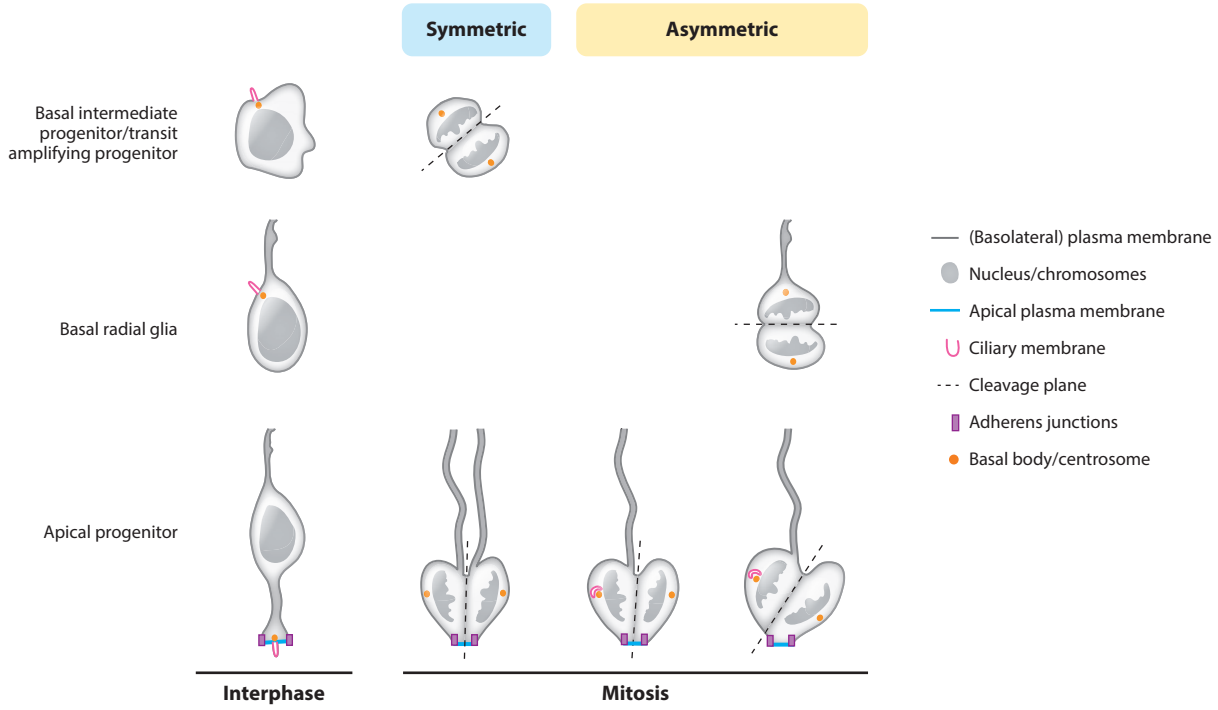

Figure 4

Polarity cues are partitioned during mitosis. In stem and progenitor cells, polarity cues are represented by the apical plasma membrane (APs), the junctional complexes (APs), the primary cilium (APs and BPs), the centrosomes (APs and BPs), and the basal process (APs and basal radial glial cells). These cues are also present in interphase and can be asymmetrically or symmetrically partitioned during mitosis. We did not depict all the possible options, but only the ones that are corroborated by data.

mother cell. A typical example of such a division is an apical radial glial cell giving rise to a neuron and a BP (e.g., a basal radial glial cell or a basal intermediate progenitor) (Hansen et al. 2010).

Despite substantial progress, a challenge for future research remains the dissection of the molecular mechanisms governing the mode of cell division of cortical stem and progenitor cells. Moreover, premature changes in the mode of stem and progenitor cell division are a cause of abnormal neocortex development, notably microcephaly. Examples include premature switching from symmetric proliferative to asymmetric AP division (Fish et al. 2006), and from asymmetric self-renewing to symmetric consumptive AP division (Fei et al. 2014).

Recent work from several investigators has shown that the asymmetry in daughter cell fate appears to be linked to the asymmetric inheritance of specific subcellular components and molecules (Knoblich 2001, Lancaster & Knoblich 2012) (**Figure 4**). Interestingly, such asymmetric inheritance by the daughter cells is a direct consequence of the polarized distribution of these subcellular components and molecules in the mother cell at mitosis, as discussed below (**Figure 4**).

The existence of various types of cortical stem and progenitor cells, which can adopt different modes of division, implies that there are a multitude of possible lineages via which neurons can be generated. The general principle of lineage progression is among APs, from APs to neurons or BPs (also via SAPs) (Haubensak et al. 2004, Miyata et al. 2004, Noctor et al. 2004, Pilz et al. 2013), among BPs (Betizeau et al. 2013, Hansen et al. 2010), and from BPs to neurons (Attardo et al. 2008, Betizeau et al. 2013, Hansen et al. 2010, Haubensak et al. 2004, Wang et al. 2011).

Despite impressive advances in reconstructing these lineages through live imaging in organotypic slice culture and clonal analyses (Noctor et al. 2004, Pilz et al. 2013), our understanding of these lineages is far from complete (Betizeau et al. 2013, Hansen et al. 2010). As different lineages have a profound impact on the number and type of neurons produced, a major challenge will be to obtain a comprehensive understanding of the lineages operating in corticogenesis in a given model organism and to uncover the lineage differences across mammalian species. Excitingly, novel electroporation-based labeling techniques, as well as microinjection into single neural stem cells in brain tissue, also now allow lineage tracing at the single-cell level in species previously not amenable to genetic changes (Chen & LoTurco 2012, García-Marqués & López-Mascaraque 2013, Loulier et al. 2014, Taverna et al. 2012).

SUBCELLULAR ORGANIZATION AND CELL FATE DETERMINATION

The apical-basal polarity of neuroepithelial cells and apical radial glial cells is a basis for their symmetric versus asymmetric division, as defined by an equal versus unequal distribution, respectively, of cellular components to the daughter cells. However, these are not the only determinants, with the mechanism of spindle orientation and partitioning of apical-basal polarity cues operating in the context of heterogeneous cell populations, such that the assignment of fate, e.g., neurogenic fate, is not necessarily linked to division orientation (Huttner & Kosodo 2005, Lancaster & Knoblich 2012, Peyre & Morin 2012, Shitamukai & Matsuzaki 2012, Shitamukai et al. 2011, Wilcock et al. 2007). To better highlight how cell fate determination can be influenced by apical-basal cues, we focus our attention separately on apical and basal components. Apical components include (*a*) the apical plasma membrane and cell cortex, (*b*) the primary cilium and the centrosomes, (*c*) the apical junctional complexes, and (*d*) the gap junctions. The basal components include (*a*) the basolateral plasma membrane and junctional complexes and (*b*) the basal process, including specific features, such as the varicosities and the basal endfeet, that are also connected by gap junctions to their neighbors as well as by focal adhesions to the basal lamina. We then discuss the role of the mitotic spindle and cleavage furrow, as both apical and basal cues impinge on this process.

APICAL COMPONENTS: GENERAL REMARKS

The apical endfoot of neuroepithelial cells, apical radial glial cells, and apical intermediate progenitors is composed of the apical plasma membrane and the junctional belt. The apical plasma membrane proper accounts for only 1–2% of the total plasma membrane and bears the primary cilium (Kosodo et al. 2004, Louvi & Grove 2011). It is delimited by the adherens junctional belt. On a cellular level, the apical junctional belt allows the separation of the apical and the basolateral plasma membrane, and on a tissue level, it allows cohesion of neighboring cells (**Figure 4**). Furthermore, the apical domain as well as the basal endfeet of apical radial glial cells contain gap junctions, which allow for intercellular communication and signaling (Sutor & Hagerty 2005, Yamashita 2013). The apical endfoot lines the ventricle filled with the cerebrospinal fluid (CSF), and it is therefore a subcellular structure that plays a crucial role in signaling from the CSF (Johansson et al. 2013, Lehtinen & Walsh 2011).

Apical Plasma Membrane

The juxtaposition of the apical plasma membranes of all neuroepithelial cells or apical radial glial cells forms the apical surface facing the ventricle of the neural tube. The lumen of the neural tube is filled with CSF and contains signaling molecules produced by the choroid plexus, including

fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), sonic hedgehog (Shh), retinoic acid, bone morphogenic proteins (BMPs), and Wnts (Johansson et al. 2013, Lehtinen & Walsh 2011, Segklia et al. 2012). All these molecules have well-established roles in brain development, and their effect is likely to be mediated by receptors localized at the apical plasma membrane. A great effort has been dedicated to the identification of molecules specifically localized at the apical plasma membrane. One of these molecules is megalin, a cell surface glycoprotein whose ligands include both BMPs and Shh (McCarthy et al. 2002, Wicher et al. 2005, Willnow et al. 1996). Following ligand binding, the cytoplasmic tail of the megalin is cleaved and translocates to the nucleus, where it might influence gene transcription, thus linking events happening at the apical plasma membrane facing the lumen to the nucleus (McCarthy & Argraves 2003). Another example is provided by the transmembrane protein prominin-1, which is specifically localized at the apical plasma membrane and its protrusions (Corbeil et al. 2010). Prominin-1 is a stem cell marker and binds cholesterol (Röper et al. 2000), a membrane lipid enriched at the apical plasma membrane of other model epithelial cells, such as MDCK cells (Schuck & Simons 2004). Interestingly, cholesterol plays essential roles in clustering receptors, thereby contributing to their activity (Simons & Toomre 2000). On a general note, the data available so far suggest a role of the apical plasma membrane in signaling from the ventricle to the intracellular milieu, notably the nucleus.

As pointed out previously, the apical plasma membrane constitutes just 1–2% of the total plasma membrane area. The area of the apical plasma membrane decreases concomitantly with development, owing to the release of extracellular membrane particles known as ectosomes, which contain a significant fraction of the apical plasma membrane (Dubreuil et al. 2007; Ettinger et al. 2011; Marzesco et al. 2005, 2009). Therefore, the apical plasma membrane not only provides a polarity cue and a platform for signaling but has very important implications for asymmetry of cell division, in particular in relation to its inheritance during mitosis. The crucial role of the apical plasma membrane in neurogenesis is also linked to the presence of a specific organelle: the primary cilium (**Figure 4**).

Primary Cilium and Centrosomes

The primary cilium is an organelle that protrudes from the apical plasma membrane into the lumen of the ventricle. It is usually considered to be an antenna to receive signals broadcasted in the CSF, such as IGF, Shh, and Wnt (Johansson et al. 2013, Lehtinen & Walsh 2011, Louvi & Grove 2011, Valente et al. 2014, Yeh et al. 2013). The primary cilium is a complex organelle, and two components have recently gathered attention, as they might play a crucial role in cellular asymmetry and neurogenesis: the centrosome and the ciliary membrane.

Centrosome/centrioles. The centrosome is directly linked to the primary cilium, as its older centriole, the so-called mother centriole, forms the so-called basal body, a structure found at the base of the cilium (Louvi & Grove 2011). After centriole duplication in S phase, the two centrosomes form the poles of the mitotic spindle. These two centrosomes are always asymmetric with regard to centriole age, as one contains the mother centriole and the other the daughter centriole. Interestingly, the centrosome containing the mother centriole is preferentially inherited by the daughter cell remaining an apical radial glial cell, whereas the centrosome containing the daughter centriole is preferentially inherited by the differentiating daughter cell (neuron or BP) (Paridaen et al. 2013, Wang et al. 2009). These data suggest that the asymmetric inheritance of centrioles/centrosome during mitosis correlates with cell fate.

The importance of the centrosome function in brain development is highlighted by primary microcephalies, a group of diseases resulting in a dramatic reduction of brain size at birth (Gilmore

& Walsh 2013, Sun & Hevner 2014, Woods 2004, Woods et al. 2005). Intriguingly, the genes mutated in this disease are associated with centrosomal proteins (Bond et al. 2002, 2003; Gilmore & Walsh 2013; Jackson et al. 2002; Nicholas et al. 2010; Sun & Hevner 2014; Thornton & Woods 2009), as in the case of *ASPM* and *CDK5RAP2* (Bond et al. 2005, Lancaster et al. 2013, Lizarraga et al. 2010, Megraw et al. 2011). Mutations in *ASPM* are the most frequent cause of microcephaly (Bond et al. 2003). Aspm has been reported recently to cause centrosome amplification, resulting in aneuploidy and tissue degeneration in the mouse neocortex (Marthiens et al. 2013). Furthermore, work in *Drosophila* has shown that Asp regulates the distribution and function of the actin cytoskeleton, affecting nuclear positioning during interphase and mitosis and compromising the organization and integrity of the neuroepithelium (Rujano et al. 2013). Cdk5Rap2 is a protein recruited at the centrosome via its interaction with pericentrin (Buchman et al. 2010, Wang et al. 2010). Depletion of Cdk5Rap2 via RNAi in mouse neocortex increases the number of basal intermediate progenitors at the expense of apical radial glial cells and promotes neuronal differentiation, ultimately leading to a reduction in the neuron number, consistent with the involvement of CDK5RAP2 in microcephaly in humans (Bond et al. 2005, Lancaster et al. 2013).

Both Aspm and Cdk5Rap2 have a very well documented role in mitosis and in spindle positioning (Buchman et al. 2010, Fish et al. 2006). However, in light of data linking centrosome inheritance to cell fate determination, it would be interesting to determine whether mutations in Aspm and Cdk5Rap2 affect the asymmetric inheritance of the mother and daughter centrioles, and to what extent this contributes to the pathophysiology of microcephaly. Recent data suggest that another subcellular structure, directly linked to centrioles/centrosome, could play a role in asymmetric cell fate specification: the ciliary membrane.

Ciliary membrane. The ciliary membrane was recently shown to be endocytosed, along with the mother centriole, at the onset of mitosis (Paridaen et al. 2013) (**Figure 4**). Interestingly, the ciliary membrane is asymmetrically distributed during mitosis and tends to be inherited by the proliferative daughter cells, as opposed as to the differentiative one. Furthermore, the daughter cell inheriting the ciliary membrane tends to reestablish the cilium earlier than the sibling cell, suggesting the exciting possibility that the two daughter cells sense extracellular signals mediated by the cilium in different ways (Paridaen et al. 2013). Of note, an interesting corollary of these data is that the composition of the apical plasma membrane must be extremely heterogeneous to allow the membrane surrounding the cilium shaft to have a specific identity and to be selectively endocytosed. Defining the composition of the apical plasma membrane and its subdomains is expected to become a very interesting direction of research in the future; in particular, it would be important to correlate the composition of the apical plasma membrane with the acquisition (or maintenance) of cell identity.

Cilium localization and fate transition. In bipolar epithelial cells, such as neuroepithelial and apical radial glial cells, the cilium is strictly localized at the apical plasma membrane. However, the Sey/Sey (Pax6 mutant) mouse cortex shows an increased occurrence of abventricular centrosomes that is paralleled with an increase in subapical and basal mitosis (Asami et al. 2011, Tamai et al. 2007). Indeed, Pax6 directly regulates ciliary and centrosomal components, such as Spag5 (Asami et al. 2011), suggesting a possible link between centrosome/cilium localization and fate transition. Consistent with this observation, it has been demonstrated recently that in cells undergoing delamination (e.g., newborn basal progenitors and neurons), the cilium is localized basolaterally rather than apically (Wilsch-Bräuninger et al. 2012). Because the cilium is considered to be a cell antenna, it would be interesting to determine whether the change in its localization corresponds to a change in its ability to receive basolateral rather than apical signals.

Ciliopathies highlight the role of the primary cilium in neurodevelopment. The data reported so far strongly suggest that primary cilium components are crucial subcellular players in progenitor fate specification. In agreement with this concept, mutations in ciliary proteins lead to severe central nervous system defects (Bettencourt-Dias et al. 2011, Valente et al. 2014). These diseases are commonly referred as to as ciliopathies (Lancaster & Gleeson 2009). Ciliopathies associated with neural defects include Bardet-Biedl syndrome (BBS) and Joubert syndrome (Bettencourt-Dias et al. 2011). BBS is characterized by cognitive disabilities, obesity, and retinal degeneration, and it is caused by mutations in BBS proteins (Scheidecker et al. 2013). BBS proteins form a stable macromolecular complex, called the BBSome, involved in trafficking of proteins to cilia (Wei et al. 2012). Joubert syndrome is characterized by variable developmental delay/intellectual impairment and hindbrain defects (Lancaster et al. 2011, Sattar & Gleeson 2011). Genes contributing to Joubert syndrome include *Arl13b* and *CEP290*. Arl13b is a small GTPase specifically enriched at the ciliary membrane, and its mutation causes structural and functional cilia abnormalities. Interestingly, the deletion of Arl13b in the mouse neocortex leads to reversal of the radial glia apical-basal polarity, with detrimental effects on cortical lamination (Higginbotham et al. 2013). CEP290 is a basal body–associated protein that regulates the function of Rab8, a small GTPase involved in ciliogenesis (Kim et al. 2008). From the data reported so far, the cilium and its components clearly are claiming center stage as main players in neural development (Louvi & Grove 2011).

Apical Junctional Complexes

The apical junctional complexes have crucial roles in establishing and maintaining cell polarity, as demonstrated by seminal work conducted in cells in culture. It is therefore not surprising that junctional complex components, such as cadherins and catenins, are involved in maintaining not only apical radial glia cell polarity but also their identity (Aaku-Saraste et al. 1996, Chenn & Walsh 2003, Kim et al. 2010, Zhang et al. 2010). Interestingly, junctional components have a structural/architectural role and also a signaling role (**Figure 4**). From a structural point of view, the junctions allow cohesion of neighboring neuroepithelial and apical radial glial cells and are therefore important to maintain the proper tissue architecture (Marthiens et al. 2010). Cadherins are transmembrane proteins that form homo-oligomers in *trans* via their extracellular domain, allowing neighboring apical radial glial cells to stick together and ultimately leading to the formation of an apical surface facing the ventricle. With their intracellular domain, cadherins interact with catenins, notably α- and β-catenin, that in turn interact with the actin cytoskeleton (Huveneers & de Rooij 2013, Kobielak & Fuchs 2004, Suzuki & Takeichi 2008). The junctional complexes are therefore a way of connecting the extracellular milieu with the intracellular actomyosin cortex. Interestingly, junctional components have been reported to be asymmetrically partitioned during mitosis (Marthiens & ffrench-Constant 2009).

As already pointed out, junctional components not only are structural players in the cell but are actively engaged in signaling. Upon Wnt pathway activation, β-catenin is accumulated into the nucleus, where it regulates transcription. The function of Wnt is due to an effect on β-catenin stability (Holland et al. 2013, Kim et al. 2013, Wodarz & Nusse 1998). In the absence of Wnt signaling, the cytoplasmic β-catenin is degraded via a GSK-3/APC/CK1-dependent pathway. However, the activation of the Wnt pathway inhibits the degradation complex, leading to accumulation of free β-catenin and its translocation to the nucleus, where it regulates proliferation and differentiation genes (Holland et al. 2013, Wodarz & Nusse 1998). Interestingly, G proteins such as Gα12/13 bound to the G protein–coupled receptor C5B can induce the dissociation of cadherin-bound β-catenin and hence activity of the canonical Wnt-β-catenin pathway, thereby linking

extracellular events to gene regulation (Kurabayashi et al. 2013, Meigs et al. 2001). Reduced levels of C5B result in reduced levels of canonical Wnt signaling via β-catenin, leading to a striking block of neuronal fate and trapping radial glial cells in a gliogenic state, generating astrocytic progeny (Kurabayashi et al. 2013). These data are also consistent with further evidence for canonical Wnt signaling (mediated, for example, by Wnt7a) positively regulating neuronal differentiation by activating expression of the proneural transcription factor neurogenin2 in basal progenitors and thereby mediating their progression toward neuronal differentiation (Hirabayashi et al. 2004, Kuwahara et al. 2010, Qu et al. 2013). However, at early developmental stages, the overexpression of a constitutively active β-catenin in the mouse neocortex leads to enlarged neuroepithelium and enlarged lateral ventricles, as a result of cell cycle reentry and increased progenitor proliferation (Chenn & Walsh 2003). Interestingly, the ablation of GSK3 leads to a very similar phenotype, consistent with the reported role of GSK3 in regulating the stability and function of β-catenin (Kim et al. 2009). When GSK3 is phosphorylated at Thr485, axin is released from its interaction with GSK3 in the cytoplasm, translocates to the nucleus, and mediates neuronal differentiation of basal intermediate progenitors in the developing cerebral cortex (Fang et al. 2013). Thus, activation of Wnt signaling has been implicated both in neuroepithelial and apical radial glial cell expansion as well as in differentiation of basal progenitors, supposedly depending on the signaling context. Another class of molecules has recently gathered attention, as they are associated with the junctions and the strength of the adhesion belt, linking apical-basal polarity and cytoskeleton remodeling: the small GTPases Cdc42, RhoA, and Rac1 (Cappello 2013). These GTPases play important roles in maintaining the balance between F- and G-actin and also affect the tubulin cytoskeleton (e.g., RhoA). This affects progenitor proliferation with intriguing region-specific differences. The conditional deletion of RhoA, for example, leads to a transient increase in progenitor proliferation in some brain regions, such as the mouse telencephalon and mesencephalon (Cappello et al. 2012, Katayama et al. 2011), and proliferation is reduced upon RhoA deletion in the spinal cord (Herzog et al. 2011). These data suggest a direct link between the regulation of the cytoskeleton and proliferation. Moreover, defects in apical radial glia morphology (i.e., reduction in basal process stability) cause defects in the cytoarchitecture. Finally, cdc42 is also involved in regulating various signaling pathways, such as integrin signaling or Par-complex signaling (Hall 2005, Jaffe & Hall 2005, Tepass 2012). Accordingly, its conditional deletion also has an effect on cell fate, converting the self-renewing apical radial glial cells into non-self-renewing basal intermediate progenitors (Cappello et al. 2006, Costa et al. 2008).

Gap junctions. Similarly to other epithelial cells, neuroepithelial and apical radial glial cells are coupled via gap junctions located within both the apical domain and the basal endfeet (Elias & Kriegstein 2008). The intercellular communication via gap junctions relies on the juxtaposition of connexin hemichannels on neighboring cells and allows the exchange of small molecules (LoTurco & Kriegstein 1991). The junctional coupling allows calcium transients to spread among clusters of cells (Owens & Kriegstein 1998) and is crucial to synchronize INM on a tissue level (Liu et al. 2010). Early work conducted on the rat neocortex demonstrated that junctional coupling is cell cycle dependent and decreases as development proceeds (Bittman et al. 1997). The decrease in junctional coupling does not correspond to a decreased use of the connexin hemichannels. Indeed, in the absence of an apical contact, the hemichannels are used either for cell migration or to release small molecules into the extracellular space, notably purines (Elias et al. 2007; Liu et al. 2008, 2010). From a cell biological point of view, the hemichannels represent a very interesting example of how the same structure can serve different purposes in different cellular types and subcellular locations.

BASAL COMPONENTS: GENERAL REMARKS

The basolateral plasma membrane constitutes the vast majority of the neuroepithelial or apical radial glial cell plasma membrane; it surrounds the nucleus and reaches the basal lamina (**Figures 2** and **4**). Interestingly, the area of the basolateral plasma membrane increases during development to match the increase in the cortical wall thickness (**Figure 5**). This increase pertains mainly to the so-called basal process (Taverna & Huttner 2010). Unlike any other epithelial cells, the neural progenitor basolateral plasma membrane consists of two subcompartments: the VZ-basolateral plasma membrane, which forms what we define as the proximal segment of the basal process, and the distal segment of the basal process. The VZ-basolateral plasma membrane accommodates the nucleus during the different phases of INM (see below) (Taverna & Huttner 2010). The distal segment of the basal process is very thin and spans the neuronal layers, reaching the basal lamina.

Basal Process

The distal segment of the basal process (defined above as the part of the basolateral plasma membrane traversing the neuronal layers) is never occupied by the nucleus during INM and is a typical feature of apical radial glial cells, and of some SAPs and basal radial glial cells. In APs, the formation of the basal process as a specialization of the basolateral plasma membrane is concomitant with the transition from neuroepithelial cells to apical radial glial cells. Originally regarded merely as a scaffold for neuron migration, the basal process is nowadays recognized as an active subcellular compartment involved in signaling and fate specification (Fietz & Huttner 2011). In particular, live-imaging experiments have shown that the basal process is asymmetrically inherited during mitosis (Miyata et al. 2001) and that the daughter cell inheriting the basal process often maintains proliferative capacities (Konno et al. 2008, LaMonica et al. 2013). In line with these observations, integrin manipulation affects neural stem and progenitor cell behavior. For example, integrin β1 inactivation leads to apical radial glia detachment from the ventricular surface and increase in basal mitosis, resulting in layering defects (Loulier et al. 2009). In addition, integrin αvβ3 activation increases proliferation of neural progenitors (Stenzel et al. 2014), while integrin α6 deletion has no influence on neural stem and progenitor cell fate and proliferation (Haubst et al. 2006). From a cell biological point of view, the basal process possesses features that should be regarded as subcompartments: the varicosities and the basal endfoot.

Varicosities. The diameter of the basal process is not homogeneous, as it contains areas of swelling, called varicosities (Bentivoglio & Mazzarello 1999). Imaging experiments have shown that varicosities are dynamic entities, as they are more abundant in mitosis than in interphase. Varicosities are believed to be generated by cytoplasm flow. It would therefore be interesting to study the dynamics of the cytoskeleton in these structures, in particular in relation to the actomyosin cortex. Furthermore, the varicosities cluster receptors, such as b3 integrin, involved in signaling, thus contributing to the signaling function of the basal process (Fietz et al. 2010).

Basal endfoot. The basal endfoot is the part of the basal process that makes direct contact with the basal lamina; therefore, it is the subcellular structure that is more likely to receive signals generated by, or enriched in, the basal lamina. Live-imaging experiments have shown that the basal endfoot is highly dynamic, and its shape changes from a club-like to a highly branched structure (Yokota et al. 2010). Interestingly, the basal endfoot dynamics depend on Cdc42, also a main regulator of apical polarity (Cappello et al. 2006). However, the importance of the basal

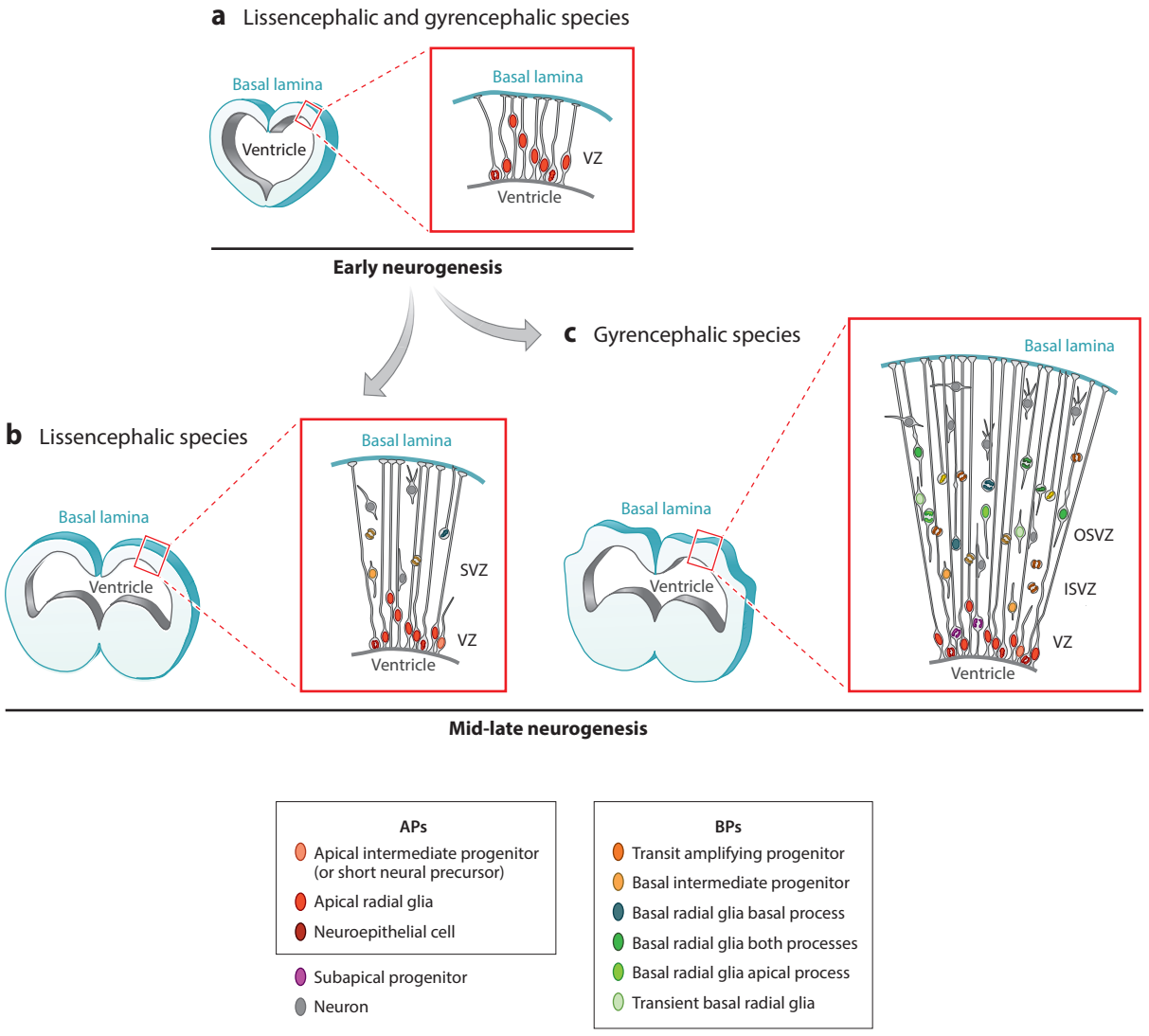

Figure 5

Progenitor subtype diversity in development and evolution. During development and evolution, the diversity and variety of progenitor cells increase. (*a*) Neuroepithelial cells constitute the ventricular zone (VZ) and are responsible for the lateral expansion during the early stages of neurogenesis. (*b*) During mid-late neurogenesis in lissencephalic species, apical progenitors (APs) divide and increasingly give rise to basal progenitors (BPs), which form a new proliferative zone, the subventricular zone (SVZ). (*c*) During mid-late neurogenesis in gyrencephalic species, the complexity and size of the progenitor pool increase. Subapical progenitors are more abundant, and BPs now comprise a higher proportion of transit amplifying progenitors and basal radial glial cells than is typically the case for lissencephalic species. The increase in the BP pool leads to the appearance of the inner SVZ (ISVZ) and outer SVZ (OSVZ).

endfoot is not limited to a structural function; it further acts as a key anchor for the overlying basal lamina, which ruptures when integrin-mediated anchoring is disrupted (see, e.g., Haubst et al. 2006). The basal endfoot is also thought to convey signals from the extracellular matrix–rich basal lamina, maintaining the proliferative capacity of cortical stem and progenitor cells (Fietz et al. 2010). A particularly critical receptor in this context is the G protein–coupled receptor 56

(GPR56) that localizes to basal endfeet and binds to extracellular matrix components in the basal lamina, such as collagen III, and that promotes proliferation of radial glial cells (Jeong et al. 2013, Singer et al. 2013). Its mutation and reduced expression result in aberrant gyrification in human patients (Singer et al. 2013). Most intriguingly, acquisition of a multitude of new transcriptional start sites resulting in alternatively spliced transcripts in placental mammals allows region-specific regulation, affecting gyrification selectively in specific areas of the cerebral cortex (Bae et al. 2014, Singer et al. 2013). Interestingly, proliferation signals can also be sustained in the basal endfoot by local protein synthesis, as shown recently for a pool of cyclin D2 mRNA (Tsunekawa et al. 2012). This suggests that protein synthesis in a distal, noncanonical, subcellular location can act as a new level of regulation for neural stem and progenitor cell behavior. Taken together, the basal endfoot emerges as a key compartment to regulate radial glia proliferation and accordingly gyrification (see also Shitamukai & Matsuzaki 2012 and below). (Importantly, various other signaling sources may act selectively on the basal endfoot, such as the Reelin-secreting Cajal-Retzius cells or the meninges that generate and overlie the basal lamina; both of these potential sources are discussed below.)

MITOTIC SPINDLE

The mitotic spindle is a key element regulating the symmetry or asymmetry of cell division (Huttner & Kosodo 2005, Peyre & Morin 2012, Shitamukai & Matsuzaki 2012). It is therefore not surprising that perturbing the spindle core components, such as microtubules and centrosomes, affects neurogenesis (Bond & Woods 2005). The role of the mitotic spindle in neurogenesis is also linked to the fine-tuning of spindle function, as in the case of spindle orientation in highly polarized cells, such as neuroepithelial and apical radial glial cells (Fish et al. 2006, Lancaster & Knoblich 2012). In neuroepithelial and apical radial glial cells of murine cerebral cortex, the spindle is oriented largely perpendicularly to the apical-basal axis of the cell, thus providing a perfect configuration to partition apical-basal polarity cues, such as the apical plasma membrane, the basal process, and the junctions (**Figure 4**). However, there is more diversity in spindle orientation relative to the apical-basal axis in other brain regions and the spinal cord (Pilz et al. 2013, Wilcock et al. 2007), resulting in oblique or horizontal cleavage of daughter cells. Interestingly, oblique and horizontal orientation of the cleavage plane accompanies the generation of basal radial glial cells in rodents and primates (see below; Gertz et al. 2014, LaMonica et al. 2012, Pilz et al. 2013, Shitamukai et al. 2011). This observation is extremely intriguing, as it suggests that the mitotic spindle orientation is one of the key players in the transition from a bipolar to a monopolar cell, in line with previous observations (Shitamukai et al. 2011).

Interestingly, proteins affecting spindle function and decreasing its precision are mutated in microcephaly, a human disease associated with a smaller brain size at birth (Bond & Woods 2005, Fish et al. 2006, Sun & Hevner 2014, Valente et al. 2014, Woods 2004). MCPH mutations lead to depletion of the neural progenitor pool and to impaired neurogenesis. Other proteins linking the cell cortex with the mitotic spindle, such as LGN, have been reported to perturb the spindle orientation (Konno et al. 2008, Morin et al. 2007). However, these perturbations do not significantly affect murine or avian neurogenesis, fueling discussion about the impact of spindle orientation on neuronal output. Given the importance of spindle orientation in the generation of basal radial glial cells, these manipulations may have stronger effects in the cerebral cortex of species with a high gyrification index (see below). The vast majority of studies reported so far have addressed the role of spindle orientation in neuroepithelial and apical radial glial cells. Interestingly, in murine and primate basal radial glial cells, the mitotic spindle is rarely oriented perfectly parallel to the radial axis of the cell but exhibits a preference for a horizontal orientation, implying that basal polarity cues will be asymmetrically inherited upon cytokinesis (Fietz et al.

2010, Hansen et al. 2010, LaMonica et al. 2013) (**Figure 4**). In the future, it would be interesting to dissect the spindle components in mitotic basal radial glial cells and their impact on the asymmetry of basal radial glia divisions. In particular, the comparison between apical radial glial cells and basal intermediate progenitors/transit amplifying progenitors is expected to provide insights into the role of polarity in relation to spindle positioning. Moreover, comparing apical to basal radial glial cells could lead to a better understanding of the nature of the polarity cues in basal radial glial cells.

CLEAVAGE FURROW

The final step in cell division, cytokinesis, allows the actual splitting of the mother cell into two daughter cells. In neuroepithelial and apical radial glial cells, the cleavage furrow is known to ingress from the basal side (Kosodo et al. 2008). However, a principal difference exists: As in early stages of development, the cleavage furrow ingression often/sometimes results in splitting of the basal process, with both daughter cells (neuroepithelial cells) maintaining a basal attachment (Kosodo & Huttner 2009, Kosodo et al. 2008). Yet in mid- and late neurogenesis, the basal process is no longer split, resulting in its asymmetric inheritance: Live-imaging experiments have suggested a link between basal process inheritance and basal radial glia self-renewal (LaMonica et al. 2012; however, see also Betizeau et al. 2013). The presence of a pool of cyclin D2 mRNA in the basal endfoot of murine apical radial glial cells provides a possible molecular mechanism linking inheritance of the process to higher proliferative potential (Tsunekawa & Osumi 2012, Tsunekawa et al. 2012).

From a molecular point of view, and similar to other systems studied so far, cleavage furrow ingression depends on anillin and the actin-based cortex (Kosodo & Huttner 2009). The main difference between neuroepithelial and apical radial glial cells therefore appears to be the location where the furrow ingresses. In future, it would be of interest to dissect the molecular mechanisms coupling furrow ingression with cell polarity.

In the final phase of furrow ingression and cytokinesis, a structure called the midbody is formed that connects the two daughter cells. In neuroepithelial cells, the midbody typically relocates to the daughter cell maintaining the apical process (Wilcock et al. 2007), and it can be released into the lumen of the neural tube via an endosomal sorting complex required for transport (ESCRT)-dependent pathway (Dubreuil et al. 2007, Ettinger et al. 2011, Marzesco et al. 2005). Although the functional significance of midbody release is still debated, an exciting hypothesis is that it serves as a mechanism of cellular communication, as in the case of exosomes and other extracellular membrane particles.

EXTRACELLULAR SIGNALS IN PROGENITOR FATE DETERMINATION

The highly polarized nature of the developing telencephalon makes this tissue ideal to generate very localized signals that are then used to regulate progenitor behavior and in turn overall brain development. Here we consider the different sources of signaling, proceeding in the apical-to-basal direction, and therefore discuss signals from the ventricular fluid, neighboring progenitor cells, blood vessels, neurons, the basal lamina, and the meninges.

Signals from the Ventricular Fluid

The ventricles are filled with the CSF that is produced mainly by the choroid plexus, a highly vascularized secretory epithelium (Dziegielewska et al. 2001; Johansson et al. 2008, 2013; Lehtinen

& Walsh 2011; Lehtinen et al. 2013). CSF is mainly composed of water, involving aquaporin-1 channels located in the apical membrane of the epithelial cells, and a lot of attention was initially focused on the role of pressure in the developing brain. Recently, the advances in mass spectrometry techniques have highlighted the complexity of the CSF composition. It is now clear that CSF in the developing brain contains a diversity of ions, proteins, lipids, signaling molecules, hormones, and even membrane-bound particles, such as released midbodies; the CSF composition is conserved among species, and it is dynamically regulated during development (Lehtinen et al. 2011). Main components of CSF include IGFs, FGFs, Shh, BMPs, and Wnts (Johansson et al. 2013, Lehtinen & Walsh 2011). Owing to this plethora of molecules, CSF regulates progenitor behavior and brain development (for a review on CSF composition and function, see Lehtinen & Walsh 2011 and references therein).

IGFs, in particular IGF2, stimulate progenitor proliferation and therefore influence neurogenesis and brain size (Lehtinen et al. 2011); IGF receptors are localized mainly on the apical surface and primary cilium of neuroepithelial and apical radial glial cells, and IGF-1 activates a cilium-localized noncanonical $G\beta\gamma$ signaling pathway that regulates cell cycle progression (Yeh et al. 2013). An additional source of IGF is represented by the vasculature, providing BPs with the potential to be regulated by IGF signals as well. FGFs positively regulate progenitor proliferation and are implicated in early brain patterning (for review, see Iwata & Hevner 2009) and in regulation of primary cilium length and function (Neugebauer et al. 2009). The cilium is also involved in *Shh* signaling via its receptor, Patched. In the neural tube, Shh is produced by the hindbrain choroid plexus and promotes progenitor proliferation nearby (Aguilar et al. 2012, Komada et al. 2008, Spassky et al. 2008). In addition, Shh has been demonstrated to synergize with IGF signaling (Fernandez et al. 2010, Rao et al. 2004). Intriguingly, however, signals released by the hindbrain choroid plexus, such as Wnt, can influence even the distant telencephalon (Johansson et al. 2013). Thus, various signaling molecules with a well-documented role in patterning influence stem cell behavior in far distant sites via this route. The receptors for these signaling molecules (e.g., Patched, frizzled) are located at the apical plasma membrane, or at the primary cilium, thus highlighting the importance of the apical domain in mediating the signaling from the ventricle.

Signals from Neighboring Stem and Progenitor Cells

There are two types of signals that stem and progenitor cells in the densely packed VZ generate and sense: chemical signals and physical signals.

Chemical signals. Neighboring cells communicate via gap junctions (see also above) (Elias & Kriegstein 2008). Gap junction communication is a way of synchronizing nuclear migration on a tissue level (Liu et al. 2010). Furthermore, progenitor cells secrete purines that affect proliferation of neighboring cells (Liu et al. 2010). Another example of chemical signaling is represented by Notch: In the developing telencephalon, it has been demonstrated that newborn basal intermediate progenitors and neurons produce Notch ligands that bind to the Notch receptor present on apical radial glial cells (Yoon et al. 2008). This very elegant example illustrates how the two daughter cells derived from an asymmetric division can influence each other (Yoon et al. 2008; see also Imayoshi et al. 2013, Kageyama et al. 2009, and references therein).

Physical signals. Recent work has demonstrated that when the VZ is overcrowded, the progenitors tend to leave the apical surface to settle and divide basally (Okamoto et al. 2013). This finding, together with observations suggesting passive nuclear displacements during INM (Kosodo et al. 2011, Leung et al. 2011), suggests that progenitors may sense mechanical stress and respond by

changing nuclear localization in the tissue. Contributions of such physical components to nuclear positioning are also in line with the classical considerations of Smart (1972a, 1972b) that basal divisions occur when the ventricular surface is congested by apical mitoses.

Signals from Blood Vessels

Apical radial glial cells receive signals from the apical and/or the basal side, reflecting the presence of an apical and basal process, respectively. However, the unpolarized basal intermediate progenitors are devoid of both apical and basal contact. So, an obvious question is where the signaling molecules and nutrients regulating these BPs are coming from. Independent work from two laboratories has shown that the temporal and spatial distributions of the basal intermediate progenitors follow the three-dimensional distribution of capillaries (Javaherian & Kriegstein 2009, Stubbs et al. 2009). This observation has led to the proposal that the vasculature in the developing brain acts as a niche for BPs, providing a source of nutrients and signaling molecules regulating their behavior. Furthermore, apical radial glia processes are the guiding structures of blood vessels invading from the pial surface, highlighting the close interrelationship between apical radial glial cells and the vasculature (Ma et al. 2013).

Signals from Neurons

One of the best examples of how neurons influence progenitor behavior is that of the Cajal-Retzius neurons. The Cajal-Retzius cells are pioneer neurons produced at the very onset of neurogenesis, and they settle in the basal-most layer of the cerebral cortex, immediately below the meninges (Soriano & del Río 2005). Cajal-Retzius cells are known to secrete several molecules, in particular Reelin (Bar et al. 2000). Although the best-documented role of Reelin is in neuronal migration, a role has also been proposed in the regulation of progenitor behavior (Hartfuss et al. 2003). In particular, Reelin was found to enhance Notch activation in apical radial glial cells and to regulate neuron and basal intermediate progenitor production (Lakomá et al. 2011). An example of long-range regulation between neurons and progenitors is represented by the cortical plate transient neurons, a class of neurons produced in the ventral telencephalon. Cortical plate transient neurons migrate a long way and eventually invade the dorsal telencephalon but later disappear. Their ablation during development results in premature neurogenesis and depletion of the progenitor pool, suggesting an effect on the progenitors' proliferative potential (Teissier et al. 2011).

Signals from Microglia

There is increasing evidence that microglia affect neurogenesis, including that in the developing neocortex (e.g., Antony et al. 2011, Cunningham et al. 2013). However, space limitations do not permit an in-depth discussion of this topic, and the reader is referred to an excellent recent review (Ueno & Yamashita 2014).

Signals from the Meninges

Besides the signals from the basal lamina described above, recent evidence also implicates signals from the meninges in regulating cortical progenitor behavior and neurogenesis. The overlying meninges are the sole source of retinoic acid for the developing cerebral cortex (Chatzi et al. 2013, Siegenthaler et al. 2009) but also provide other key signaling factors, such as chemokines [e.g., Cxcl12 (Borrell & Marin 2006), see also the discussion of Cajal-Retzius cell migration below]. Retinoic acid has been proposed to reduce radial glia self-renewal and tangential expansion and

promote basal intermediate progenitor generation and neuronal differentiation (Siegenthaler et al. 2009). This has been deduced from the effects seen after (genetic) removal of meninges and from similar defects in mice hypomorphic for the retinoic acid synthesizing enzyme Rdh10 (Siegenthaler et al. 2009). However, this interpretation could not be confirmed by $Rdh10^{-/-}$ mice that were entirely devoid of retinoic acid signaling from the meninges and within the cerebral cortex (Chatzi et al. 2013). When these mice were rescued from earlier severe patterning defects owing to the failure of neural crest–derived meningeal cell immigration, lack of retinoic acid no longer mattered for neurogenesis in the cerebral cortex (Chatzi et al. 2013). The emerging message thus appears to be that meninges release key signals in addition to retinoic acid for cerebral cortex development, including molecules affecting early neurogenesis and growth of the cerebral cortex.

INTRACELLULAR ASPECTS OF PROGENITOR FATE

As stated above, we focus here on cell biological mechanisms of intrinsic fate determination. Concerning events within the nucleus, notably transcriptional regulation and epigenetics, and regulation by microRNAs, we refer the reader to recent reviews (Cremisi 2013, Hirabayashi & Gotoh 2010, Tuoc et al. 2014). With regard to cell biological mechanisms, we do not describe the role of transmembrane and cytoplasmic proteins in this section, as these are addressed, at least in part, in other sections.

Intracellular Traffic

The crucial role of intracellular traffic in brain development is highlighted by the α-SNAP and ArfGEF mutants, both of which show severe neurodevelopmental defects. In the α-SNAP mutant, progenitors undergo premature neurogenesis, leading to hydrocephalus (Chae et al. 2004). *ARFGEF2* mutations in humans are associated with microcephaly and periventricular heterotopia (Sheen et al. 2004). This has been linked to decreased progenitor proliferation and to perturbed cadherin transport to the cell surface. In agreement with the crucial role of cell polarity in maintaining cell fate and securing proper corticogenesis, blocking Numb function disrupts junction insertion at the plasma membrane; affects cell polarity, including the maintenance of adherens junctions (Rasin et al. 2007); and perturbs corticogenesis (Kim & Walsh 2007). As to Numb and Notch signaling, there is further cross-talk with the cell polarity determinant Par3 (Bultje et al. 2009). Numb also affects corticogenesis via a Golgi-dependent pathway, because the asymmetric distribution of Numb during cell division depends on the Golgi disassembly at the onset of mitosis (Zhong et al. 1996, Zhou et al. 2007).

Lipids

Regarding the issue of cell polarity, the asymmetry of cell components pertains not only to proteins but also to lipids, specifically membrane lipids. Seminal work on model epithelial cells, such as MDCK cells, demonstrated that membrane lipids are crucial in establishing and maintaining cell polarity (Martin-Belmonte et al. 2007, Shewan et al. 2011, Simons & Fuller 1985, Simons & van Meer 1988). Given the vast body of literature available, it is somewhat surprising that so little is known about the role of membrane lipids in neural progenitor architecture and fate determination. The gangliosides GM1 and GM3 are highly enriched in the apical endfoot of human apical radial glial cells (Stojiljkovic et al. 1996), consistent with the reported role of glycosphingolipids and gangliosides in signal transduction in stem cells (Jung et al. 2009). ABBA, a protein connecting membrane PIP2 and the actin cytoskeleton, is localized mainly in the basal endfoot of apical radial glial cells, and its downregulation inhibits process extension in vitro, suggesting a link between the

membrane lipid–actin cytoskeleton interaction and cell polarity (Saarikangas et al. 2008). It has also been observed that the *fatty acid binding protein* (*Fabp7*) is a downstream target of Pax6 (Arai et al. 2005), a master regulator of neurogenesis (Heins et al. 2002, Ninkovic et al. 2013, Osumi et al. 2008). Interestingly, reducing the level of Fabp7 via RNAi leads to decreased cell proliferation and increased neuronal differentiation, strongly linking lipids and cell fate determination (Arai et al. 2005). Finally, the requirement of cholesterol, a crucial membrane lipid, has been investigated by conditional ablation of squalene synthase, a key enzyme for endogenous cholesterol biosynthesis, in neural stem and progenitor cells (Saito et al. 2009). Remarkably, neuroepithelial and apical radial glial cells evaded the likely detrimental consequences of impaired endogenous cholesterol biosynthesis by increased VEGF expression, which in turn resulted in increased angiogenesis in the VZ and thus elevated supply of exogenous cholesterol to these cells.

COMPLEX PROCESSES IN PROGENITORS

Interkinetic Nuclear Migration

INM is a hallmark of neuroepithelial cells and apical radial glial cells and refers to the fact that the nucleus moves in phase with the cell cycle (Sauer 1935). Namely, mitosis of neuroepithelial cells and apical radial glial cells occurs at the apical surface of the VZ, whereas S phase usually takes place at a more basal location, with apical-to-basal nuclear migration in G1 and basal-to-apical nuclear migration in G2 (Lee & Norden 2013, Taverna & Huttner 2010). INM is therefore responsible for the pseudostratified appearance of the VZ (Sauer 1935). A major question in the field has been why the nucleus migrates toward the apical cell surface for mitosis. A possible reason is the fact that in canonical APs, the apical domain harbors, throughout the cell cycle, the primary cilium that provides the centrosomes needed to build the mitotic spindle. In this context, it is interesting to note that SAPs exhibit an apical process but do not perform apically directed INM and undergo mitosis at an abventricular location (Pilz et al. 2013). Here, it will be important to determine whether their centrosomes remain in the vicinity of the nucleus throughout the cell cycle or translocate during interphase toward the nucleus for mitosis.

An additional reason for INM could be that the apical domain of APs contains many of the polarity cues [e.g., apical cell cortex, apical adherens junctions (Bultje et al. 2009, Cayouette & Raff 2002, Kosodo et al. 2004, Marthiens & ffrench-Constant 2009)] that must be either symmetrically or asymmetrically distributed to the daughter cells on cytokinesis for symmetric or asymmetric division, respectively; therefore, an apical mitosis offers obvious advantages for controlling symmetric versus asymmetric AP division (Huttner & Kosodo 2005).

Molecular mechanism of interkinetic nuclear migration. Microtubule-based and actin-based proteins constitute the molecular machinery of INM (Lee & Norden 2013, Taverna & Huttner 2010). The relative contribution of microtubule- and actin-based proteins depends on the species and on the tissue under study (Kosodo et al. 2009, Lee & Norden 2013, Norden et al. 2009, Schenk et al. 2009, Taverna & Huttner 2010). In the case of the developing rodent neocortex, early work has demonstrated that microtubule-based motors, in particular dynein, are involved in the G2 basal-to-apical nuclear migration (Cappello et al. 2011, Faulkner et al. 2000, Tanaka et al. 2004, Tsai et al. 2005, Vallee et al. 2001, Wynshaw-Boris & Gambello 2001). The nucleus is transported as a cargo along microtubules toward their minus end, and the coupling between dynein and the nucleus is achieved via the SUN-KASH protein complex (Zhang et al. 2009). Consistent with a major role of microtubules in INM, mutations affecting microtubule-based motor proteins produce devastating effects on neurodevelopment, as in the case of lissencephaly,

a disorder characterized by a smooth cerebral cortex surface in species that normally have a folded cerebral cortex (Bahi-Buisson & Guerrini 2013; Moon & Wynshaw-Boris 2013; Morris et al. 1998a,b; Poirier et al. 2013; Reiner & Sapir 2013). The molecular mechanisms underlying the G1 apical-to-basal nuclear migration appear to be more complex, as they possibly involve both actomyosin and microtubule-based motors, such as unconventional kinesins (Schenk et al. 2009, Tsai et al. 2010). Interestingly, a recent report suggests a passive component for nuclear migration during G1: This conclusion is based on the observation that the G1 apical-to-basal migration could result from passive nuclear displacement caused by the apically directed, actively migrating G2 nuclei (Kosodo et al. 2011).

Interkinetic nuclear migration and cell cycle progression. Consistent with the idea that the nucleus moves in concert with the cell cycle, blocking cell cycle progression prevents INM (Murciano et al. 2002, Taverna & Huttner 2010). How, then, is the speed of INM adapted to the various cell cycle phases? A possible molecular mechanism that may account for this synchrony has been proposed recently and involves Tpx2, a microtubule-associated protein that shuttles between the nucleus and the cytoplasm in a cell cycle–dependent manner (Kosodo et al. 2011). During G2, Tpx2 accumulates in the apical process, where it binds to microtubules and promotes G2 microtubule-dependent nuclear migration (Kosodo et al. 2011). Although INM requires cell cycle progression, the converse does not hold true: Perturbing or slowing INM has no apparent effect on cell cycle parameters (Schenk et al. 2009).

Functions of interkinetic nuclear migration. Smart (1972a, 1972b) proposed that the primary function of INM is to achieve pseudostratification of the VZ and thus to maximize the mitoses of neuroepithelial and apical radial glial cells. According to Smart, INM is a crucial step to secure the expansion of the apical radial glial cell pool and to allow for the evolution of animals with higher encephalization. Given that the apical and basal environment are different, INM has the potential to influence progenitor fate by regulating the time the neural progenitor nucleus spends at any given location along the apical-basal axis during the cell cycle (Murciano et al. 2002, Taverna & Huttner 2010). This hypothesis (called the nuclear residence hypothesis) predicts that the factor(s) influencing progenitor fate should be polarized along the apical-basal axis of the cortical wall. One of these factors is Notch, which prevents cells from differentiating and is highly enriched at the apical domain: When the basal-to-apical INM is inhibited, APs exit the cell cycle prematurely in a Notch-dependent manner (Del Bene et al. 2008). Furthermore, in zebrafish, the more basally the nucleus migrates, the more likely it is to undergo a neurogenic division (Baye & Link 2007, 2008). Taken together, these data suggest that INM influences progenitor fate by controlling the exposure of progenitor nuclei to proliferative versus neurogenic signals.

Nucleokinesis in the Basal Compartment

In contrast to APs, SAPs and BPs do not perform INM, suggesting that INM may be a process characteristic of those progenitors with apical-basal cell polarity in which the centrosomes are located at the apical cell cortex throughout interphase whereas the nucleus is not. However, nucleokinesis as such is not a prerogative of neuroepithelial and apical radial glial cells, as BPs also show specific patterns of nuclear migration. Most notably, the SVZ arises owing to the migration of the newborn BPs from the VZ toward this germinal layer, and this apical-to-basal nuclear migration is believed to involve actomyosin contractility (Schenk et al. 2009).

Furthermore, live-imaging experiments have shown that basal radial glial cells and SAPs undergo a fast phase of nuclear movement (typically in the basal direction) just before mitosis, called

mitotic somal translocation (MST) (Betizeau et al. 2013, Hansen et al. 2010, LaMonica et al. 2013, Pilz et al. 2013). The molecular mechanism underlying MST is currently unknown. However, considering the analogy with INM in APs, one may predict that microtubules and/or actomyosin may be involved. Concerning the functional significance of MST, it would be interesting to investigate whether it is used to position a given cell nucleus nearer to a hypothetical basal or further away from a hypothetical apical signaling source.

Cell Cycle Length

One of the key determinants of neurogenesis is cell cycle length (Dehay & Kennedy 2007). The initial finding, based on the comparison between neurogenic and proliferative neural progenitors, suggested that at the onset of neurogenesis, neural progenitors lengthen the G1 phase of the cell cycle (Calegari & Huttner 2003, Calegari et al. 2005, Dehay & Kennedy 2007, Lukaszewicz et al. 2005, Pilaz et al. 2009). This G1 lengthening appears to be a cause, rather than a consequence, of the commitment toward the neuronal lineage (Calegari & Huttner 2003, Calegari et al. 2005). Accordingly, the forced reduction of G1 via cyclinD manipulation promotes expansion of neural progenitors (Lange et al. 2009, Pilaz et al. 2009). Recently, the availability of more sophisticated techniques and the use of progenitor type-specific markers allowed researchers to compare the neurogenic versus proliferative potential of different progenitor types, namely apical radial glial cells and basal intermediate progenitors (Arai et al. 2011). In general, basal intermediate progenitors were found to have a substantially longer G1 phase than apical radial glial cells, consistent with a role of G1 lengthening in differentiation (Arai et al. 2011, Calegari et al. 2005).

Interestingly, both neurogenic apical radial glial cells and basal intermediate progenitors were found to markedly shorten their S phase as compared with their proliferative counterpart. Intriguingly, the shortening of S phase appears to reflect a reduced investment in DNA repair, rather than an increased rate of DNA replication (Arai et al. 2011). In other words, proliferative progenitors appear to spend more time repairing their DNA after replication than do neurogenic ones. A possible reason for a need of higher fidelity of DNA replication in proliferative apical radial glial cells may be that errors would be passed on to multiple radial units, whereas in the case of neurogenic apical radial glial cells, these would remain confined to the progeny in a given radial unit. The functional significance of S-phase shortening is currently unknown, but it would be interesting to determine if it is one of the causes of the high occurrence of somatic mutations observed in neurons, and whether it contributes to the generation of neuronal diversity (Arai et al. 2011, Poduri et al. 2013).

Interestingly, the cell cycle length appears to be differently regulated in the ventral telencephalon of mice, where each subsequent symmetric proliferative cell division has a shorter cell cycle, thereby profoundly increasing the number of daughter cells generated (Pilz et al. 2013). It will thus be interesting to compare the molecular mechanisms governing cell cycle regulation in the ventral versus dorsal telencephalon—in particular with regard to DNA repair and its relevance for self-renewal, as this is the region where the long-term self-renewing adult neural stem cells emerge in mice.

NEOCORTEX EXPANSION DURING DEVELOPMENT AND EVOLUTION

In this section, we discuss neocortex expansion during development and evolution specifically from a cell biological perspective. Complementary perspectives are addressed in several excellent reviews on these topics (Borrell & Götz 2014, Borrell & Reillo 2012, Lui et al. 2011, Sun & Hevner 2014).

Radial Versus Lateral Expansion

The expansion of the neocortex involves growth in two principal directions, lateral and radial (Fish et al. 2008). Regarding growth in the lateral direction, expansion at the ventricular versus pial surface should be distinguished. These distinct forms of neocortex expansion primarily reflect different modes of cell division of the various cortical stem and progenitor cells, as follows.

Lateral expansion of the ventricular zone. Symmetric proliferative divisions of neuroepithelial cells, which constitute the initial mode of division of these cells, and of the neuroepithelial cell–derived apical radial glial cells, cause the lateral (tangential) expansion of the VZ (**Figure 5**). As discussed above, signaling from the CSF may be a key factor driving these divisions, as APs have direct access to this signaling source. Enforced β-catenin signaling has been shown to cause lateral expansion of the VZ (Chenn & Walsh 2002, 2003). Moreover, the transcription factor FoxG1 or the novel nuclear regulator Trnp1 potently promotes AP amplification (Stahl et al. 2013, Xuan et al. 1995).

Increasing the radial thickness of the ventricular zone. Concomitant with the lateral expansion of the VZ due to the symmetric proliferative divisions of neuroepithelial and apical radial glial cells, these cells increase their basolateral-to-apical plasma membrane ratio and thus become more elongated. Hence, this lateral expansion of the VZ is accompanied by growth in the radial dimension (**Figure 5**), that is, an increase in the thickness of the VZ and in the extent of its pseudostratification (Smart 1972a,b; 1973).

Radial expansion of the cortical wall. In contrast to symmetric proliferative divisions, asymmetric self-renewing division of APs, which constitute the original source of BPs and produce more BPs the more often they occur, are the primary basis of neocortex expansion in the radial dimension (**Figure 5**). A second, and crucially important, parameter for radial neocortex expansion is the number of proliferative and self-renewing divisions of the various types of BPs (Noctor et al. 2007). In fact, the evolution of animals with higher encephalization has been linked to expansion and diversification of the SVZ, which reflects a striking increase in BP diversity and population size (Betizeau et al. 2013, Fietz et al. 2010, García-Moreno et al. 2012, Hansen et al. 2010, Kelava et al. 2012, LaMonica et al. 2013, Reillo & Borrell 2012, Reillo et al. 2011, Shitamukai et al. 2011, Wang et al. 2011). This increase is ultimately responsible for the increase in neuron output, which is reflected in the thickness of the cortical layers (Cheung et al. 2010, Kriegstein et al. 2006, Molnar 2011).

Lateral expansion of the cortical wall via cone-shaped, basally enlarged radial units. The increase in BP diversity and population size also leads to a change in the shape of radial units from nearly cylindrical to conical (with the tip of the cone being at the ventricle) (Fietz & Huttner 2011, Lui et al. 2011), an important aspect for generating more neurons and glia per apical surface area (Borrell & Götz 2014, Rakic 2000). In this context, three questions must be answered: What are the mechanisms that force BPs to move basally? What are the mechanisms that increase BP diversity? And what are the molecular signatures of the various types of BPs?

Outer Subventricular Zone Progenitor Proliferation and Self-Renewal: Cell Biological Considerations

Over the last five years, several studies in various species have revealed an increasing diversity of cortical stem and progenitor cells. Following the seminal study by Smart and colleagues (2002) describing the OSVZ, independent work from three different laboratories recently culminated

in the identification of two new cortical progenitor types that are particularly expanded in the neocortex of species with a high encephalization and gyrification index: basal radial glial cells and basal radial glia–derived transit amplifying progenitors, collectively called OSVZ progenitors (Borrell & Reillo 2012, Fietz & Huttner 2011, Fietz et al. 2010, Hansen et al. 2010, Lui et al. 2011, Reillo et al. 2011) (**Figure 5**). Basal radial glial cells lack ventricular contact but characteristically maintain basal lamina attachment via their basal process. The latter is thought to be involved in basal radial glia self-renewal. In addition, as with apical radial glial cells, the basal radial glial cell basal process serves as a scaffold to guide and distribute migrating neurons according to the gyrified architecture (Reillo et al. 2011). A recent study on developing monkey neocortex has revealed an unexpected complexity of basal radial glial cells, with basal radial glial cell subtypes that extend an apical rather than basal process (albeit not to the ventricle) or that extend an apical process in addition to the basal process (Betizeau et al. 2013) (**Figure 5**). Intriguingly, long-term imaging of the progeny of these cells showed that the largest neuronal output was generated by the latter subtype of basal radial glial cell (Betizeau et al. 2013). It will therefore be important to further dissect the roles of apical and basal processes in basal radial glial cell proliferation and self-renewal, and to identify the relevant molecular players.

Such a dissection is even more important in light of two lines of consideration. First, basally dividing progenitors are particularly abundant in the developing neocortex of mammals with a high gyrification index (for a recent review, see Borrell & Götz 2014), such as the monkey (Betizeau et al. 2013, Smart et al. 2002), sheep (Pilz et al. 2013, Reillo et al. 2011), and human (Fietz et al. 2010, Hansen et al. 2010, Reillo et al. 2011). Second, these progenitors comprise both BPs and SAPs [bipolar radial glia with ventricular contact (Pilz et al. 2013)], that is, progenitors with or without cell polarity (basal radial glia/SAPs versus transit amplifying progenitors), with or without basal lamina contact (basal radial glia versus SAPs/transit amplifying progenitors), and with or without ventricular contact (SAPs versus BPs) (**Figure 5**).

As mentioned above, in contrast to basal radial glial cells and SAPs, transit amplifying progenitors do not extend an apical or basal process at mitosis (**Figure 5**). However, transit amplifying progenitors are capable of undergoing multiple rounds of cell division. Hence, if the apical and basal processes of basal radial glial cells and SAPs were to harbor features contributing to their proliferative capacity, how then would transit amplifying progenitors sustain the latter capacity? A possible clue to answering this question has come from comparative transcriptome analyses of proliferating versus neurogenic progenitors in developing mouse neocortex (Arai et al. 2011) and of the VZ, ISVZ, and OSVZ of fetal human neocortex (Fietz et al. 2012). These studies have raised the possibility that progenitor-autonomous production of extracellular matrix constituents may contribute to the proliferative capacity of progenitors that are not in contact with the basal lamina or the ventricular fluid, such as transit amplifying progenitors. Supporting this notion, integrin $\alpha v\beta 3$ activation has recently been found to increase the cell cycle reentry of basal intermediate progenitors (Stenzel et al. 2014).

Generation of Outer Subventricular Zone Progenitors

The correlation between the increased proportion of progenitors in the OSVZ and the increased brain size/gyrification stimulated a tremendous effort in understanding how basal radial glial cells are generated. We here report on recent studies focusing on molecular and cell biological aspects.

Molecular aspects. Fast downregulation of the nuclear-localized protein Trnp1 (which promotes neuroepithelial and apical radial glial cell expansion in mouse cerebral cortex) is sufficient to elicit an entire program of SAP and basal radial glial cell generation and thereby induce the subsequent formation of cortical foldings reminiscent of gyri in the normally lissencephalic murine cerebral

cortex (Stahl et al. 2013). Notably, Trnp1 knockdown elicits not only SAP and basal radial glial cell generation in large numbers but also formation of a basal SVZ with heterogeneous basal radial glial cells, including those with bipolar processes, and transit amplifying progenitors. Three cell biological processes have been identified in the context of Trnp1 knockdown-mediated SVZ expansion: (*a*) the fast delamination of progenitors, preceded by an alteration in the cleavage plane angle; (*b*) a fast cell cycle of all of the SAPs, basal radial glial cells, and transit amplifying progenitors after delamination (Pilz et al. 2013, Stahl et al. 2013); and (*c*) fast neuronal migration (for a recent review see Borrell & Götz 2014). Interestingly, in the developing human neocortex, Trnp1 mRNA is downregulated in the prospective gyrus. This finding demonstrated that the mechanisms for SVZ expansion and heterogeneity are present in the murine cerebral cortex and are also sufficient to elicit some degree of folding in the normally lissencephalic murine cerebral cortex.

Cell biological aspects. The process through which a newborn BP (or a neuron) loses ventricular contact is called delamination. Delamination shows interesting parallels with the epithelial-to-mesenchymal transition (EMT) (Borrell et al. 2012, Itoh et al. 2013b). In agreement with this concept, the EMT-associated transcription factors Scratch 1 and 2 have been shown to induce detachment of progenitors from the apical surface and their migration in the developing mouse neocortex (Itoh et al. 2013a). Interestingly, Scratch enhances apical detachment by downregulating the adhesion molecule cadherin (Itoh et al. 2013a).

Konno et al. (2008) observed that the spindle orientation contributes to the generation of BPs. Ablating LGN in the mouse neocortex increases the occurrence, in APs, of horizontal cleavage planes at the expense of vertical ones. Interestingly, these horizontal divisions generate basal radial glia–like cells that keep the basal attachment but lack the apical one (Shitamukai et al. 2011). Supporting a causal link between spindle orientation and basal radial glial cell generation, Trnp1 knockdown increases not only the number of basal radial glial cells but also the occurrence of horizontal divisions in apical radial glial cells (Stahl et al. 2013).

CONCLUDING REMARKS

Over the past few years, novel types of cortical stem and progenitor cells have been identified and characterized. Many of the cell biological features of these cells have been dissected. Key molecules governing cortical stem and progenitor cell behavior have been placed in a cell biological context. Intriguingly, comparative studies of the cell biological and molecular aspects underlying progenitor behavior have provided increasing insight into the development and evolution of the neocortex. As a result of these studies, several conceptual aspects have emerged. First, the sequential up- and downregulation of the same master gene can drive both the lateral and then radial expansion, respectively, of the neocortex. Insights such as these set the stage for a better understanding of the developmental mechanisms of cerebral cortex expansion and the temporal and spatial regulation of these processes. Second, there is greater diversity in cortical stem and progenitor cells than previously assumed—in particular in the OSVZ. This poses challenges with regard to not only reconciling the cell biological features of cortical stem and progenitor cells with their behavior but also identifying the molecular processes underlying their proliferation versus differentiation. The next big challenge is to move from the molecular dissection of neocortex development to the molecular and cellular understanding of neocortex evolution.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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