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Review

Basal process and cell divisions of neural progenitors in the developing brain

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The basal process is an extension of certain types of neural progenitors during brain development; that is, the neuroepithelial and radial glial cells, which show radial orientation, emanating from their cell body. Originally, the basal process was considered to serve as a scaffold for the migration of newborn neurons, but recent observations obtained by advanced genetic manipulations and microscopic methods show that the basal process has additional roles. In this review, we first summarize the role of the radial glial basal process for neuronal migration and signaling and for the proper organization of the developing brain. We then focus on the emerging roles of the basal process during the division of neural progenitor cells, specifically the various modes of division of neuroepithelial and radial glial cells.

Key words: anillin, asymmetric division, cell polarity, cleavage plane, neurogenesis.

Introduction

During development of the vertebrate central nervous system, neuroepithelial cells have the potential to generate neurons and glial cells, including radial glial cells, astrocytes and oligodendrocytes. The molecular and cellular mechanisms of how, during brain development, the transition from the primary progenitors, the neuroepithelial cells, to the more differentiated cells occurs have been discussed for more than a century.

During brain development, the neuroepithelium, a single-cell layer, transforms into a tissue with a multiple-layer architecture. The apical-most layer is defined as the 'ventricular zone' where progenitor cells initially increase in number by proliferative divisions, followed by the generation of neurons from these progenitors directly or indirectly. During development, neuroepithelial cells give rise to radial glial cells, a more fate-restricted progenitor (Williams and Price 1995; Malatesta *et al*. 2000). Neuroepithelial cells and radial glial cells share several properties (see Table 1 in Götz and Huttner 2005). Among these, we will focus especially on the following aspects: (i) their morphology, with both neuroepithelial cells and radial glial cells being characterized by a bipolar, highly elongated shape along their apical-basal axis; and (ii) their function as neural progenitor cells, with both neuroepithelial cells and radial glial cells giving rise to neurons and to progenitors committed to the neuronal lineage (Malatesta *et al*. 2000; Miyata *et al*. 2001; Noctor *et al*. 2001; Tamamaki *et al*. 2001; Haubensak *et al*. 2004; Miyata *et al*. 2004; Noctor *et al*. 2004; Götz and Huttner 2005).

From a morphological perspective, neuroepithelial and radial glial cells have unique features, which were initially described after staining using the Golgi silver impregnation method (for review, see Bentivoglio and Mazzarello 1999). They are both polarized epithelial cells, with distinct plasma membrane domains, the so-called apical, basal, and lateral membranes, each of which can be identified by molecular markers such as prominin-1 (Weigmann *et al*. 1997; Marzesco *et al*. 2005; Dubreuil *et al*. 2007), alpha6-integrin (Wodarz and Huttner 2003; Nakaya *et al*. 2008), and cadherins (Aaku-Saraste *et al*. 1996; Chenn *et al*. 1998; Yagi and Takeichi 2000), respectively. Neuroepithelial and radial glial cells are highly elongated along their apical-basal axis, with their apical membrane facing the ventricular

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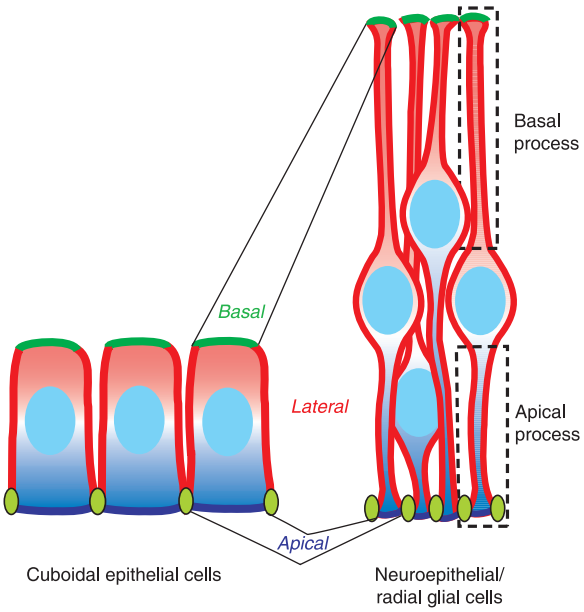

Fig. 1. Comparison of plasma membrane domains of cuboidal epithelial cells (left) and neuroepithelial and radial glial cells (right). Blue, apical plasma membrane; red, lateral plasma membrane; green, basal plasma membrane. Apical and basal processes of neuroepithelial and radial glial cells are indicated by dashed boxes. Large, light-blue ellipses; nuclei. Small, light-green ellipses at apical surface; adherens junctions.

lumen of the neural tube. In synchrony with the progression of the cell cycle of a given neuroepithelial/radial glial cell, the nucleus migrates from apical to basal (in the G1 phase) and from basal to apical (in the G2 phase), a process referred to as 'interkinetic nuclear migration' (Sauer 1935; Sauer and Walker 1959; Fujita 1960; Xie *et al*. 2007; Del Bene *et al*. 2008). As the cell cycles of the various neuroepithelial/radial glial cells are not synchronized, these progenitor cells form a pseudostratified epithelium (Götz and Huttner 2005; Miyata 2008).

The nucleus of neuroepithelial/radial glial cells occupies most of the cell body volume, with the surrounding cytoplasm being relatively low in volume when compared with other, cuboidal epithelial cells (Fig. 1). The processes emanating from the cell body in the apical (ventricular) and basal (pial) direction ('apical process' and 'basal process', respectively; see Fig. 1) are very thin and hence have a low cytoplasmic volume relative to the surface of the neuroepithelial cell plasma membrane. It should be emphasized that the limiting membrane of both apical and basal processes of neuroepithelial and radial glial cells consists of lateral plasma membrane (except for the apical and basal plasma membrane proper, Fig. 1), as evident from the presence of cadherin and the lack of apical and basal plasma membrane constituents (Fig. 1).

In this review, we focus on the basal process of neuroepithelial and radial glial cells in the developing vertebrate, notably rodent brain. An increasing number of reports suggest multiple roles of the basal process in neurogenesis, both in forming the architecture of neuronal layers and in signaling from the basal lamina to organize the brain properly, as will be summarized in the first part. In the second part, we discuss the behavior of basal processes and their possible roles in the division of neuroepithelial and radial glial cells, and the current view of proliferative versus neurogenic divisions of these apical neural progenitor cells.

Roles of the basal process in mammalian brain development

Guide for newborn neurons

The first well-described function of the basal process was reported by Rakic in classic electron microscopic studies of radial glial cells in fetal monkey cortex (Rakic 1972), in which it was proposed that the basal process serves as a guide for newborn neurons. This work led to the concept that the basal process of radial glia acts as a scaffold in the migration of neurons from the ventricular side of the neuroepithelium towards the pial surface. Indeed, the radial glial fiber of the macaque monkey in the final stage of cortical neurogenesis can be 3000–7000 μm long, while the leading process of a migrating neuron is 50–200 μm long (Rakic 1972). The glial scaffolding for neuronal migration might be particularly important at late stages of mammalian, notably primate, brain development, when newborn neurons have to migrate long distances (Rakic 2003).

During the earlier stages of cortical development, particularly in rodents, however, an alternative mode of neuronal migration, called 'somal translocation', has been proposed (Nadarajah *et al*. 2001; Nadarajah *et al*. 2003). Here, the basal process of apical progenitors is inherited by the newborn neuron and used as a cue for its migration from the ventricular to the pial surface; this might be a feasible mechanism when the thickness of the cortical layers does not exceed the length of the leading process of the migrating neuron (for review, see Fishell and Kriegstein 2003; Kriegstein and Noctor 2004). Accurate microsurgical cutting of the leading process of newborn neurons indeed inhibits their migration to the pia in slice cultures of the developing mouse cortex (Miyata and Ogawa 2007). An interesting mechanical role of the basal process has been proposed in which the twisting and stretching of the basal process can

generate the spring-like pulling force for somal translocation (Miyata and Ogawa 2007).

Basal lamina contact in the developing brain

The morphology of the basal process of radial glial cells appears to be determined by both intrinsic (i.e. Pax6: Götz *et al*. 1998; Osumi *et al*. 2008) and extrinsic (i.e. Reelin: Hartfuss *et al*. 2003; Zhao *et al*. 2004; Nomura *et al*. 2008) factors. Pax6 is a transcription factor, which is expressed in specific regions of the developing central nervous system including the dorsal telencephalon and which has multiple roles in brain development (for review, see Osumi *et al*. 2008). It has been reported that the morphology of the radial glial basal process is altered, and neuronal migration is defective, in the embryonic dorsal telencephalon of Pax6-deficient mice (Götz *et al*. 1998). Moreover, transplantation experiments from Pax6-deficient mice to wild-type rat cortex show that the migration defect is non-cell autonomous (Caric *et al*. 1997), indicating the importance of radial glial morphology in neuronal migration. For the importance of Reelin for basal process morphology, see the review by Nomura (in press). Here, we summarize the present knowledge about the physical contact between the basal process and the basal lamina, and its role in brain development.

The basal end of most neuroepithelial and radial glial basal processes remains attached to the basal lamina throughout the cell cycle (revealed by time-lapse imaging, see below). The basal lamina is composed of extracelluar matrix (ECM), which forms a thin, sheet-like structure and provides spatially specific signaling information (Li *et al*. 2003). The laminin family of proteins, type IV collagen, nidogen and proteoglycans (e.g. perlecan) are components of the ECM (Paulsson 1992; Timpl 1996; Erickson and Couchman 2000). Signaling between the basal end of the basal process and the basal lamina takes place through integrin receptors and may also involve growth factors and their receptors (Colognato and Ffrench-Constant 2004). The basal lamina has multiple roles in the establishment of epithelial cell polarization and the generation of differentiated cells (Li *et al*. 2003).

In the developing cerebral cortex, a basal lamina is found at the pia and around blood vessels (Costell *et al*. 1999; Halfter *et al*. 2002). Ablation of basal lamina components either chemically (Sievers *et al*. 1994) or genetically (e.g. laminin alpha5 [Miner *et al*. 1998]; laminin gamma1 [Halfter *et al*. 2002]), was known to result in brain malformation. However, whether the connection between the radial glial endfoot (that is, the basal process) and the basal lamina is important for the proliferation and differentiation of neural progenitors, has only been investigated in detail recently. Specifically, the developing cerebral cortex of knock-out mice for laminin gamma1III4, perlecan and alpha6 integrin was studied (Haubst *et al*. 2006). Although the radial glial cells in the mutant embryos lost the attachment between their basal processes and the basal lamina, there was no major difference in their proliferation and capacity for neurogenesis. However, the integrity of the basal lamina and its contact to the basal process were found to have a critical role for the proper neuronal migration and cortical layer formation (Haubst *et al*. 2006).

More recent studies suggest that the issue of the relevance of radial glial–basal lamina contact for neurogenesis is more complex. In another analysis of perlecan knock-out mice, it was shown that there were less mitotic cells in the early medial ganglionic eminence (E12–E13) and impaired cell cycle progression in the late neocortex (E17.5) (Giros *et al*. 2007). Regarding beta1 integrin, it has been proposed that its expression in radial glia is critical for the formation of cell layers in the cerebral cortex, while its expression in neurons is not essential for radial glia-guided neuronal migration (see above) or reelin signaling (Belvindrah *et al*. 2007). Clearly, further investigations are required to determine the precise role(s) of basal lamina attachment of the basal process of neuroepithelial and radial glial cells in the various stages of brain development.

GPR56, a G protein-coupled receptor, is concentrated at the endfoot of the radial glial basal process, and its ablation in mice results in abnormal positioning of radial glial endfeet in the developing cerebral cortex (Li *et al*. 2008). Human genetic studies have revealed that *GPR56* mutations are associated with disorganized cortical lamination, particularly in the frontal cortex (Piao *et al*. 2004). It might therefore be worth investigating the contact between the basal lamina and radial glial endfeet in other human cortical disorders (listed in Francis *et al*. 2006).

Roles of the basal process in neural progenitor cell divisions

Maintenance of basal lamina contact during M-phase

In contrast to the physical and signaling properties of the basal process in the later stages of brain development described in the previous section, the behavior and functions of basal processes in the earlier stages, and in particular with regard to the mitoses of neuroepithelial and radial glial cells, are less understood. In vertebrate brains, mitosis of neuroepithelial and radial glial cells takes place at the apical surface of the ventricular zone (Sauer 1935; Sauer and Walker 1959; Fujita 1960). In previous transmission electron microscopic (Hinds

and Ruffett 1971) and scanning electron microscopic (Seymour and Berry 1975) studies, it was concluded that, during the M-phase, the basal process of neuroepithelial and radial glial cells loses contact to the basal lamina and is retracted to the apical cell body. More recent live-imaging studies, however, have shown that this is not the case for the basal process of radial glial cells in the rodent cerebral cortex. Fluorescent labeling of single radial glial cells by green fluorescent protein (GFP) or DiI combined with embryonic brain slice culture and time-lapse microscopy showed that the basal process is retained during cell division and maintains basal lamina contact, although the diameter of the process becomes extremely thin (rat: Noctor *et al*. 2001; mouse: Miyata *et al*. 2001). Following these pioneering observations, retention of the basal process during M-phase of apical progenitors was shown for the developing central nervous systems of various vertebrates; (mouse retina: Cayouette and Raff 2003; Saito *et al*. 2003; zebrafish retina: Das *et al*. 2003; chick neural tube: Afonso and Henrique 2006).

However, it still needs to be clarified whether the basal process of all neuroepithelial and radial glial cells retains contact to the basal lamina during M-phase (for the 'short neural precursors', see below). For example, in the study of radial glial cells in the mouse retina, the basal process could be visualized in only 19% of dividing cells (Cayouette and Raff 2003). This number may reflect the experimental design, such as the labeling methods, culture conditions, and microscopes used. Still, there is a possibility that retraction of the basal process does occur during M-phase in certain apical progenitors, as previously concluded. If retraction indeed occurs, re-extension of the basal process (that is, of basal and lateral plasma membrane, see Introduction) to the pial surface also should occur to re-establish contact with the basal lamina. It would then be interesting to investigate the possible existence of 'path-finding molecules' that would direct the endfoot of the basal process towards the pial surface.

Inheritance of the basal process by the daughter cells

It has been an attractive idea that neuroepithelial and radial glial cells receive certain signals regulating cell fate (e.g. proliferation vs. neurogenesis) *via* their basal process (Miyata *et al*. 2001), see reviews (Fishell and Kriegstein 2003; Wodarz and Huttner 2003). How, then, is the basal process inherited upon division of neuroepithelial and radial glial cells? Most of the neurogenic divisions of progenitors at the apical surface are asymmetric (Noctor *et al*., 2004; Haubensak *et al*., 2004; Miyata *et al*., 2004), and in apparent accordance with this, the basal process has been reported to be inherited asymmetrically, that is, by one of the daughter cells (Miyata *et al*. 2001; Cayouette and Raff 2003; Saito *et al*. 2003). However, the fate of the daughter cell inheriting the basal process (i.e. progenitor vs. neuron) has been a controversial issue (Miyata *et al*. 2001; Fishell and Kriegstein 2003), for review see (Huttner and Kosodo 2005). Moreover, in these studies, the behavior of the basal process at the onset of neurogenesis, when most divisions of apical progenitors are still proliferative rather than neurogenic, was not investigated in detail.

Focusing on the inheritance of the basal process upon apical progenitor divisions at the onset of neurogenesis, we recently reported that a considerable percentage of basal processes are actually split during the M-phase and inherited by both daughter cells (Fig. 2) (Kosodo *et al*. 2008). It is currently an open question whether splitting of the basal process occurs not only at the early stage of neurogenesis, but also at later stages, at which previous investigators (Miyata *et al*. 2001; Cayouette and Raff 2003) did not notice any splitting of the basal process. It should be noted that the resolution of conventional light microscopy might not allow to discriminate between two thin processes when these are adjacent to each other (Fig. 2A,B) (Kosodo *et al*. 2008). Moreover, time-lapse imaging of zebrafish spinal cord neuroepithelial cells showed that, surprisingly, a split basal process (Fig. 2C) can even be inherited asymmetrically by only one of the daughter cells (Kosodo *et al*. 2008). Clearly, the relationship between basal process behavior during the M-phase (i.e. splitting and inheritance) and daughter cell fate is a complex issue that needs further investigation.

Cytokinesis machinery in the splitting of the basal process

Interestingly, when the basal process splits in neuroepithelial cells, cytokinesis begins before anaphase. Anillin, an essential actin-binding/–bundling protein and conserved cleavage furrow component (Field and Alberts 1995; Oegema *et al*. 2000; Kinoshita *et al*. 2002; Hickson and O'Farrell 2008), localizes, together with F-actin, to the basal process branching point at the pro- and prometa-phase, and migrates in the apical direction towards the origin of the basal process at the cell body before anaphase onset (Fig. 3) (Kosodo *et al*. 2008).

Recent evidence indicates that anillin functions as a scaffolding protein for critical components of cytokinesis (Hickson and O'Farrell 2008). In particular, the conserved C-terminal domain of anillin binds RhoA, and it has been suggested that through this binding, RhoA is linked to the contractile ring components actin and

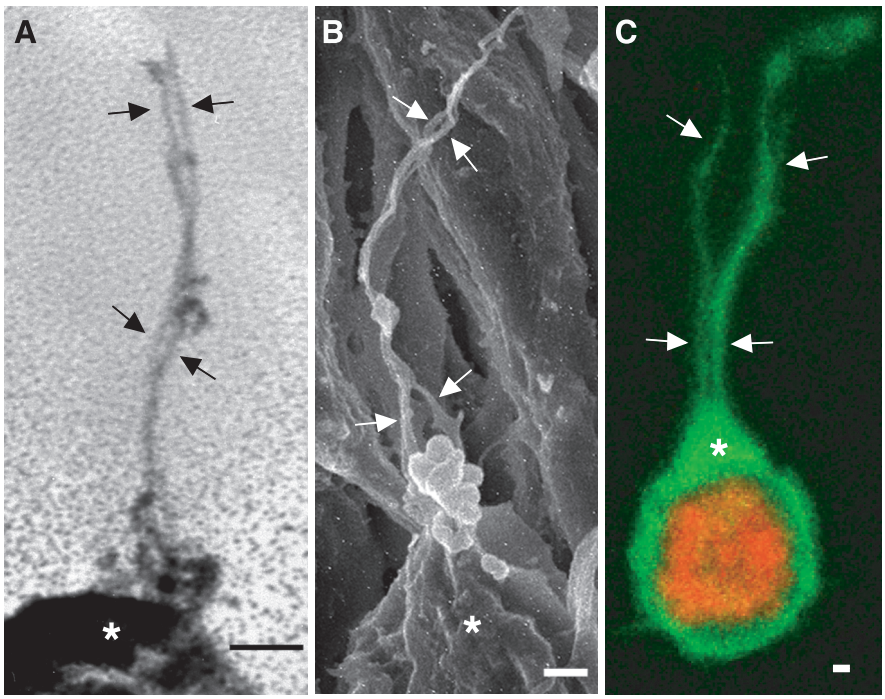

Fig. 2. (A, B) Ultrastructure of the basal process extending from an apical, mitotic neuroepithelial cell body in mouse E10.5 cortex as revealed by high-voltage electron microscopy after Golgi impregnation (A) or scanning electron microscopy (B). Note the pair of twisted thin processes (arrows) arising from the cell body (asterisks). Bars, 1 μm. (C) Dividing neuroepithelial cell in the anterior spinal cord of a 24 hpf (hours postfertilization) zebrafish embryo (early neurogenic stage). Green, membrane-enahnced green fluorescent protein (EGFP); red, nuclear-red fluorescent protein (RFP). Note the pair of thin processes (arrows) arising from the cell body (asterisk). For further details, see Kosodo *et al*. (2008). Bar, 1 μm. Reproduced with permission from Kosodo *et al*. (2008).

myosin (Piekny and Glotzer 2008). RhoA has been implicated in several critical steps during cell division, including the positioning of the cleavage furrow (Piekny *et al*. 2005). These data raise the possibility that anillin, together with RhoA, may have a role in controlling cleavage plane orientation. Indeed, when a dominant-negative form of RhoA was expressed in chick neuroepithelial cells, the orientation of the mitotic spindle was randomized (Roszko *et al*. 2006).

Cue for vertical cleavage plane orientation of apical progenitor cells

The orientation of the cleavage plane of dividing neuroepithelial and radial glial cells is perpendicular (vertical) to the apical surface, and essentially unchanged throughout brain development in various vertebrate species (Smart 1973; Landrieu and Goffinet 1979; Das *et al*. 2003; Lyons *et al*. 2003; Kosodo *et al*. 2004; Wilcock *et al*. 2007; Konno *et al*. 2008; Noctor *et al*. 2008). These observations are not consistent with a 'cleavage plane rotation model' (Chenn and McConnell 1995) to explain the switch of apical progenitors from proliferative to neurogenic divisions (for an alternative model, see below). In addition, the cleavage furrow of neuroepithelial cells ingresses in the basal-to-apical direction (Fig. 4; Hinds and Ruffett 1971; Kosodo *et al*. 2004; Dubreuil *et al*. 2007; Kosodo *et al*. 2008), as has also been observed in cultured MDCK (Madin-Darby canine kidney) cells (Reinsch and Karsenti 1994) and mouse intestinal epithelial cells (Fleming *et al*. 2007). Interestingly, the basal-to-apical migration of the cytokinesis protein anillin in the basal process and its clustering at the basal-most cortex of the cell body of apical progenitors before anaphase onset suggest a mechanistic explanation why, in addition to the determining role of mitotic spindle orientation, the contractile ring shows a vertical orientation and basal-to-apical ingression (Fish *et al*. 2008; Kosodo *et al*. 2008).

The relationship between vertical cleavage planes, basal-to-apical cleavage furrow ingression and apical plasma membrane inheritance upon neural progenitor cell division has been investigated extensively (Fig. 4, see reviews in Götz and Huttner 2005; Huttner and Kosodo 2005; Knoblich 2008). In proliferative divisions of neuroepithelial and radial glial cells in wild-type mouse brains, the apical membrane and adjacent apical junctional complexes are typically bisected and inherited symmetrically by both daughter cells, and maintained throughout the ensuing cell cycle (Fig. 4 Kosodo *et al*. 2004; Fish *et al*. 2006; Dubreuil *et al*. 2007; Konno *et al*. 2008). In neurogenic divisions, one daughter cell, which becomes a neuron or basal progenitor (Noctor *et al*., 2004; Haubensak *et al*., 2004; Miyata *et al*., 2004) (for review see Götz and Huttner 2005), typically loses its apical membrane and apical junctional complexes, either upon cytokinesis (Kosodo *et al*. 2004; Fish *et al*. 2006; Konno *et al*. 2008) or, if the apical membrane was bisected upon cytokinesis, after cytokinesis (Dubreuil *et al*. 2007; Konno *et al*.

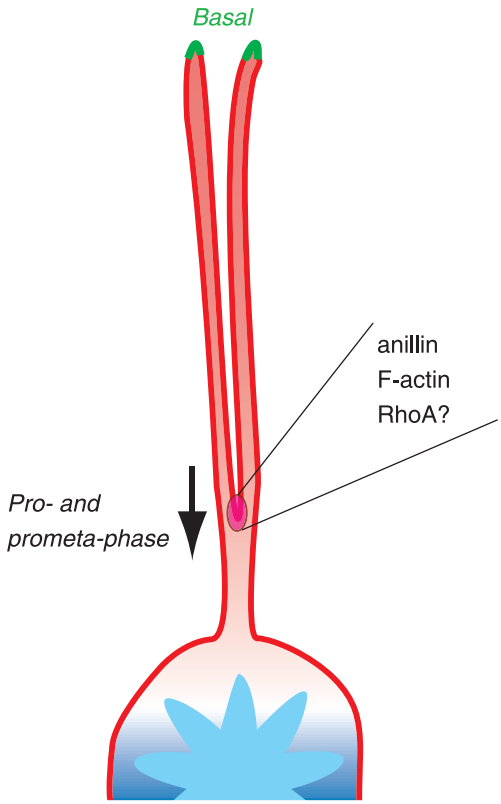

Fig. 3. Model of basal-to-apical (arrow) anillin 'spot' (magenta ellipse) migration in the basal process during neuroepithelial cell division (see Kosodo *et al*. 2008). This migration and basal process splitting occur in the pro- and prometa-phase, before cytokinesis of the cell body takes place in the telophase. F-actin and presumably RhoA are colocalized with the anillin spot, and possibly become a directional cue for vertical cleavage plane orientation (for details see text). Light-blue, condensed chromatin. Red and green lines, lateral and basal plasma membrane, respectively.

2008), while the other daughter cell maintains apical membrane and apical junctional complexes during the ensuing cell cycle and thus remains as an apical progenitor cell (Fig. 4, Kosodo *et al*. 2004; Fish *et al*. 2006; Attardo *et al*. 2008; Konno *et al*. 2008). This 'apical-last' principle of apical membrane and junctional complex distribution upon cytokinesis helps to preserve the epithelial characteristics of apical progenitor cells (for review, see Fish *et al*. 2008). In terms of interkinetic nuclear migration (see above), the daughter cell that undergoes a full round of this migration, with its nucleus returning to the centrosomes localized at the apical cell cortex (Chenn *et al*. 1998; Tamai *et al*. 2007; Xie *et al*. 2007), maintains an apical progenitor cell status. By contrast, the other daughter cell, the nucleus of which does not migrate back to the apical cell cortex, has adopted basal progenitor or postmitotic neuron fate (Fig. 4, Attardo *et al*. 2008; Kawaguchi *et al*. 2008).

Apical cell cortex, neuroepithelial cell polarity, and neurogenesis

Having discussed the basal process in the context of neuroepithelial cell division, in particular its putative role in (i) positioning the cytokinesis machinery, and hence the nascent contractile ring, along the apical-basal axis, and (ii) providing a cue for the basal-to-apical ingression of the cleavage furrow, which results in the 'apical-last' distribution of apical membrane and junctional complexes upon cytokinesis, we now turn to the apical cell cortex and its relevance for cell fate decisions of neuroepithelial and radial glial cells. It has been hypothesized that key components of the molecular machinery maintaining proliferation of 'apical' progenitors, such as epithelial polarity controllers (see below) and signaling organizers, are recruited to the apical cell cortex (including apical membrane and junctional complexes) (for review, see Huttner and Brand 1997; Huttner and Kosodo 2005). In this context, it is important to note that neural progenitor proliferation as such can occur in the absence of an apical cell cortex and does not depend on the progenitor cell being integrated into the neuroepithelial cell layer. Thus, a subpopulation of rodent basal (intermediate) progenitors, which have delaminated from the neuroepithelial cell layer, has been shown to undergo cell division repeatedly (Noctor *et al*. 2004), despite the lack of apical constituents (Attardo *et al*. 2008). Moreover, interfering with the function of, or ablating, LGN (named after the repetitive Leu-Gly-Asn tripeptide in the protein), which results in the loss of maintenance of horizontal mitotic spindle and hence vertical cleavage plane orientation of apical progenitors, leads to the generation of progeny that delaminates from the neuroepithelial cell layer and lacks apical membrane, but nonetheless continues to divide (Morin *et al*. 2007; Konno *et al*. 2008). An important issue arising from the latter studies is the possible effect of such manipulation on the subcellular localization and activity of molecules normally associated with the apical membrane, cortex and junctional complexes, and involved in the control of cell fate. This requires further, systematic investigation.

Cdc42, a Rho-family member GTPase, has been shown to have an essential role in maintaining the apical progenitor state of neural precursor cells. When Cdc42, which is concentrated at the apical cell cortex, is conditionally removed in the mouse embryonic telencephalon, apical progenitors retract their apical endfoot and turn into basal progenitors, resulting in an increase in neurogenesis at early stages (Cappello *et al*.

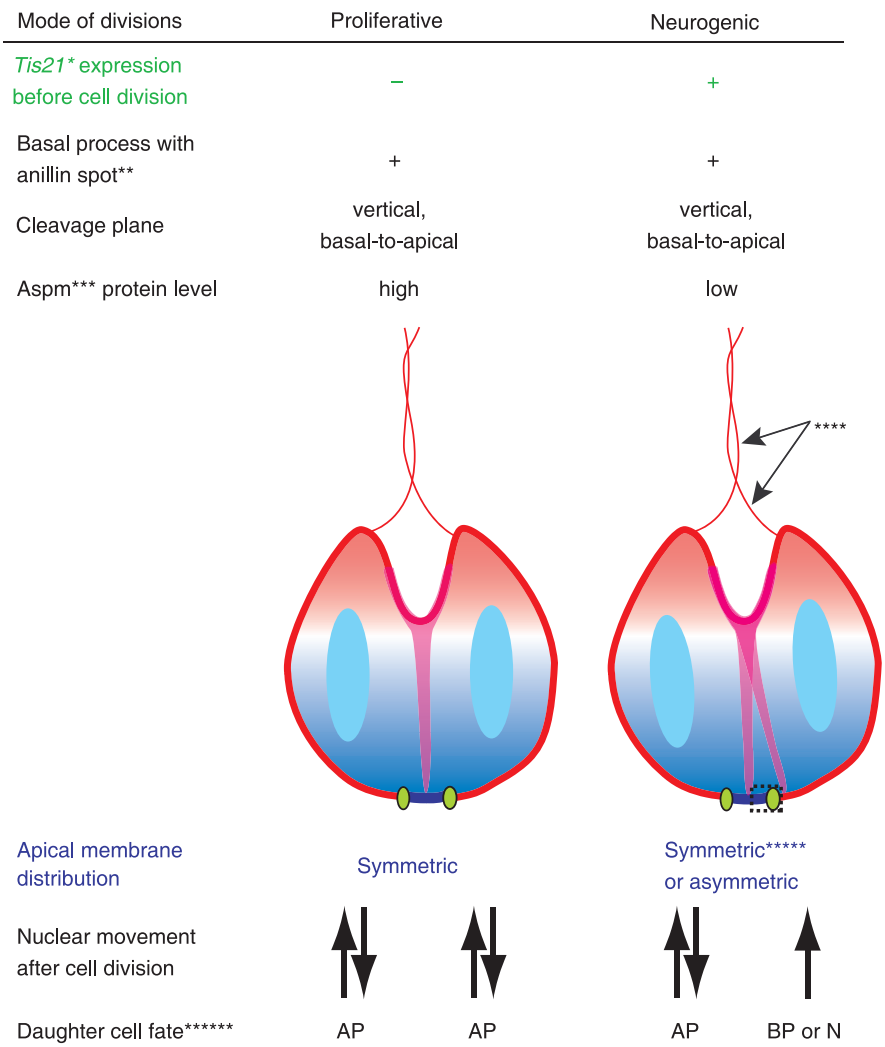

Fig. 4. Model of cell division of neuroepithelial and radial glial cells. For details on cleavage plane orientation, direction of cleavage furrow ingression, and apical membrane inheritance in proliferative and neurogenic divisions, see text. *Expression of *Tis21* mRNA starts in the G1 phase preceding a neurogenic cell division (Iacopetti *et al*. 1999; Haubensak *et al*. 2004; Attardo *et al*. 2008). **Anillin spots are observed with essentially identical frequency in the basal processes of *Tis21*-GFP-negative and -positive M-phase neuroepithelial cells in mouse E10.5 cortex (Kosodo *et al*. 2008). ***The level of Aspm, a centrosomal spindle orientation controller in mammalian proliferating tissues (Kouprina *et al*. 2005) as well as in neuroepithelial cells (Fish *et al*. 2006, 2008), and target of mutations causing autosomal recessive primary microcephaly in humans (Bond *et al*. 2002), is decreased in *Tis21*-GFP-positive cells compared to -negative cells (Fish *et al*. 2006). ****Bisection of basal process; inheritance of the bisected basal process can be either symmetric or asymmetric; the fate of the inheriting daughter cell(s) is an open issue (see text). *****Apical plasma membrane inherited by basal progenitor or neuron daughter due to symmetric distribution upon cytokinesis (dashed box) is presumably lost subsequently (see text). ******Presumptive daughter cell fate; note that the proportion of the three modes of apical progenitor division (proliferative/symmetric, neurogenic/asymmetric or neurogenic/symmetric) observed by time-lapse recordings differ significantly between various investigations (Miyata *et al*. 2004; Noctor *et al*. 2004; Konno *et al*. 2008); only the asymmetric neurogenic fate is illustrated in the figure, as neurogenic/symmetric divisions of apical progenitors have been rarely observed at the stages of neurogenesis so far studied by live imaging (Noctor *et al*., 2004; Haubensak *et al*., 2004; Miyata *et al*., 2004; Attardo *et al*. 2008), and a detailed investigation of these divisions at the late stage of neurogenesis still needs to be carried out. AP, apical progenitor; BP, basal progenitor; N, neuron. Light-blue, condensed chromatin. Small light-green ellipses, adherens junctions. Magenta, anillin on the cleavage furrow. Red and blue lines, lateral and apical plasma membrane, respectively.

2006). However, the structure of basal processes and their contact to the basal lamina are unchanged upon conditional Cdc42 ablation (Cappello *et al*. 2006). Together, these observations suggest that an alteration in cell fate can occur by interference with apical cell cortex function, and without apparent defects in the basal process.

There are three identified complexes (CRB/PALS1/PATJ, PAR3/PAR6/aPKC and MALS/PALS1) that are crucial for maintaining epithelial polarity, and most of their components are located to the apical cell cortex in MDCK cells (Margolis and Borg 2005). With regard to neural precursor cells, a recent report shows that Par3 or Par6 overexpression increases the proliferation of apical progenitors, whereas Par3 loss-of-function leads to premature cell cycle exit (Costa *et al*. 2008). However, conditional removal of a PKC-lambda at a late stage of neurogenesis (E15 mouse cortex) has not been found to cause significant defects (Imai *et al*. 2006). These reports indicate that epithelial polarity organizers concentrated at the apical cell cortex have key roles in neural progenitor proliferation versus differentiation, but appear to exhibit a certain functional redundancy. Alternatively, or in addition, these molecules

may be more important for cell fate determination at early (rather than late) stages of neurogenesis, when the stem cell-like character of apical progenitors is more pronounced (Nishino *et al*. 2008).

Indeed, the localization of endogenous PAR3/PAR6/aPKC at the apical cell cortex is significantly decreased at later stages (E16 mouse cortex) of brain development (Costa *et al*. 2008). In addition, MALS triple-knockout mice show perturbed proliferation of neuroepithelial cells and increased neurogenesis (Srinivasan *et al*. 2008). Importantly, this abnormal neurogenesis was observed particularly at early stages (until E12.5), whereas the brain at birth showed normal size and cortical lamination (Srinivasan *et al*. 2008). These results not only support the idea that epithelial polarity organizers at the apical cell cortex may be particularly important for apical progenitor proliferation versus differentiation at early stages of neurogenesis, but also imply the existence of a kind of surveillance system that senses, and induces recovery from, aberrant neurogenesis during brain development.

Conclusions and perspectives

The basal process of neuroepithelial and radial glial cells has recently received increasing attention. This thin progenitor cell extension appears to have multiple roles in the developing vertebrate brain, including those of a scaffold for migrating newborn neurons, a signal transducer, and a subcellular structural determinant for cleavage plane orientation, cytokinesis and daughter cell fate during the process of cell division. Compared with the long history since its first description in the nineteenth century, most of our knowledge about the basal process has been obtained during the last decade. A major reason for this is clearly the advance in live-cell imaging (including time-lapse recording) of subcellular structures using fluorescence microscopy, which has greatly contributed to the present knowledge of basal process morphology and behavior. For example, advanced imaging techniques revealed the existence of neural progenitor cells whose basal processes do not reach the basal lamina (short neural precursor) (Gal *et al*. 2006). It has been shown that these short neural precursors, like radial glial cells, can either directly or indirectly generate neurons, although the lineage potential and lineage relationship of these progenitors still need to be determined (Corbin *et al*. 2008). At any rate, comparative investigations of short neural precursors and radial glial cells may reveal new roles for the basal process during brain development.

Neurogenesis occurs not only in the developing embryonic brain, but also in particular regions of the adult brain (adult neurogenesis, for reviews see Kempermann *et al*. 2004; Merkle and Alvarez-Buylla 2006; Zhao *et al*. 2008). Recently, basal (and also apical) process-like structures have been identified in neural stem cells retained in the wall of the lateral ventricle, one of the neurogenic regions of the adult brain (Mirzadeh *et al*. 2008). Specifically, adult neural stem cells retain basic epithelial properties, even though their cell body is localized in the subventricular zone, being separated from the ventricular surface by the ependymal cell layer through which an apical process extends into the ventricular lumen. Interestingly, the endfoot of the basal process terminates on blood vessels, where extracelluar matrix is abundant, and seems to have a role in the regulation of adult neurogenesis (Mirzadeh *et al*. 2008). Clearly, the investigation of the structure and function of basal and apical processes of neural stem and progenitor cells during embryonic development and adult maintenance of the brain will be an important area of future research.

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