

Chapter 15

The Golgi Apparatus in Polarized Neuroepithelial Stem Cells and Their Progeny: Canonical and Noncanonical Features



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Abstract Neurons forming the central nervous system are generated by neural stem and progenitor cells, via a process called neurogenesis (Götz and Huttner, *Nat Rev Mol Cell Biol*, 6:777–788, 2005). In this book chapter, we focus on neurogenesis in the dorsolateral telencephalon, the rostral-most region of the neural tube, which contains the part of the central nervous system that is most expanded in mammals (Borrell and Reillo, *Dev Neurobiol*, 72:955–971, 2012; Wilsch-Bräuninger et al., *Curr Opin Neurobiol* 39:122–132, 2016). We will discuss recent advances in the dissection of the cell biological mechanisms of neurogenesis, with particular attention to the organization and function of the Golgi apparatus and its relationship to the centrosome.

15.1 Introduction

15.1.1 *The Developing Mammalian Neocortex: Nomenclature and General Organization*

The neocortex, which is the evolutionary younger part of the cortex involved in higher-order cognitive functions, develops around a central cavity, called the ventricle (Borrell and Reillo 2012; Götz and Huttner 2005; Noctor et al. 2007b) (see also Fig. 15.1). The portion of the developing neocortex that occupies the apical-most region of the tissue and is in contact with the ventricle is called ventricular zone (VZ). The VZ contains a class of neural stem and progenitor cells collectively called

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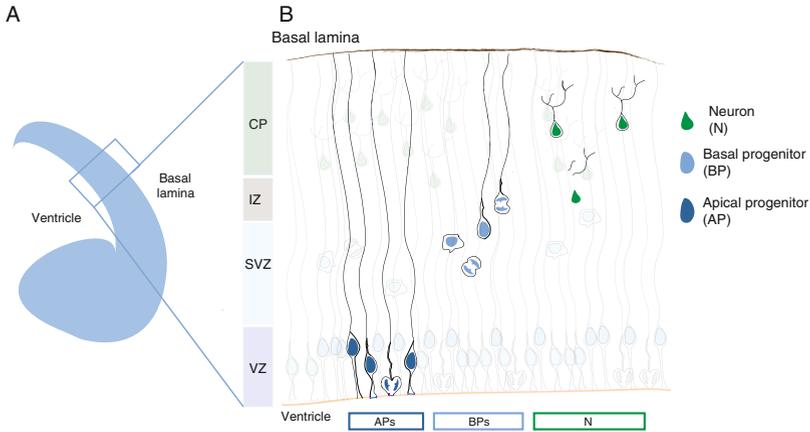


Fig. 15.1 Nomenclature and general organization of the developing mammalian neocortex. (a) Cartoon illustrating the general structure of the mammalian developing telencephalon. The neocortex develops around a central cavity, called the ventricle. Opposite to the ventricle, the neocortex is delimited by a basal lamina. (b) Schematic representation of the different zones (vertical axis) and cell types (horizontal axis) forming the developing neocortex. From apical to basal: VZ ventricular zone, SVZ subventricular zone, IZ intermediate zone, CP cortical plate

apical progenitors (APs). APs give rise, via mitosis, to the second class of progenitor cells, called basal progenitors (BPs). BPs occupy a region basal to the VZ, called subventricular zone (SVZ). Neurons generated in either the VZ (minor source) or SVZ (major source) migrate through the intermediate zone (IZ) and settle in the basal-most region of the developing neocortex called cortical plate (CP). The CP is delimited on the basal side by a basal lamina (see Fig. 15.1 for a summary scheme).

15.1.2 Neural Stem Cell Types and Their Cell Biological Features

We will here review the principal neural cell types found in the developing neocortex (Borrell and Reillo 2012; Götz and Huttner 2005; Noctor et al. 2007b). For every cell type, after a description of the cell's general features (see Sect. 15.2.1 and Fig. 15.2), we will report and discuss what is known about the centrosome and Golgi organization.

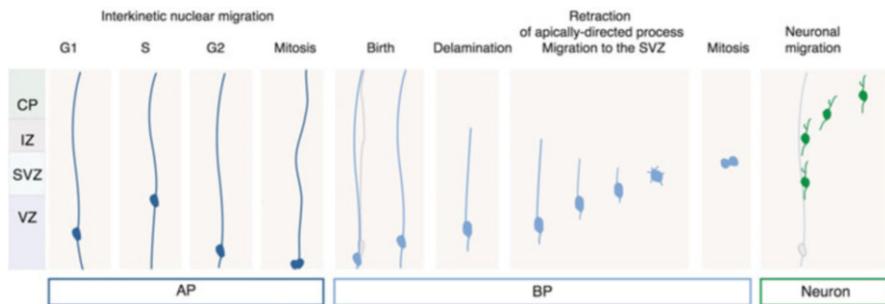


Fig. 15.2 A cell biological perspective on neural stem cell fate transition and neuron generation. Crucial cell biological steps in lineage progression and cell fate transition during neurogenesis. From left to right: apical progenitors (APs) undergo *interkinetic nuclear migration*, moving the nucleus in concert with the different phases of the cell cycle. Apical progenitors via *mitosis* give rise to basal progenitors (BPs). After being generated (*birth*), BPs initially maintain contact with the ventricular surface. BPs then lose their contact with the apical surface via *delamination*, *migrate* to the SVZ, and eventually undergo *mitosis* to give rise to neurons. The neurons in turn undergo *neuronal migration* toward the basal lamina to reach their correct position in the cortical plate

15.2 Apical Progenitors (APs)

15.2.1 General Remarks

APs are highly polarized epithelial cells, exhibiting apicobasal polarity, and undergo mitosis at the ventricular surface (Fig. 15.2). Their apical plasma membrane represents only a minor fraction (typically 1–2% (Kosodo et al. 2004)) of the total plasma membrane, is delimited by the adherens junction belt, and lines the lumen of ventricle. The basolateral plasma membrane of APs can span the VZ, SVZ, IZ, and CP and reach the basal lamina (Fig. 15.2). Such APs represent an extreme case of cell elongation along the apicobasal axis. This elongation is most prominent in human and other primates, where the thickness of the cortical wall reaches several millimeters (Smart et al. 2002). One characteristic feature of APs is their ability to undergo interkinetic nuclear migration (INM), that is, APs move their nuclei in the VZ in concert with the cell cycle (Norden et al. 2009; Taverna et al. 2014; Taverna and Huttner 2010) (Fig. 15.2). After completing mitosis at the ventricular surface, APs nuclei undergo apical-to-basal migration during G1. After S-phase in the basal part of the VZ, the nuclei undergo basal-to-apical migration. Interestingly, INM is confined to the VZ, and the AP nucleus never moves into the part of the cell spanning the SVZ, IZ, and CP. A key aspect of INM is that AP mitosis typically occurs at the ventricular surface, thereby maximizing the number of AP divisions per apical surface area. An underlying reason why APs mitosis typically occurs at the ventricular surface is that the AP apical plasma membrane bears a primary cilium throughout interphase, as is explained below. AP mitoses can give rise directly to APs, BPs, and/or (rarely) neurons (Figs. 15.1 and 15.2).

15.2.2 *Centrosome and Golgi Apparatus in Interphase APs*

15.2.2.1 **The Centrosome**

As for other epithelial cells (Bacallao et al. 1989), the centrosome of APs is associated with the apical plasma membrane. This association has been dissected with regard to centrosome structure. It is known that the centrosome's older centriole (the basal body) is nucleating the microtubules of the primary cilium that, as a specialization of the apical plasma membrane, protrudes into the ventricle. This implies that the cilium's basal body-containing centrosome and the second centrosome that in mitosis builds the mitotic spindle are confined to the apical cell cortex during interphase. Hence, for entry into mitosis, the AP nucleus needs to approach the apical centrosomes (rather than the other way round).

The importance of centrosome function in brain development is highlighted by primary microcephaly, a group of disorders associated with a dramatic reduction in brain size at birth (Bond et al. 2002; Bond and Woods 2005). The mutated genes identified so far in these disorders are associated either with the cytokinesis machinery or with centrosomal proteins.

Cytokinesis Machinery Citron kinase (CRIK) is a RhoA modulator whose ablation results in massive reduction in brain size (Di Cunto et al. 2000; Gai and Di Cunto 2017; Sarkisian et al. 2002). CRIK is expressed by neural stem and progenitor cells and localizes to the midbody bridge, where it is necessary for the final phase of cell division, the abscission (Gai et al. 2011; Naim et al. 2004; Di Cunto et al. 1998). Mutations in CRIK alter abscission, driving neural APs into apoptosis, thereby leading to the observed reduction in brain size. The cytokinesis machinery is also one of the targets of Zika virus infection, which is associated with neurological alterations in both newborn and adult. The Zika protease NS2B-N3, required for virus replication, cleaves Septin-2, a protein that is crucial for the assembly and stability of the midbody bridge (Li et al. 2019). As a consequence, neural stem and progenitor cells are unable to divide, and this drives them into apoptosis. This mechanism might, at least in part, explain the severe reduction in brain size associated with Zika virus infection (Li et al. 2016a, b).

Centrosomal Proteins ASPM (abnormal spindle microcephaly associated) is a centrosomal protein, the gene of which is frequently found to be mutated in microcephaly patients. In mouse brain, *ASPM* mutations cause centrosome amplification, aneuploidy, and tissue degeneration (Marthiens et al. 2013). Cdk5Rap2 represents an additional case of a centrosomal protein implicated in primary microcephaly (Bond et al. 2005). Cdk5Rap2 is recruited to the centrosome via its interaction with pericentrin, and its depletion induces neuronal differentiation by promoting the generation of BPs at the expense of APs. Both *Aspm* and *Cdk5Rap2* have a very well documented role in mitosis and in spindle positioning.

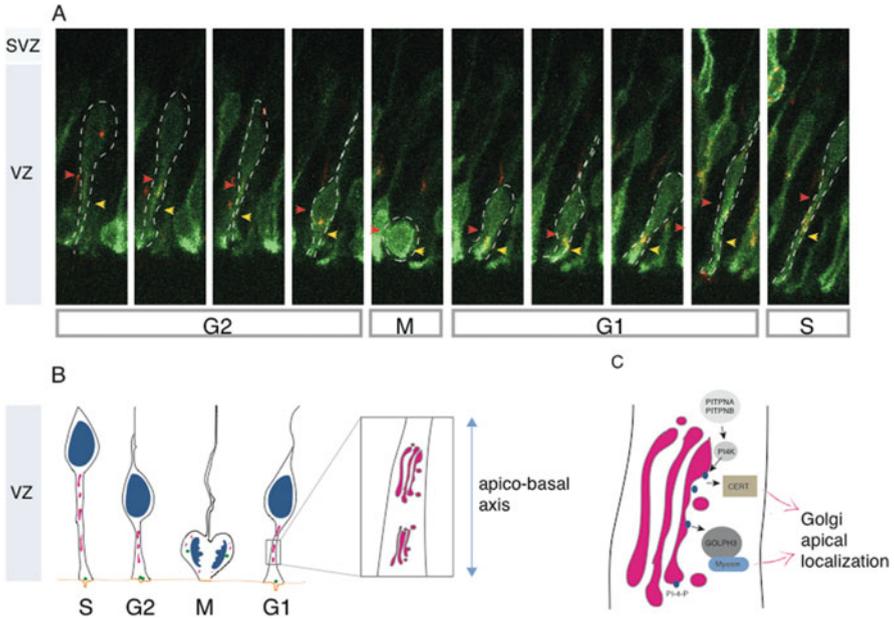


Fig. 15.3 Noncanonical Golgi apparatus organization in apical progenitors. **(a)** Live imaging of the Golgi apparatus. APs were electroporated with plasmids for a Golgi-resident red fluorescent protein (red) and for cytosolic GFP (green) to visualize the cell boundaries (white dashed line). Yellow arrowheads indicate the apical-most Golgi, while orange arrowheads indicate the basal-most Golgi. Note the Golgi apparatus compression in G2-phase, Golgi fragmentation and partitioning during mitosis (M), followed by Golgi extension and stretching in G1-S-phase. **(b)** Cartoon illustrating the Golgi apparatus (magenta) and centrosome (green) organization throughout the cell cycle (Taverna et al. 2016). Orange: apical plasma membrane with primary cilium. Inset on the right: Golgi apparatus orientation in relation with the AP's apicobasal axis (light blue arrow) (Taverna et al. 2016). **(c)** Molecular mechanisms responsible for the apical Golgi confinement (Xie et al. 2018)

15.2.2.2 The Golgi Apparatus...

Unlike what has been described for other epithelial cells, the Golgi apparatus in interphase APs shows very specific and noncanonical features, related to (1) the organization and orientation of the Golgi relative to the cell's apicobasal axis, (2) the dynamics during cell cycle progression, and (3) the lack of association with the centrosome (Taverna et al. 2016).

...Is Confined to the Apical Process

In APs, the Golgi apparatus is organized in stacks distributed in the apical process, between the apical plasma membrane and the nucleus. Interestingly, the stacks are not forming a typical ribbonlike structure, but appear to be separated entities (Fig. 15.3a, b). No membrane structures identifiable as Golgi cisternae have been observed in the basal process.

Unlike the Golgi apparatus which is confined to the apical process, the endoplasmic reticulum (ER) is evenly distributed in the apical and basal process. The uneven distribution of the Golgi apparatus as a canonical intermediate station within the secretory pathway was found to have consequences regarding the composition of the lateral plasma membrane in the apical vs basal AP process. While proteins carrying ER-derived glycans were found to be evenly distributed along the apicobasal axis of APs, proteins carrying Golgi-modified glycans were found to be confined to the apical process only (Taverna et al. 2016). These data suggest that the apical process relies on the conventional ER-to-Golgi-to-plasma membrane traffic route for membrane supply, while the basal process relies on the unconventional pathway, that is a direct traffic route from the ER to the plasma membrane (Grieve and Rabouille 2011).

It is known that the apical and basal processes perform different functions. For example, the apical process is permissive for INM, while the basal process is heavily involved in cell-to-cell signaling and regulation of cell proliferation vs differentiation. The question arises as to whether the distribution of the Golgi apparatus and the sub-compartmentalization of the basolateral plasma membrane are related to the functional diversity of the apical and basal process. We would like here to propose some speculation that might be interesting to investigate. As to the apical process, the presence of Golgi-derived glycans might render the plasma membrane more fluid, so that it can better adapt to the migration of the nucleus during INM. As to the basal process, work in *Drosophila* has established that integrins are sorted to the basal-most part of epithelial plasma membrane via an unconventional secretory pathway (Schotman et al. 2008). Interestingly, functional manipulations in mouse, ferret, and human developing brain demonstrated that the integrin signaling that regulates progenitor proliferative potential is initiated in the basal process (Fietz et al. 2010; Stenzel et al. 2014). Another hypothesis worth testing is that the ER-derived glycans in the basal process are involved in the radial migration of neurons along the radial fiber. Although highly speculative, this hypothesis is very attractive, considering that a large proportion of disorders of cortical migration are associated with defects in glycosylation (Freeze et al. 2015).

... Is Parallel to the Apicobasal Axis of the Cell

It has been recently shown that in APs the Golgi stacks are oriented with their cis-to-trans axis perpendicular to the apicobasal axis of the cell (Taverna et al. 2016; Xie et al. 2018) (Fig. 15.3b). This organization is somewhat surprising, as in all epithelial cells analyzed so far the cis-to-trans Golgi axis was reported to be parallel to the cell's polarity axis. One can speculate that this orientation minimizes the distance a vesicle has to travel from the trans Golgi network (TGN) to the target plasma membrane. This organization might be instrumental to optimize the membrane supply in APs, as they represent a highly dynamic and fast-elongating cell type.

... Is Reorganized During INM

Since the Golgi apparatus in APs stretches between the nucleus and the apical plasma membrane, what happens during INM, when the nucleus either moves toward or away from the apical plasma membrane? Live imaging experiments have revealed that in APs the Golgi apparatus is reorganized in concert with INM

(Taverna et al. 2016) (Fig. 15.3a, b). In particular, the Golgi apparatus is compressed during the G2-phase basal-to-apical nuclear migration, and then is stretched during the G1-phase apical-to-basal phase of nuclear migration. These observations prompted the authors to propose that the Golgi apparatus in APs is behaving like an accordion, undergoing several phases of compression followed by stretching depending on the cell cycle's phase. The functional consequences of stretching and compressing the Golgi apparatus have not been addressed yet. In this regard, results in tissue culture cells show that mechanical forces applied to the Golgi apparatus perturb the dynamics of Golgi-associated actin and potentially affect membrane trafficking (Guet et al. 2014).

...Is Not Pericentrosomal

In mammalian cells, the Golgi apparatus has always been reported to be organized around the centrosome. This organization is called "pericentrosomal" and is considered to be the canonical and well-conserved configuration of the Golgi apparatus in interphase in all mammalian cells, including epithelial cells (Bacallao et al. 1989). This rule does not apply to APs, however, in which the centrosome is strictly located at the apical cell cortex where it nucleates the primary cilium, whereas the Golgi is stretched in the apical process, with no sign of connection with the centrosome (Taverna et al. 2016) (see scheme in Fig. 15.3b).

15.2.2.3 Mechanism of Golgi Apparatus Apical Localization

The confinement of the Golgi apparatus to the apical process of APs is actively maintained via a lipid signaling pathway involving the Golgi-localized pool of phosphatidylinositol-4-phosphate, in addition to GOLPH3 (Golgi phosphoprotein 3) and CERT (ceramide transfer protein) as downstream effectors (Xie et al. 2018) (Fig. 15.3c). In particular, PITPNA and PITPNB, two phosphatidylinositol transfer proteins (PITPs) stimulate the synthesis of phosphatidylinositol-4-phosphate on the Golgi membrane. The phosphatidylinositol-4-phosphate pool in turn recruits GOLPH3, which serves as an adaptor to link the Golgi cisternae to the actin cytoskeleton (Fig. 15.3c). The pathway linking phosphatidylinositol-4-phosphate to actin is necessary for the apical localization of the Golgi apparatus in APs. PITPNA and PITPNB are essential for normal brain development, as their ablation in the embryonic mouse neocortex causes severe developmental defects, characterized by the almost complete absence of the dorsal telencephalon (Xie et al. 2018). The cellular basis for the detrimental effect of PITPNA and PITPNB ablation is the disarrangement of AP structure and architecture, and the subcellular basis for that in turn is the lack of apical confinement of the Golgi apparatus (Xie et al. 2018). Taken together, these data strongly suggest that not only Golgi function is necessary for brain development, but also the Golgi localization and apical confinement (Taverna et al. 2016; Xie et al. 2018) are crucial aspects securing a correct brain development.

15.2.2.4 Centrosome and Golgi Apparatus in Mitotic APs

In mammalian cells, the centrosomes are essential to build the mitotic spindle. In any given cell, the two centrosomes are always asymmetric with respect to centriole age, as one contains the so-called mother centriole and the other the so-called daughter centriole, which were synthesized in different cell cycles (Paridaen and Huttner 2014). For APs undergoing asymmetric cell division, the question arises as to whether the centrosome's asymmetry correlates with the asymmetric fate of the daughter cell. It has been shown (Wang et al. 2009) that 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 (a BP, and less frequently a neuron).

Interestingly, also the ciliary membrane is asymmetrically distributed during mitosis, as it—being a single-copy organelle—is inherited by only one of the daughter cells, which tends to be the proliferative daughter cell (Paridaen et al. 2013). Furthermore, the daughter cell inheriting the ciliary membrane tends to re-establish the cilium earlier than the sibling cell (Paridaen et al. 2013). These data suggest that in APs there are most likely two pathways contributing to the biogenesis of the primary cilium: a pathway depending on inheritance of ciliary membrane and a pathway depending on de novo biosynthesis of ciliary membrane (Paridaen et al. 2013). The de novo biosynthesis pathway has been typically linked to Golgi-derived traffic. It would be interesting to understand if and how Golgi traffic contributes to the biogenesis of the primary cilium in newborn BPs.

It is known that in mammalian cells the Golgi undergoes fragmentation during mitosis (Levine et al. 1995). This fragmentation step is necessary for the cell to enter mitosis, and is the cellular basis of the so called “Golgi mitotic checkpoint” (Ayala and Colanzi 2017; Persico et al. 2009, 2010). The distribution of the Golgi in mitotic APs has been analyzed by immunofluorescence and electron microscopy (Taverna et al. 2016). During prophase, the Golgi apparatus of APs appears to undergo fragmentation, and the Golgi remnants are distributed at the cell periphery where they only partially associate with the spindle poles. Interestingly, the Golgi remnants do not form the so called “Golgi haze” (Axelsson and Warren 2004), but rather consist of partially stacked cisternae (as revealed by electron microscopy). In telophase, when the Golgi apparatus is known to re-assemble, the Golgi fragments are still distributed at the cell periphery. Unlike the ciliary membrane, the Golgi apparatus does not seem to be asymmetrically partitioned during mitosis (Taverna et al. 2016).

15.3 Basal Progenitors (BPs)

15.3.1 General Remarks

BPs are cells lacking ventricular contact and apical polarity cues. There are two major subtypes of BPs, the intermediate progenitor cells (IPCs) and the basal radial glial cells (bRGCs) (Fietz et al. 2010; Hansen et al. 2010; Martinez-Cerdeno et al. 2006; Noctor et al. 2004, 2007a; Reillo and Borrell 2012; Reillo et al. 2011; Wang et al. 2011). IPCs are abundant in rodents and are considered to be non-polarized cells, as they lack both apical and basal polarity cues. bRGCs lack apical polarity cues but maintain basal polarity cues, often associated with their attachment to the basal lamina. bRGCs are particularly abundant in gyrencephalic species like human (Reillo et al. 2011). BPs are typically born from an asymmetric division of an AP, in which one daughter cell maintains the AP-fate of the mother cell and the other daughter cell becomes a BP. It has been shown that immediately after being generated, the majority of BPs still retain ventricular contact and feature an apical plasma membrane that is flanked by the apical adherens junction belt (see Fig. 15.2). By the end of G1-phase, BPs have lost their apical attachment in a process called delamination. At the cellular level, delamination is crucial for the basal migration of BPs. At the tissue level, delamination is crucial for the generation of the SVZ, the second germinal zone in the developing brain, the size of which underwent dramatic expansion during human evolution. Reflecting the relevance of delamination for brain development and evolution, considerable efforts have recently been made to dissect the cellular and molecular mechanisms responsible for it. We will here describe this crucial step focusing mainly on the centrosome and primary cilium (see Fig. 15.2 for a general summary of the above-described steps).

15.3.2 Centrosome and Golgi Apparatus in Nascent BPs

Very much like an AP, a newborn BP retains ventricular contact and its apical plasma membrane is delimited by the apical adherens junction belt (Wilsch-Bräuninger et al. 2012), as mentioned above. Which then are the cell biological features that set a newborn BP apart from an AP, allowing a BP to eventually lose apical polarity cues? The disengagement of the BP from the apical adherens junction belt is preceded by the relocation of the centrosome-cilium (Wilsch-Bräuninger et al. 2012). Using electron microscopy, researchers have shown that the first cell biological signature in the generation of a BP is the relocation of the centrosome-cilium from an apical location (which is typical for epithelial cells such as APs) to a basolateral location (Wilsch-Bräuninger et al. 2012). Functional manipulations suggested that the relocation of the centrosome-cilium to the basolateral plasma membrane is a necessary step in delamination. Overexpression of *Insm1* (insulinoma-associated 1), a transcription factor known to promote the generation of BPs (Farkas et al. 2008; Tavano

et al. 2018), increases the proportion of basolateral cilia (Wilsch-Bräuninger et al. 2012). Furthermore, microinjection of recombinant dominant-negative Cdc42 into single APs in organotypic slice culture of developing mouse hindbrain leads to their delamination (Taverna et al. 2012). Interestingly, the microinjected cells that were not yet delaminated featured a basolateral (rather than apical) centrosome (Taverna et al. 2012), strongly suggesting that the relocation of the centrosome (and most likely the primary cilium) is a necessary step for the complete disengagement of a delaminating cell from the apical adherens junction belt.

The organization of the Golgi apparatus in nascent BPs is very similar to the one present in G1-phase APs (Taverna et al. 2016), that is, it exhibits multiple non-interconnected stacks distributed between the apical plasma membrane and the nucleus.

Taken together these data suggest that from a cell biological point of view, the organelles orchestrating cell fate transition are most likely the centrosome-cilium (Wilsch-Bräuninger et al. 2012, 2016).

15.3.3 Golgi and Centrosome in Delaminated BPs

In delaminated BPs, the Golgi appears to be localized around the centrosome (Taverna et al. 2016). This aspect is interesting, as it means that during delamination, concomitant with the loss of apical contact, the Golgi shifts from a noncanonical to a canonical, pericentrosomal location. One can wonder how and why cell fate transition and delamination are accompanied by a reorganization of these two organelles. Although there is not a definitive answer, a tempting speculation is that the reorganization at the centrosome-Golgi axis has to do with the different migration characteristics of APs and BPs. As described above, APs undergo INM, which is a very specific type of migration, as it consists of nucleokinesis (movement of the nucleus) without a net translocation of the cell body. Indeed, the AP remains anchored to the apical and basal side while the nucleus is moving. In contrast, upon delamination the newborn BPs translocate both their nucleus and cell body from the VZ to the SVZ. Seminal work performed on neurons in 2D tissue culture has shown that the proximity of the centrosome and the Golgi apparatus is crucial for their directed cell migration (Hurtado et al. 2011). One can therefore speculate that the reorganization of the centrosome and Golgi apparatus helps the directed migration of BPs to the SVZ. It follows that the reorganization at the Golgi-centrosome interface should be regarded as a crucial cell biological step for the generation of the basal germinal zone, the SVZ.

15.3.4 Golgi and Centrosome in bRGCs

As mentioned, all BPs lack apical polarity cues and apical attachment (Fig. 15.1). However, while iPCs lack also basal polarity cues, bRGCs maintain basal polarity

cues. Two questions are of interest regarding the cell biology of bRGCs: (1) which are the mechanisms responsible for the selective loss of apical contact, and (2) which is the organization of their intracellular compartments? A recent study suggests that PLEKHA7 acts downstream of INSM1 to promote the generation of bRGCs. PLEKHA7 is an adherens junction belt-specific protein that, when down-regulated, results in the selective loss of apical contact. Hence, the PLEKHA7-manipulated cells maintain their basal attachment and are therefore bRGCs (Tavano et al. 2018). This is the first reported case of a polarity protein selectively regulating apical polarity cues, independently of the basal ones. As for the organization of the intracellular compartments, electron microscopy studies have shown that in bRGCs the centrosome is close to the nucleus (Fietz et al. 2010) and presumably is associated with the Golgi apparatus.

15.3.5 Centrosome and Golgi Apparatus in Mitotic BP

While the Golgi apparatus in mitotic APs is found at the cell periphery, far away from the centrosomes/spindle poles, the Golgi apparatus in mitotic BPs appears to be close to the centrosomes (Taverna et al. 2016). In prophase and metaphase, the Golgi apparatus is compact and mostly found in close proximity to the centrosomes/spindle poles. In telophase BPs, the Golgi structures were largely observed near the midbody bridge, which harbors the remnants of the mitotic spindle. Taken together, these data show that the two main classes of neural progenitor cells in the developing mouse neocortex, APs and BPs, differ with regard to the Golgi apparatus-centrosome relationship not only in interphase, but also during mitosis.

15.4 Neurons

15.4.1 General Remarks

Neurons are the final cell output of neurogenesis (Fig. 15.1). Their structural, biochemical, and functional polarization secures the unique ability of neurons of exchanging and storing information. As mentioned above, neurons are mainly produced via divisions of BPs in the SVZ. After being generated, a newborn neuron starts the long journey that will allow it to settle in the forming CP (Fig. 15.2). The CP in turn will give rise to the six-layered cortex, a hallmark of mammals. A newborn neuron engages in two processes that underlie its function and connectivity: the establishment of polarity and the migration to the correct cortical layer. Seminal studies using primary neurons in 2D culture established that the centrosome and the Golgi apparatus play crucial roles in both polarization and migration (Bradke and Dotti 1998, 2000; de Anda et al. 2005; Huttner and Dotti 1991). We will here review some of the main findings in the field. Given the breadth of the subject, we invite the

reader to refer to other reviews for a more detailed description of the topic. We also apologize to those colleagues the work of which could not be mentioned for space issues.

15.4.2 Golgi and Centrosome Function in Neuronal Migration

Neuronal migration consists of different phases (Hatten 1999; Marin et al. 2010; Martinez-Martinez et al. 2018; Valiente and Marin 2010). After being generated, a newborn neuron polarizes and starts migrating toward the basal lamina in a process called radial migration (Figs. 15.1 and 15.2). During radial migration, neurons are bipolar and move along the radial fibers (or basal processes) of APs and bRGCs (Martinez-Martinez et al. 2018; Reillo and Borrell 2012; Reillo et al. 2011). While migrating through the IZ, neurons change their morphology from bipolar to multipolar, forming multiple processes and reducing their migration speed (Cooper 2014). During this phase, they can undergo tangential displacement, a crucial process affecting the dispersion of neurons in the tangential dimension and possibly the establishment of connectivity. Eventually neurons acquire a clear bipolar morphology while migrating through the CP (Ayala et al. 2007). Studies from several labs have clearly demonstrated that the centrosome and the Golgi apparatus (along with the actin and microtubule cytoskeleton) work in concert to allow neuronal migration (Bellion et al. 2005; Solecki et al. 2009; Tsai and Gleeson 2005). In particular, the movement of centrosome and Golgi into the leading process precedes and allows nucleokinesis. This is because the centrosome works as a microtubule organizing center, nucleating microtubules that in turn are responsible for force generation on the nucleus. Interestingly, genes associated with disorders of cortical development often perturb neuronal migration by influencing either cytoskeletal elements, the centrosome and/or the Golgi apparatus (Tanaka et al. 2004; Valiente and Marin 2010).

15.4.3 Golgi and Centrosome Function in Neuronal Polarity

15.4.3.1 Centrosome

The centrosome is essential not only for neuronal migration, but also for polarity establishment and neurite outgrowth (Bradke and Dotti 1998, 2000), as demonstrated by studies with 2D neuronal cultures in which the orientation of the centrosome was found to provide spatial cues for axon emergence from the cell body (de Anda et al. 2005; Gärtner et al. 2012). Interestingly, a study suggests that after having set the initial axonal polarity, the centrosome is dispensable for axon extension (Stuess et al. 2010).

15.4.3.2 Golgi Apparatus

The Golgi apparatus plays a key role in establishing and maintaining the highly polarized structure of neurons. A prime example are pyramidal neurons, which feature a prominent dendrite (called the apical dendrite) extending hundreds of microns in the direction of the basal lamina. Several studies have shown that the Golgi apparatus extends into the apical dendrite (Huang et al. 2014; Matsuki et al. 2010; O'Dell et al. 2012). This extension (called dendritic Golgi deployment) depends on the Reelin-Dab1-GM130 pathway (Huang et al. 2014; Matsuki et al. 2010) and is crucial for cell polarization, axon specification, and dendrite growth (Huang et al. 2014; Matsuki et al. 2010). Of note, ubiquitin-protein ligase E3A (Ube3a), a gene mutated in Angelman syndrome, was found to inhibit apical dendrite outgrowth and polarity by disrupting the polarized distribution of the Golgi apparatus (Miao et al. 2013). This finding is interesting, as it illustrates the relevance of the localization of the Golgi apparatus in neurodevelopmental disorders.

Neurons rely not only on a perinuclear or cell body-localized Golgi apparatus but also on the so-called Golgi outposts (Horton and Ehlers 2003; Horton et al. 2005; Ye et al. 2007). These Golgi outposts are small Golgi cisternae often found in dendritic spines, far away from the cell body, where they represent a way to secure the local processing of newly synthesized proteins (Valenzuela and Perez 2015). Golgi outposts influence dendrite architecture by functioning as sites of acentrosomal microtubule nucleation in neurons (Ori-McKenney et al. 2012). This independent traffic route is important as it allows distal compartments such as dendritic spines to become independent from the cell body with regard to protein processing (Quassollo et al. 2015). Furthermore, electrical activity of neurons has been shown to influence protein translation (Evans et al. 2017) and may affect Golgi outpost function as well. This possibility would tremendously increase the level of regulation and fine-tuning at individual synapses, the subcellular structures responsible for neuron-to-neuron communication in the brain.

15.5 Concluding Remarks

Regarding the study of cell fate transition in the developing mammalian brain, classical studies in developmental neurobiology have concentrated on the identification of the transcription factors involved. More recently, thanks to the availability of more sophisticated techniques of manipulation and analysis, we have witnessed an increasing interest in the dissection of the cell biological mechanisms responsible for cell fate transition in brain development and evolution. We have here discussed the main findings linking the centrosome and the Golgi apparatus to neural stem and progenitor cells and brain development.

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