Published in final edited form as:
Dev Dyn. 2011 August ; 240(8): 1865–1879. doi:10.1002/dvdy.22684.

Cell biological regulation of division fate in vertebrate neuroepithelial cells

Minde I. Willardsen and **Brian A. Link**
Dept. Cell Biology, Neurobiology, and Anatomy, Medical College of Wisconsin, Milwaukee, WI 53226

Summary

The developing nervous system derives from neuroepithelial progenitor cells that divide to generate all of the mature neuronal types. For the proper complement of cell types to form, the progenitors must produce postmitotic cells, yet also replenish the progenitor pool. Progenitor divisions can be classified into three general types: symmetric proliferative (producing two progenitors), asymmetric neurogenic (producing one progenitor and one postmitotic cell) and symmetric neurogenic (producing two postmitotic cells). The appropriate ratios for these modes of cell division require intrinsic polarity, which is one of the characteristics that define neuroepithelial progenitor cells. The type of division an individual progenitor undergoes can be influenced by cellular features, or behaviors, which are heterogeneous within the population of progenitors. Here we review three key cellular parameters, asymmetric inheritance, cell cycle kinetics, and interkinetic nuclear migration, and the possible mechanisms for how these features influence progenitor fates.

Keywords

Neurogenesis; Cortex; Retina; Centriole; Nuclear migration; Notch; Cell behavior; Cell cycle; Apical membrane

Introduction

The brain has often been referred to as one of the most complex structures known. Indeed, the vertebrate central nervous system (CNS) is amazingly intricate and comprised of a vast array of cell types, each which must be generated at the right time and place and in the correct proportions for normal development and proper function. The diversity of neurons and glia of the mature CNS all arise from multipotent neuroepithelia in a process termed neurogenesis (reviewed in Goetz and Huttner, 2005; Farkas and Huttner, 2008). During neurogenesis, a proliferative progenitor cell can divide in one of three basic modes: symmetric proliferative, asymmetric, or symmetric differentiative (Fig 1.). A fundamental question, then, is what controls the mode of division in the progenitor cells? Too much cell cycle exit and the progenitor pool will be depleted. Too little cell cycle exit and not enough early-born cell types will be generated, or worse, oncogenesis would be primed. While it is clear that changes in gene expression ultimately determine cell fates, recent evidence suggests that basic cellular processes, some with stochastic elements, acting just prior to or during the terminal mitosis, influence the mode of division in neural progenitors (Cayouette et al., 2006; Knoblich 2008; Jukam and Desplan, 2010). In this review we highlight recent evidence from multiple regions of the developing vertebrate CNS that supports significant

Correspondence: mwillardsen@mcw.edu or blink@mcw.edu.

roles for fundamental cell biological features of cells that act upstream of signaling and transcriptional networks to impact neurogenesis. In particular we focus on distribution of heritable determinants, cell cycle kinetics, and interkinetic nuclear migration.

Although different regions of the CNS are comprised of unique neuron types and have very different functions, basic features of neurogenesis are shared. The patterning mechanisms that direct and restrict the identities of neuroepithelial progenitor cells for specific regions and structures have been reviewed elsewhere (Wilson and Houart, 2004; Schulte and Bumsted-O'Brien, 2008; O'Leary et al., 2007; Dasen and Jessel, 2009; Caviness et al., 2009). In general, the position of progenitor cells within the developing nervous system defines the repertoire of differentiated cell types they can generate. In addition to regional identity, neuroepithelial progenitor cells also show temporal-specific potentials. Indeed, throughout the vertebrate CNS, there is a link between birthdate/birthorder and cell-type fate (Kao and Lee, 2010; Jacob et al., 2008). In the developing *Drosophila* nervous system, the relationship between birth-order and cell-type fate is essentially invariant. For some parts of the developing vertebrate CNS, however, the strict birth-order rule observed in *Drosophila* does not appear to exist. In order to more fully appreciate vertebrate neurogenesis, it is critical to understand how the progenitor versus postmitotic cell fate decision is determined. How can a single progenitor divide to produce two daughters that adopt different fates? What generates this asymmetry and what are the cellular mechanisms behind these cell fate choices?

A review of the literature suggests that three general classes of cell behaviors can play important roles in neurogenesis: asymmetric inheritance, cell cycle kinetics, and interkinetic nuclear migration (INM). Each of these cellular behaviors exhibit elements of stochasm. Recent data suggests that in some cases, neurogenic cell fate decisions also show stochastic features (Slater et al., 2009; Gomes et al., 2011). Stochasticity has been defined and used in many ways but for the purposes of this review, stochasticity is not limited to perfectly random processes, but also includes chance with bias. Or by analogy, stochastic influences are similar to throwing weighted dice. The relative influences of stochastic and deterministic inputs are not known and are currently the subject of much debate within the field (Losick and Desplan, 2008; Zernicka-Goetz and Huang, 2010; Oats 2011). How then does each of these cellular mechanisms, irrespective of the underlying stochasm or determinism, influence cell fate? Similarly, how does each influence combine to keep a cell proliferative or push it towards a postmitotic fate? The evidence suggests a model in which each cell biological feature adds a weighted influence, the sum of which biases, but does not absolutely restrict the progenitor cell towards particular fates. Here we discuss the various biasing mechanisms, how these influences may combine to affect cell fate decisions, and finally the challenges facing the field moving forward.

Stochasticity and determinism in cell division mode

In addition to influencing cell type identity, neuroepithelial progenitors must decide their mode of cell division. During neurogenesis, a proliferative progenitor cell can divide in one of three basic modes: symmetric proliferative, asymmetric, or symmetric differentiative (Fig 1A.). For the purposes of this review, asymmetric division is defined as divisions resulting in daughters that adopt different fates. For example, asymmetric divisions may result in one progenitor and one neuron or two neurons of different classes. However, asymmetric divisions can also occur without cell cycle exit, such as the generation of two proliferative daughter cells with different lineage restrictions. In *Drosophila* neuroblasts, the mode of division appears fixed where progenitors divide solely in a self-renewing, asymmetric manner (Fig 1B, left; Skeath, 1999; Bossing et al., 1996; Schmid et al., 1999; Matsuzki, 2000). Although full lineage reconstructions are more limited for vertebrates, analyses

indicate that significant heterogeneity exists in the composition of lineage trees. For example in the retina, hindbrain and parts of the forebrain, once neurogenesis commences, all three division modes take place among the progenitors and individual lineages can show shifts between symmetric proliferative, asymmetric, or symmetric differentiative divisions (Cai et al., 2002; Cayouette et al., 2006; Byerly and Blackshaw, 2009; Fig 1B, right). For cortical and retinal progenitors in vitro, statistical analyses support stochastic elements to the mechanisms underlying division choice (Slater 2009; Gomes 2011). Comparison of the lineages between these two neuronal regions, however, indicates that cortical progenitors exhibit more stereotyped patterns, than those of the retina (Fig 1B). Importantly, these culture paradigms match in vivo lineage diversity for their respective neuronal regions in terms of cell-type fate compositions and clone sizes. Stochastic models suggest that for each round of division, the progenitor cell 'chooses' its mode of cell division based on weighted probabilities. These set probabilities along with cell type fate competence become a defining feature of the progenitor cell. Alternatively, deterministic models in which cell fate is prescribed by autonomous programs, or intrinsic timers, have also been put forth (Durand and Raff, 2000; Okano and Temple, 2009; Kao and Lee, 2010). In addition, it is possible that apparently stochastic events are actually determined, but the underlying mechanisms are as yet too complicated to be recognized by current experimental and observational methods. However, it is also possible, even likely that a combination of stochastic and deterministic inputs interact to influence cell fate. In the following sections we review experimental observations that indicate intrinsic cellular features and stochastic behaviors of neuroepithelial cells that influence neurogenesis and underlie the choice for division mode.

The importance of cell polarity

Neuroepithelial progenitor cells are highly polarized along their apicobasal axis and form pseudostratified sheets (Fig 2). Apicobasal cell polarity of neuroepithelial cells is critical for many of the cellular mechanisms that regulate neurogenesis and when disrupted, the normal ratio between self-renewal and differentiation is often altered. Neuroepithelial progenitors have an elongated, bipolar appearance with thin attachments to both the apical and basal surfaces, and typically a prominent bulk of cytoplasm surrounding the nucleus. Neuroepithelial cells are connected to each other at the apical surface by adherens junctions. The adherens junctions also serve as a boundary between the apical domain and basolateral domain of the cell. Components of tight junctions are also associated with the apical domains of neuroepithelia and can form extracellular diffusion barriers at late stages of neurogenesis (Balselv et al., 1997; Abdelliah-Seyfried, 2010). As a consequence of the junctional components, as well as directed intracellular trafficking, the apical domain contains proteins and lipids that are distinct from those in the basolateral membrane. A prominent feature of the apical domain is the primary cilium. This microtubule-based protrusion is now well known to localize signaling components (Han and Alvarez-Buylla, 2010; Goetz and Anderson, 2010). It is a dynamic structure maintained by intraflagellar transport and is disassembled prior to the appearance of the mitotic spindle (Seeley and Nachury, 2010). During disassembly, at least for cortical neuroepithelia, primary cilia can shed apical membrane and associated proteins into the extracellular space (Dubreuil et al., 2007). The primary cilium typically re-emerges during G1 phase, being nucleated by the inherited centriole. The centrioles, or basal bodies, remain associated with the apical domain throughout interphase and during duplication (Norden et al., 2009; Tsai et al., 2010). The apical surface area of interphase neuroepithelial cells is variable in size, but as a proportion of the total plasma membrane it is relatively small (1-4%) (Kosodo et al., 2004; Nishizawa et al., 2007). In contrast to the apical surface, basal endfeet of neuroepithelial cells are not coupled to each other. Instead, these extensions form contacts with basal lamina. Consequently, proteins associated with focal adhesions are often concentrated in the basal endfeet (Chenn et al., 1998; Li and Sakaguchi 2002; Martinez-Morales 2009).

The establishment of apicobasal cell polarity has been extensively studied and the mechanisms are highly conserved among cell types and between species (Yamanaka and Ohno, 2008; Insolera et al., 2010). In general, apicobasal cell polarity is facilitated by protein complexes that are mutually antagonistic for their location within cells. Examples include the apical PAR complex (Par6, Par3 and aPKC), the apical Crumbs complex (Crumbs, Pals1, and Patj) and the basolateral Scrib complex (Lgl, Scrb, Dlg). Therefore, as long as key polarity proteins are expressed, many aspects of apicobasal cell polarity are self-assembling (Afonso and Henrique, 2006; Tanentzapf and Tepass, 2003; Humbert et al., 2008; Bilder, 2004). This can be observed when neuroepithelial cells are placed in culture and apicobasal polarity and bipolar morphology is established with minimal external cues (Cayouette et al., 2003; Qian et al., 1998). Primarily through mutational analysis in *Drosophila* and other experimental animals, it was found that disruption of genes encoding cell polarity components often affect the proportion of progenitor cells leaving the mitotic cycle and can lead to tumor formation (Bilder, 2004; Dow and Humbert, 2007). Mutations that disrupt the polarity of vertebrate neuroepithelial cells can result in changes in cell division plane, INM, proliferation, and neurogenesis (Yamaguchi et al., 2010; Sottocornola et al., 2010; Costa et al., 2007; Roberts and Appel, 2009; Cappello et al., 2006). Ongoing research into the relationships between cell polarity and proliferation control has generated many of the observations reviewed here.

Asymmetric inheritance – bias at birth

The best-studied cellular behavior known to affect neurogenesis is partitioning of determinants at cytokinesis (Fig 3). For invertebrates it is well established that when a neuroblast progenitor cell divides, it partitions fate-influencing proteins to the daughter cells (Wodarz 2005; Zhong and Chia, 2008; Betschinger and Knoblich, 2004; Gonczy, 2008). Such determinants can be distributed equally or unequally to the two offspring cells, creating either symmetric or asymmetric divisions respectively. For invertebrates there is clear evidence that the orientation of the mitotic spindle apparatus can affect the distribution of fate determinants that have been localized in a polarized manner within the cell. In accord with the stereotyped division patterns observed in invertebrates, the orientation of the mitotic spindle is highly coordinated to ensure proper partitioning of determinants. For vertebrates, the role of the mitotic cleavage plane orientation in regulating cell fate has been more controversial. Timelapse studies, birthdating and clonal analyses showed that horizontal divisions correlate with asymmetric cell fates (Cai et al., 2002; Mione et al., 1997; Chenn and McConnell, 1995; Cayouette et al., 2001; Cayouette and Raff, 2003; Miyata et al., 2001). However, part of the controversy stems from the fact that the orientation of division plane for vertebrates is less predictive of cell fates than for invertebrates and the relatively small number of horizontal divisions cannot account for the neurons generated (Silva et al., 2002; Das et al., 2003; Wilcock et al., 2007; Kosodo et al., 2004; Roberts and Apel, 2009; Lyons et al., 2003; Morin et al., 2007; Konno et al., 2008; Noctor et al. 2008). Furthermore, some of the vertebrate homologs of invertebrate fate determinants initially investigated, such as Prox1 or Lgl, were not as obviously polarized in M-phase vertebrate neuroepithelial progenitor cells nor asymmetrically partitioned to daughter cells (Dyer, 2003; Klezovitch et al., 2004). That said, Notch, Numb, EGFR, and TRIM32 among other proteins can show asymmetric distribution in neural progentors (Chenn and McConnell, 1995; Cayouette et al., 2001; Sun et al., 2005; Schwamborn et al., 2009). These observations and new evidence does support a significant role for asymmetric segregation of fate determinants during vertebrate neurogenesis. Next we review some of the most recent examples for segregation of determinants in vertebrate neuroepithelia to complement other examples that have been previously reviewed (Zhong and Chia, 2008; Betschinger and Knoblich, 2004; Knoblich 2008; Sawa 2010).

Some clarity to the controversy of vertebrate cleavage plane division and neurogenesis came from a detailed study conducted in the Huttner laboratory (Kosodo et al., 2004). They found that although cleavage plane orientation was a poor predictor for the mode of cell division in mouse cortical and midbrain progenitor neuroepithelia, asymmetric segregation of the apical domain did correlate with generation of neurons. Importantly, the apical domain could be differentially partitioned even when the cleavage plane was vertical and therefore perpendicular to the ventricular surface – an orientation previously assumed to indicate symmetric divisions (Kosodo et al., 2004). This study emphasized the need to identify and follow specific cellular components, as opposed to simply monitoring anaphase spindle orientation or the cleavage plane. In addition, it highlighted the role of the apical domain, as defined by Par3 and Prominin-1 expression, in potentially influencing the mode of cell division in vertebrate neuroepithelia. Kosodo and colleagues went on to show that for symmetric proliferative divisions of cortical neuroepithelia, the apical domain was divided equally between the daughter cells in every case observed (for example cell B in Fig 3). For neurogenic divisions, which are nearly always asymmetric in the ventricular zone of the developing cortex, a high proportion showed unequal partitioning of the apical domain (for example cell A in Fig 3). Furthermore, when neuroepithelial cells switch from symmetric proliferative to asymmetric differentiative divisions, the size of the apical membrane decreases, presumably allowing for more asymmetric (bypassing) divisions of the apical region (Kosodo et al., 2004). However, the correlation between inheritance of apical membrane and mode of cell division varied over developmental time and depended on which CNS compartment was analyzed. Nonetheless, this correlation was confirmed and extended in separate studies (Marthiens and ffrench-Constant, 2009; Alexandre et al., 2010). Interestingly, which daughter cell becomes the neuron when the apical domain is differentially partitioned may depend on the progenitor cell type. For mammalian cortical neuroepithelia, it was noted that Prominin-1 staining was absent in newly generated neurons, suggesting by inference that for those progenitors, the cell that received the apical domain remained in the cell cycle (Kosodo et al., 2004). Direct imaging will be necessary to confirm that interpretation. In contrast, for zebrafish hindbrain and spinal cord neuroepithelia, time-lapse imaging showed that following asymmetric divisions, the daughter cell that received the apical domain most often differentiated as a neuron (Alexandre et al., 2010). In such divisions, the other daughter cell usually inherited the basal process, and when it did, that cell always remained mitotically active.

Neurogenesis and the apical domain

How does the apical domain influence neurogenesis? Recent evidence suggests that the apical PAR complex directly interacts with factors that influence the mode of cell division. Through gain and loss of function studies of Par3 and Par6 in mouse cortical neuroepithelia, it was found that increasing the amount of PAR proteins promoted proliferative divisions, while depleting these proteins resulted in elevated cell cycle exit (Costa et al., 2008). The effects on proliferation were limited to the initial stages of neurogenesis. This temporal consideration is consistent with observations from conditional aPKCλ deletion at a late stage of cortical development, which did not reveal changes in the number of proliferating neuroepithelia (Imai et al., 2006). At earlier stages, when aPKC activity was depleted in the frog neural plate, cell cycle exit and primary neurogenesis was promoted (Ossipova et al., 2009). Somewhat paradoxical to these findings, when Par3 or aPKC were depleted in zebrafish spinal cord or retinal neuroepithelia, proliferative divisions were significantly promoted (Alexandre et al., 2010; Baye and Link, 2007; Roberts and Appel, 2009). Likewise, when other apical polarity components were mutated in zebrafish retinal neuroepithelia, including N-Cadherin/Cdh2 and Nagie oko/Pals1, proliferative divisions increased and cell cycle exit was inhibited (Yamaguchi et al., 2010). Conversely, when Pals1 was deleted in the developing mouse cortex, neuroepithelia exhibited premature

withdrawal from the cell cycle and excessive generation of early-born neurons, and subsequently showed elevated cell death (Kim et al., 2010). These effects were attributed to loss of mTOR signaling. Reconciliation to these findings may lie in how overall apicobasal polarity was affected by each manipulation, when during development the effects were measured, or the differences may simply reflect cell type specificity. Nonetheless, these data clearly indicate the importance of the apical domain in the decision between proliferative and neurogenic divisions.

Several recent studies indicate that Par complex proteins regulate and depend on Notch signaling during neurogenesis, suggesting a mechanism by which the apical domain may influence cell fates (Bultje et al., 2009; Smith et al., 2007; Ossipova et al., 2009; Yamaguchi et al., 2010). For example, in frog neural plate neuroepithelia, aPKC was found to phosphorylate Par1, itself a protein kinase that is expressed along the basolateral domain of polarized cells. Phospho-Par1 can then phosphorylate Mindbomb, a ubiquitin ligase that activates Notch ligands. When phosphorylated, Mindbomb is destabilized, resulting in repression of Notch signaling and reduced neuronal differentiation (Ossipova et al., 2009). In those studies, however, the specific effects of Par1 on division modes were not directly assessed nor probed in other neuroepithelia – issues that will be important to test in future experiments. Other substrates of aPKC include Lgl, which affects Numb segregation, and Numb itself (Klezovith et al., 2004; Nishimura and Kaibuchi, 2007; Smith et al., 2007). It should be noted, however, that the role of Numb and Numb-like during neurogenesis is complicated by the fact that these endocytic adaptors can regulate trafficking of adherens junction components, and thus affect polarity, as well as directly modulate Notch signaling (Rasin et al., 2007). Relevant to this issue is the observation that when alpha-E-catenin or rhoA was deleted in mouse cortical neuroepithelia, adherens junctions and apicobasal polarity were disrupted, but Notch pathway genes were unaffected. Instead, targets of Hedgehog signaling were found to be upregulated (Lien et al., 2006; Katayama et al., 2011). By extension, the latter studies argue that indeed, the effect of Numb on Notch activity is independent from its role in maintaining cell polarity.

Centrosome inheritance

One feature of the cell that is clearly segregated in an asymmetric fashion during mitosis are the differently-aged centrosomes (Delattre and Gonczy, 2004; Bettencourt-Dias and Glover, 2007). The centriole pair, which comprises the centrosome, is itself asymmetric. The older, mother centriole contains distal appendages and is associated with distinct proteins and pericentriolar material (PCM) that define its maturation. The younger centriole lacks these specializations. During S-phase the centrosome is duplicated in a semi-conservative manner, resulting in centrosomes with mother centrioles at different maturation states (Fig 4). Therefore at mitosis, differentially aged centrosomes are always segregated. Recent experiments have demonstrated that this can impart differences between daughter cells. The consequences of asymmetric centrosome inheritance were first described for *Drosophila* neuroblasts and male germline stem cells (Rusan and Peifer, 2007; Yamashita et al., 2007; Yamashita and Fuller, 2008). In the case of neuroblasts, the mother centrosome, which maintains robust microtubule organizing activity and more PCM, is preferentially localized to the apical niche. This creates a stereotyped spindle orientation such that the apical progeny cell inherits the mother centrosome and presumably based on the apical signaling niche and/or PCM-associated cues differentiation. The basal cell inherits the daughter centrosome and remains a proliferative stem cell neuroblast (Januschke and Gonzalez, 2010; Conduit and Raff, 2010). For mammalian neural progenitors, the influence of centrosome asymmetry has been probed in mouse cortical neuroepithelia (Wang et al., 2009). Using a photoconversion protocol to birthdate centrioles, the authors found that mother centrosomes are biased (~85% of the time) in segregation to daughter cells that remain ventricular zone

progenitors, while those inheriting the younger daughter centrosome typically become migrating neurons. Furthermore, when centrosome maturation was inhibited by disrupting Ninein, the number of ventricular zone progenitor cells was depleted, and a concomitant elevation in number of post-mitotic neurons was measured, consistent with a critical role for centrosome inheritance in cell fate. The mechanisms underlying these effects have not yet been solved. One possibility includes the association of specific fate-determining factors with one centrosome, such as specific regulatory proteins or organelles (Fuentealba et al., 2008; Fig 3A and 4, red dots). Another provocative idea is that the daughter cell that inherits the mother centrosome can more efficiently initiate primary cilia formation, and is therefore more receptive to external signals such as Hedgehog and Wnt that are facilitated by the apical appendage (Anderson and Stearns, 2009).

Differential degradation

Factors that control protein degradation have recently been found as another cellular feature that is asymmetrically segregated and that can regulate neurogenesis (Stegmuller and Bonni, 2010; Tuoc and Stoykova, 2010). This was nicely demonstrated through analysis of Trim32 in the developing mouse cortex. Trim32 is a tripartite interaction motif E3 ubiquitin ligase (Schwamborn et al., 2009). Like the *Drosophila* homolog, Brat, Trim32 can be asymmetrically distributed in neuroepithelia at cytokinesis. Interestingly, Trim32 did not colocalize with centrosomes, the apical domain, or the metaphase plate. Instead, the protein was enriched just basal to the soma. Consequently, Trim32 segregation correlated tightly with inheritance of the basal process (Fig 3, represented in green). When Trim32 was overexpressed in neural progenitors, neuronal differentiation was induced. When Trim32 was deleted, both daughter cells remained as proliferative progenitors. Mechanistically, it was found the Trim32 ubiquinates and degrades cMyc, but also binds and activates the proneural microRNA Let-7a. In this manner, Trim32 coordinates the suppression of self-renewal and promotes neuronal differentiation. Other examples of Ubiquitin-mediated turnover of specific pro- or anti-neurogenic proteins have also been demonstrated more generally in regulation of neurogenesis (Tuoc and Stoykova, 2008; Westbrook et al., 2008; Zhao et al., 2008; Zhao et al., 2009; D'Arca et al., 2010).

Cell Cycle Kinetics – Windows of Opportunity

In addition to differences imparted at cytokinesis, interphase neuroepithelial cells also display asymmetries, or heterogeneities in behaviors, that have been studied in the context of regulating fate of division mode. Prime among these is variance in cell cycle kinetics between proliferative progenitor cells (Salomoni and Calegari, 2010; Lange and Calegari, 2010). In particular, the length of G1 phase has been linked to the decision of cortical progenitor cells to eiher divide to generate proliferative daughters or to produce more differentiated progeny (Calegari et al., 2005; Pilaz et al., 2009). The general idea of the ‘cell cycle length hypothesis’ is that factors that regulate the mode of cell division, or other cell fates, have a restricted ‘window’ within the cell cycle in which they function (Calegari and Huttner, 2003). For example, if neuroepithelia have heightened responses to particular fate determinants during G1 phase, cells with a shorter G1 phase would respond differently than cells with a longer G1 phase -- even if exposed to equivalent amounts of the fate-stimulus (Fig 5). In support of this idea, there are long-standing observations from the cortex and retina that a progenitor cell's ability to respond to external signals depends on the phase of the cell cycle (McConnell and Kaznowski, 1991; Belliveau and Cepko, 1999). The length of G1 phase, or other parts of the cell cycle, may also affect intrinsic activities within the cell. For example transcriptional activity, protein degradation, or post-translational modifications (acetylation, SUMO-lation, ubiquitination, phosphorylation, among others), may be regulated in a cell cycle phase dependent manner. Testing the cell cycle length hypothesis

has proven difficult, as many of the factors known to affect cell cycle kinetics have also been implicated in directly regulating cell fate (Budirahardja and Gonczy 2009; Bilitou and Ohnuma, 2010).

From recent experiments conducted in the Calegari Lab, data indicated that limiting the normal developmental expansion of G1 phase in mouse cortical neuroepithelia inhibited neurogenic divisions (Lange et al., 2009). Experimentally lengthening G1 phase showed opposite effects. Manipulation of G1 phase was achieved by altering the levels of the Cdk4/cyclinD1 complex. At the time of those studies, the only described role of the Cdk4/cyclinD1 active kinase complex was on targets that directly control kinetics of G1 phase. Furthermore, when levels of the kinase complex were manipulated, no measurable effects on cleavage plane orientation or other progenitor cell behaviors were noted. It was therefore concluded that cortical progenitor cells with long G1 phases are biased to undergo neurogenic cell divisions. A similar relationship between cell cycle kinetics and neurogenesis was noted when cyclinD1 was deleted from mouse retinal neuroepithelial cells (Das et al., 2009). However, recent studies have identified an additional role for the Cdk4/cyclinD1 complex in recruiting histone modifying enymes to promoters in S-phase, resulting in either activation or repression of target genes (Aggarwal et al., 2010). This ectopic activation of the Cdk4/cyclinD1 complex was associated with cancers and thought to contribute to neoplastic cell proliferation. Therefore, additional work on other key cell cycle regulators is warranted to further probe the cell cycle length hypothesis. One opportunity may come from recent observations of manipulation to E2F transcription factors. In mice for triple deletion of E2F1-3, retinal progenitor cells showed a 6-fold expansion of G1-phase, as well as the other phases of the cell cycle, resulting in a massively slowed, but not stalled cell cycle period (Chen et al., 2009). As E2Fs 1-3 have not been described to regulate cell-type fates in the nervous system, it would be interesting to know the effect of triple deletion on the proportions of different cell types generated.

Consistent with the observations that cell cycle length influences neurogenesis, though, when slice cultures of spinal cord neuroepithelium were exposed to Fgf, the cell cycle period was accelerated and neurogenesis was inhibited (Wilcock et al., 2007). In contrast, for *Xenopus* retinal neuroepithelia, activation of Hedgehog signaling shortened both G1 and G2 phases and promoted neurogenesis (Locker et al., 2006). As both Fgf and Hedgehog may affect neurogenesis at multiple levels, the causative relationship between cell cycle phase and mode of division is difficult to discern. Assuming that cell cycle kinetics do directly regulate the mode of cell division, apparent differences between species or regions of the CNS may be due to differences in the proliferative potentials of transit amplifying cells. That is, for all neural progenitors, longer cell cycle kinetics may promote differentiative divisions where daughter neuroepithelia either exit the cell cycle or show more restricted fates, as in the case of transit amplifying cells, which remain in the mitotic cycle for a limited time, but are dedicated to generate specific neuronal types.

An essential requirement of the cell cycle length hypothesis is that the duration of the critical phase actually correlates with fate. This phenomenon has been investigated at the population level in the developing mouse cortex. For example, cumulative BrdU labeling has shown that in the developing mouse telencephalic neuroepithelium, the neurogenic progenitor cell population exhibits a longer G1 phase than the non-neurogenic cells (Claregari et al., 2005). Similarly, when comparing progenitor cells from different areas of the primate cortex, it was revealed that the population with higher rates of cell cycle exit exhibited longer average cell cycles and expanded G1 phases (Lukaszewicz et al., 2005). In a recent follow-up study, cumulative BrdU labeling was used in combination with molecular markers to characterize the cell cycle kinetics of distinct types of cortical progenitor cells (Arai et al., 2011). These experiments revealed that Tbr2-positive basal progenitor cells have a significantly longer

G1-phase than Pax6-positive apical progenitors. Furthermore, the neurogenic apical progenitor population could be distinguished from the neurogenic basal progenitor population by the length of S-phase, where on average basal progenitor cells take longer to replicate their DNA.

Ideally, as the cell cycle length hypothesis is explored for other neuronal progenitor types, cell cycle kinetics should be investigated on an individual cell basis and when cell fates can be directly tracked. Along those lines, the full cell cycle period has been measured for individual retinal neuroepithelia. Interestingly, the cell cycle length in those progenitor cells did not correlate with neurogenesis (Baye and Link, 2007; Gomes et al. 2011). However, the length of specific phases of the cell cycle was not investigated in those studies. Potentially, a critical phase may yet be linked with fate, but the kinetics of the key phase is not proportional to the overall cell cycle period. Indeed, in *Drosophila* wing disc progenitor cells, changes in the length of one phase of the cell cycle can be compensated for by changes in another phase such that homeostasis of the cell cycle period is maintained (Reis and Edgar, 2004). The advent of technologies to directly monitor cell cycle phase kinetics in living cells should ultimately resolve this important question with regard to the relationship of cell cycle kinetics and cell fate across multiple types of progenitor cells (Sakaue-Sawano et al., 2008; Sugiyama et al., 2009).

Interkinetic nuclear migration – location matters

Interkinetic nuclear migration (INM) is another interphase cell behavior that has been linked with neurogenesis (Baye and Link, 2008; Taverna and Huttner, 2010). INM is the process by which nuclei of neuroepithelial cells move in concert with progression through the cell cycle. M-phase nuclei are positioned at the apical-most region. G1/S-phase nuclei move to more basal locations. During G2 phase nuclei rapidly move back to the apical surface to re-enter M-phase and undergo cytokinesis again (Fig 2). This phenomenon is conserved from mammals to Cnidaria and evidence suggests that cell cycle progression is required for INM (Baye and Link, 2008; Meyer et al., 2011). Both microtubule motors and actomyosin contraction play roles in nuclear movement, although the relative influences appear to vary between species and/or regions of the CNS (Del Bene et al., 2008; Norden et al., 2009; Tsai et al., 2010; Meyer et al., 2011; Kosodo et al., 2011). In addition to directed nuclear migration, there are also large non-autonomous effects where the movements and jostling of adjacent nuclei affect each other (Norden et al., 2009; Kosodo et al., 2011). The nuclear movements, therefore, are not completely stereotyped and the basal apex of the migration cycle is variable, fitting a normal distribution (Baye and Link, 2007; Norden et al., 2009; Meyer et al., 2011; Kosodo et al., 2011). The first insights to a possible fate-influencing role for INM came from pharmacological manipulations to the cytoskeleton which showed alterations to INM and affected neurogenesis (Murciano et al., 2002; Frade, 2002). Potentially, such disturbances perturbed multiple parameters that affected neurogenesis. Significantly however, within zebrafish retinal neuroepithelial cells, the pattern of INM was found to correlate with neurogenesis (Baye and Link, 2007). Specifically, cells with nuclei that moved more basally during interphase were highly biased to divide neurogenically in the next mitosis. In fact, the farther nuclei moved from the apical surface, the more likely the progenitor cell produced neurons in the next division. This relationship between nuclear position and neurogenesis was found to depend on apicobasal cell polarity and blocking neurogenesis did not change the patterns of nuclear migration (Baye and Link, 2007). In a subsequent study, INM was assessed in a mutant for *dynactin/p150*, an activating subunit of cytoplasmic Dynein (Del Bene et al. 2008). Mutant cell nuclei were found to migrate more basally and neurogenesis was accelerated. Furthermore, computational analysis of imaged mouse retinal neuroepithelial cell behaviors in vitro revealed that one of the parameters that could be used to predict the mode of cell division was nuclear movements (Cohen et al.,

2010). Overall, these results suggest that nuclear position during interphase influences the mode of cell division in the subsequent mitosis by responding to polarized signals within the cell (Fig 6). Experimental perturbation of the developing mouse cortex also supports a role for INM in influencing neurogenesis. For example, in cortical progenitors, if microtubule coupling between the apical centrosome and the nucleus is disrupted, INM is impaired and the progenitor pool is depleted through excessive cell cycle exit. Additional experiments that affected microtubule motors, interactions of motors with the nucleus, or actomyosin contraction also altered neurogenesis in mouse neural progenitors (Ge et al., 2010; Schenk et al., 2009; Tsai et al., 2005; Xie et al., 2007; Zhang et al., 2009; Tsai et al., 2010). However, for the mouse cortex, time-lapse analysis to test whether the depth of nuclear movements correlate with the mode of cell division is lacking.

Intrinsic polarity and localized signaling

How might nuclear position influence the mode of cell division? Because the normal ratios for the different kinds of cell division, as well as cell types, can be replicated in clonal density cell cultures in vitro, the mechanisms that facilitate the relationship of nuclear position and neurogenesis must be intrinsic and/or locally mediated (Jensen and Raff, 1997; Qian et al., 1998; Cayouette et al., 2003; Shen et al., 2006). One signaling pathway supported by experimental observations is the Notch pathway. Multiple studies have shown that high Notch activity in neural progenitor cells favors proliferative cell divisions and cell cycle re-entry. Within the developing retinal neuroepithelium of fish and chick, markers of Notch activity are highly polarized across the apicobasal axis (Murciano et. al., 2002; Del Bene et al., 2008; Cisneros et al., 2008). For instance, time-lapse analysis revealed that nuclei approaching the apical surface showed elevated activity from the Notch target gene promoter *her4* (Del Bene et al., 2008; Yeo et al., 2007). While immunolocalization of the non-processed Notch receptor has been elusive for vertebrates, in *Drosophila* the signaling protein is highly enriched within the apical domain (Genevet et al., 2009; Maitra et al., 2006; Vaccari and Bilder, 2005). Potentially, multiple cues associated with the apical domain may affect neurogenesis by several mechanisms. These include establishing polarized signals that can differentially influence fate through nuclear position during interphase, and by asymmetric inheritance to daughter cells at cytokinesis. Within the basal endfeet, localized signals associated with the basal lamina or with vascular endothelial cells have also been proposed to modulate neurogenesis, although the role of INM in mediating the observed affects is unknown (Shen et al., 2004; Tsuda et al. 2010; Siegenthaler et al., 2009).

Robustness through feedback

So far, we have discussed some of the key cell biological influences of cell fate decisions in the developing nervous system. These features are heterogeneous within neural progenitor populations and elements of these behaviors appear stochastic. As discussed, many cell fate decisions of vertebrate neuroepithelia themselves appear to be selected in part through probabilistic mechanisms. However, while clone size and composition may vary widely across a population of progenitors, the final size and composition of any particular region in the CNS is tightly controlled (Leber et al., 1990; Walsh and Cepko, 1992; Ware et al., 1999; Turner and Cepko, 1987; Turner et al., 1990). This appears to be accomplished in part through feedback among cells within the system. For instance, postmitotic cells can release signals that help control the number of a given cell type that is generated. One of the best examples of this is retinal ganglion cell secretion of Hedgehog, which blocks formation of more ganglion cells in the retina (Wang et al., 2005; Locker et al, 2006). Ablation of retinal ganglion cells decreases the amount of Hedgehog in the environment and encourages increased production of additional retinal ganglion cells (Wang et al., 2005; Wang et al., 2002; Poggi et al., 2005). Another classic example of feedback at the signaling level is with

Notch activity and lateral inhibition (Cau and Blader, 2009; Fortini et al., 2009; Tien et al., 2009). Feedback and homeostatic control also occurs at the cell biological level. During INM – when one cells nucleus travels toward the apical surface, neighboring nuclei are displaced (Norden et al., 2009; Kosodo et al., 2011). In this way, non-autonomous effects from neighboring cells influence how far a given nucleus travels toward the basal surface, which preserves set proportions of nuclei in 'active' signaling zones and thereby may help maintain the correct ratios of each division mode or other cell fate decisions. Similarly, non-autonomous effects may occur at the apical surface to control appropriately proportioned fates. Because of apical junction coupling between cells in the epithelium, when one cell increases the size of its apical membrane, neighboring cells may decrease the size of their apical domain. This could result in changes in signaling activity associated with the apical domain or alter the probability of asymmetric segregation. Thus, as a result of tight packing and polarization, feedback and homeostasis is facilitated and adds predictability to division fates for the neuroepithelial population as a whole.

Parameter interactions

Collectively, experimental observations suggest that multiple cell biological inputs influence neurogenic decisions in progenitor cells (Fig 7). For example, while individual manipulations to spindle orientation, cell cycle kinetics or INM each affect the mode of cell division in multiple types of neuroepithelial cells, the effects are seldom absolute. That is, fate proportions may be shifted but they are rarely, if ever, completely blocked. It is therefore likely that many of the parameters discussed here cooperate to bias fate, perhaps over multiple cell cycles. Parameter interactions may be antagonistic, additive, synergistic, or may require coincidence. They may interact simultaneously such as for cell cycle kinetics and nuclear position, or sequentially such as asymmetric inheritance at cytokinesis and the following interphase influences. As a hypothetical example, a progenitor cell undergoing cytokinesis may distribute its apical domain and basal process unilaterally. The cell that received the apical domain may have also inherited the mother centriole (Fig 3, cell A). The fate determinants associated with these cellular features could initiate heterogeneity between the sibling cells. Further fate biases may then be set by differences in the length of G1 phase and the depth of nuclear migration, all which combine to yield distinct modes of division and perhaps differential cell-type fates in the next mitosis.

Challenges moving forward

Many challenges remain before a more complete picture of vertebrate neurogenesis can emerge. One challenge is addressing the unique qualities of specific neuronal regions or even restricted progenitor cells from a single brain area. Most neuronal progenitors exhibit all of the features discussed here, but important exceptions are exemplified from studies of the developing mammalian cortex (reviewed in Fietz and Huttner, 2010). After the onset of neurogenesis, ventricular zone neuroepithelial progenitors (also known as radial glia) primarily divide asymmetrically and generate additional progenitors and neurons or, later, glia cells (Malatesta et al., 2000; Miyata et al., 2001; Noctor et al., 2001). As development progresses, it is now well established that the progenitors do not simply produce more ventricular zone neuroepithelial progenitors, but instead can generate distinct types of progenitors that can be classified based on their polarity and position. Furthermore, there seems to be some variability in morphology and properties of the various progenitors depending on the species. For example, basal progenitors (also known as intermediate progenitors or subventricular zone progenitors) appear not to be polarized, do not undergo INM, and divide symmetrically to generate either two more progenitors or two neurons (Miyata et al., 2004; Noctor et al., 2004; Haubensak et al., 2004; Englund et al., 2005). In addition, another class of progenitor cells has recently been described for the mammalian

cortex, termed outer subventricular zone progenitors (and also known as outer radial glia) (Reillo et al., 2010; Hansen et al., 2010; Fietz et al., 2010; Wang et al., 2011). In contrast to basal progenitors, outer subventricular zone progenitor cells are polarized and always divide asymmetrically to generate another outer radial glial cell and a neuron. In addition, they lack an apical process and undergo mitotic somal translocation instead of INM. While some of the cellular influences discussed here may still direct cell fate choices in these various progenitors, those cells which lack features such as a defined apical domain or interkinetic nuclear movements, must employ other mechanisms to parse cell fate. Further investigation is required to determine the exact cellular regulatory features and their relative contributions to neurogenic fates for each type of progenitor cell. Overall, the diversity of progenitor types described for the developing mammalian cortex highlights the importance of studying the cell biological inputs on a cell-by-cell basis.

Perhaps paramount among the challenges for developmental neurobiologists is filling in the mechanistic details for how the various cell biological phenomena regulate neurogenesis. For example what precisely are the fate determinants associated with the apical domain or with mother versus daughter centrosomes? From a molecular perspective, how does the length of G1 phase influence cell cycle exit? How do polarized signals transit to the nucleus to regulate cell fates? Do developmental timers exist and how do they modulate intrinsic competency states of progenitor cells? While the contribution of stochastic cell biological inputs and deterministic programs for cell fate can currently be best determined on a per cell basis, deeper descriptive characterizations of whole progenitor lineages and sophisticated cell-cell behaviors are also needed, particularly in vivo. This will require novel imaging strategies and technologies, as well as computational methodologies for identifying complex interactions among fate-influencing parameters. In addition, identification of markers for specific progenitor lineages will be required to assay the influence of cell biological inputs on the decisions that regulate different types of division modes and differentiated cell types.

Another challenge arises from the functional pleiotropy of the molecules and signaling pathways that affect the cellular behaviors implicated in neurogenesis. For example, cytoplasmic dynein can affect nuclear position, spindle orientation, and apicobasal cell polarity, among other processes. Many of the other proteins and signaling pathways that underlie the cellular processes discussed here also exhibit significant pleiotropy. Therefore, techniques for disrupting protein functions in a process-dependent fashion, subcellular manner, or with exquisite temporal precision will be required in many instances to accurately parse cause and effect between cellular features and fate. Such challenges will undoubtedly keep developmental and cellular neurobiologists busy for years to come.

Acknowledgments

We thank the following for funding research related to this topic: The National Institutes of Health for grant R01EY014767 (BAL) and an E. Matilda Ziegler Foundation Award (BAL). We also thank Dr. Kathy Moore for critical reading of drafts for this manuscript, to all members of the Link lab for thoughtful discussions, and finally two anonymous reviewers for their insightful suggestions.

References

Abdelilah-Seyfried S. Claudin-5a in developing zebrafish brain barriers: another brick in the wall. Bioessays. 2010; 32:768–776. [PubMed: 20652895]

Afonso C, Henrique D. PAR3 acts as a molecular organizer to define the apical domain of chick neuroepithelial cells. J Cell Sci. 2006; 119:4293–4304. [PubMed: 17003110]

Aggarwal P, Vaites LP, Kim JK, Mellert H, Gurung B, Nakagawa H, Herlyn M, Hua X, Rustgi AK, McMahon SB, Diehl JA. Nuclear cyclin D1/CDK4 kinase regulates CUL4 expression and triggers

neoplastic growth via activation of the PRMT5 methyltransferase. Cancer Cell. 2010; 18:329–40. [PubMed: 20951943]

Alexandre P, Reugels AM, Barker D, Blanc E, Clarke JD. Neurons derive from the more apical daughter in asymmetric divisions in the zebrafish neural tube. Nat Neurosci. 2010; 13:673–679. [PubMed: 20453852]

Anderson CT, Stearns T. Centriole age underlies asynchronous primary cilium growth in mammalian cells. Curr Biol. 2009; 19:1498–1502. [PubMed: 19682908]

Arai Y, Pulvers JN, Haffner C, Schilling B, Nusslein I, Calegari F, Huttner WB. Neural stem and progenitor cells shorten S-phase on commitment to neuron production. Nat Commun. 2010; 2:154. [PubMed: 21224845]

Balslev Y, Saunders NR, Mollgard K. Ontogenetic development of diffusional restriction to protein at the pial surface of the rat brain: an electron microscopical study. J Neurocytol. 1997; 26:133–148. [PubMed: 9192282]

Baye LM, Link BA. Interkinetic nuclear migration and the selection of neurogenic cell divisions during vertebrate retinogenesis. J Neurosci. 2007; 27:10143–10152. [PubMed: 17881520]

Baye LM, Link BA. Nuclear migration during retinal development. Brain Res. 2008

Belliveau MJ, Cepko CL. Extrinsic and intrinsic factors control the genesis of amacrine and cone cells in the rat retina. Development. 1999; 126:555–566. [PubMed: 9876184]

Betschinger J, Knoblich JA. Dare to be different: asymmetric cell division in Drosophila, C. elegans and vertebrates. Curr Biol. 2004; 14:R674–685. [PubMed: 15324689]

Bettencourt-Dias M, Glover DM. Centrosome biogenesis and function: centrosomics brings new understanding. Nat Rev Mol Cell Biol. 2007; 8:451–463. [PubMed: 17505520]

Bilder D. Epithelial polarity and proliferation control: links from the Drosophila neoplastic tumor suppressors. Genes Dev. 2004; 18:1909–1925. [PubMed: 15314019]

Bilitou A, Ohnuma S. The role of cell cycle in retinal development: cyclin-dependent kinase inhibitors co-ordinate cell-cycle inhibition, cell-fate determination and differentiation in the developing retina. Dev Dyn. 2010; 239:727–736. [PubMed: 20108332]

Budirahardja Y, Gonczy P. Coupling the cell cycle to development. Development. 2009; 136:2861–2872. [PubMed: 19666818]

Bultje RS, Castaneda-Castellanos DR, Jan LY, Jan YN, Kriegstein AR, Shi SH. Mammalian Par3 regulates progenitor cell asymmetric division via notch signaling in the developing neocortex. Neuron. 2009; 63:189–202. [PubMed: 19640478]

Byerly MS, Blackshaw S. Vertebrate retina and hypothalamus development. Wiley Interdiscip Rev Syst Biol Med. 2009; 1:380–389. [PubMed: 20836003]

Calegari F, Huttner WB. An inhibition of cyclin-dependent kinases that lengthens, but does not arrest, neuroepithelial cell cycle induces premature neurogenesis. J Cell Sci. 2003; 116:4947–4955. [PubMed: 14625388]

Calegari F, Haubensak W, Haffner C, Huttner WB. Selective lengthening of the cell cycle in the neurogenic subpopulation of neural progenitor cells during mouse brain development. J Neurosci. 2005; 25:6533–38. [PubMed: 16014714]

Cappello S, Attardo A, Wu X, Iwasato T, Itohara S, Wilsch-Brauninger M, Eilken HM, Rieger MA, Schroeder TT, Huttner WB, Brakebusch C, Gotz M. The Rho-GTPase cdc42 regulates neural progenitor fate at the apical surface. Nat Neurosci. 2006; 9:1099–107. [PubMed: 16892058]

Cau E, Blader P. Notch activity in the nervous system: to switch or not switch? Neural Dev. 2009; 4:36. [PubMed: 19799767]

Caviness VS Jr, Nowakowski RS, Bhide PG. Neocortical neurogenesis: morphogen gradients and beyond. Trends in Neurosci. 2009; 32:443–50.

Cayouette M, Raff M. The orientation of cell division influences cell-fate choice in the developing mammalian retina. Development. 2003; 130:2329–39. [PubMed: 12702648]

Cayouette M, Barres BA, Raff M. Importance of intrinsic mechanisms in cell fate decisions in the developing rat retina. Neuron. 2003; 40:897–904. [PubMed: 14659089]

Cayouette M, Poggi L, Harris WA. Lineage in the vertebrate retina. Trends Neurosci. 2006; 29:563–570. [PubMed: 16920202]

Cayouette M, Whitmore A, Jeffery G, Raff M. Asymmetric segregation of Numb in retinal development and the influence of the pigmented epithelium. J Neurosci. 2001; 21:5643–5651. [PubMed: 11466435]

Chen D, Pacal M, Wenzel P, Knoepfler PS, Leone G, Bremner R. Division and apoptosis of E2f-deficient retinal progenitors. Nature. 2009; 462:925–929. [PubMed: 20016601]

Chenn A, McConnell SK. Cleavage orientation and the asymmetric inheritance of Notch1 immunoreactivity in mammalian neurogenesis. Cell. 1995; 82:631–641. [PubMed: 7664342]

Chenn A, Zhang YA, Chang BT, McConnell SK. Intrinsic polarity of mammalian neuroepithelial cells. Mol Cell Neurosci. 1998; 11:183–193. [PubMed: 9675050]

Cisneros E, Latasa MJ, Garcia-Flores M, Frade JM. Instability of Notch1 and Delta1 mRNAs and reduced Notch activity in vertebrate neuroepithelial cells undergoing S-phase. Mol Cell Neurosci. 2008; 37:820–831. [PubMed: 18289870]

Cohen AR, Gomes FL, Roysam B, Cayouette M. Computational prediction of neural progenitor cell fates. Nat Methods. 2010; 7:213–218. [PubMed: 20139969]

Conduit PT, Raff JW. Cnn dynamics drive centrosome size asymmetry to ensure daughter centriole retention in Drosophila neuroblasts. Curr Biol. 2010; 20:2187–2192. [PubMed: 21145745]

Costa MR, Wen G, Lepier A, Schroeder T, Gotz M. Par-complex proteins promote proliferative progenitor divisions in the developing mouse cerebral cortex. Development. 2008; 135:11–22. [PubMed: 18032449]

D'Arca D, Zhao X, Xu W, Ramirez-Martinez NC, Iavarone A, Lasorella A. Huwe1 ubiquitin ligase is essential to synchronize neuronal and glial differentiation in the developing cerebellum. Proc Natl Acad Sci U S A. 2010; 107:5875–5880. [PubMed: 20231446]

Das G, Choi Y, Sicinski P, Levine EM. Cyclin D1 fine-tunes the neurogenic output of embryonic retinal progenitor cells. Neural Dev. 2009; 4:15. [PubMed: 19416500]

Das T, Payer B, Cayouette M, Harris WA. In vivo time-lapse imaging of cell divisions during neurogenesis in the developing zebrafish retina. Neuron. 2003; 37:597–609. [PubMed: 12597858]

Dasen JS, Jessell TM. Hox networks and the origins of motor neuron diversity. Curr Top Dev Biol. 2009; 88:169–200. [PubMed: 19651305]

Del Bene F, Wehman AM, Link BA, Baier H. Regulation of neurogenesis by interkinetic nuclear migration through an apical-basal notch gradient. Cell. 2008; 134:1055–1065. [PubMed: 18805097]

Delattre M, Gonczy P. The arithmetic of centrosome biogenesis. J Cell Sci. 2004; 117:1619–1630. [PubMed: 15075224]

Dow LE, Humbert PO. Polarity regulators and the control of epithelial architecture, cell migration, and tumorigenesis. Int Rev Cytol. 2007; 262:253–302. [PubMed: 17631191]

Dubreuil V, Marzesco AM, Corbeil D, Huttner WB, Wilsch-Brauninger M. Midbody and primary cilium of neural progenitors release extracellular membrane particles enriched in the stem cell marker prominin-1. J Cell Biol. 2007; 176:483–495. [PubMed: 17283184]

Durand B, Raff M. A cell-intrinsic timer that operates during oligodendrocyte development. Bioessays. 2000; 22:64–71. [PubMed: 10649292]

Dyer MA. Regulation of proliferation, cell fate specification and differentiation by the homeodomain proteins Prox1, Six3, and Chx10 in the developing retina. Cell Cycle. 2003; 2:350–357. [PubMed: 12851489]

Englund C, Fink A, Lau C, Pham D, Daza RAM, Bulfone A, Kowalczyk T, Hevner RF. Pax6, Tbr2, and Tbr1 are expressed sequentially by radial glia, intermediate progenitor cells, and postmitotic neurons in developing neocortex. J Neurosci. 2005; 25:247–51. [PubMed: 15634788]

Farkas LM, Huttner WB. The cell biology of neural stem and progenitor cells and its significance for their proliferation versus differentiation during mammalian brain development. Curr Opin Cell Biol. 2008; 20:707–715. [PubMed: 18930817]

Fietz SA, Huttner WB. Cortical progenitor expansion, self-renewal and neurogenesis-a polarized perspective. Curr Opin Neurobiol. 2010; 21:23–35. [PubMed: 21036598]

Fietz SA, Kelava I, Vogt J, Wilsch-Brauninger M, Stenzel D, Fish J, Corbeil D, Riehn A, Distler W, Nitsch R, Huttner W. OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. Nature Neurosci. 2010; 13:690–699. [PubMed: 20436478]

Fortini ME, Bilder D. Endocytic regulation of Notch signaling. Curr Opin Genet Dev. 2009; 19:323–328. [PubMed: 19447603]

Frade JM. Interkinetic nuclear movement in the vertebrate neuroepithelium: encounters with an old acquaintance. Prog Brain Res. 2002; 136:67–71. [PubMed: 12143404]

Fuentealba LC, Eivers E, Geissert D, Taelman V, De Robertis EM. Asymmetric mitosis: Unequal segregation of proteins destined for degradation. Proc Natl Acad Sci U S A. 2008; 105:7732–7737. [PubMed: 18511557]

Gauthier-Fisher A, Lin DC, Greeve M, Kaplan DR, Rottapel R, Miller FD. Lfc and Tctex-1 regulate genesis of neurons from cortical precursor cells. Nat Neurosci. 2009; 12:735–46. [PubMed: 19448628]

Ge X, Frank CL, Calderon de Anda F, Tsai LH. Hook3 interacts with PCM1 to regulate pericentriolar material assembly and the timing of neurogenesis. Neuron. 2010; 65:191–203. [PubMed: 20152126]

Genevet A, Polesello C, Blight K, Robertson F, Collinson LM, Pichaud F, Tapon N. The Hippo pathway regulates apical-domain size independently of its growth-control function. J Cell Sci. 2009; 122:2360–2370. [PubMed: 19531586]

Goetz SC, Anderson KV. The primary cilium: a signalling centre during vertebrate development. Nat Rev Genet. 2010; 11:331–344. [PubMed: 20395968]

Gomes FL, Zhang G, Carbonell F, Correa JA, Harris WA, Simons BD, Cayoutte M. Reconstruction of rat retinal progenitor cell lineages in vitro reveals a surprising degree of stochasticity in cell fate decisions. Development. 2011; 138:227–35. [PubMed: 21148186]

Gonczy P. Mechanisms of asymmetric cell division: flies and worms pave the way. Nat Rev Mol Cell Biol. 2008; 9:355–366. [PubMed: 18431399]

Gotz M, Huttner WB. The cell biology of neurogenesis. Nat Rev Mol Cell Biol. 2005; 6:777–788. [PubMed: 16314867]

Han YG, Alvarez-Buylla A. Role of primary cilia in brain development and cancer. Curr Opin Neurobiol. 2010; 20:58–67. [PubMed: 20080044]

Hansen D, Lui J, Parker P, Kriegstein A. Neurogenic radial glia in the outer subventricular zone of human neocortex. Nature. 2010; 464:554–561. [PubMed: 20154730]

Haubensak W, Attardo A, Denk W, Huttner WB. Neurons arise in the basal neuroepithelium of the early mammalian telencephalon: a major site of neurogenesis. Proc Natl Acad Sci U S A. 2004; 101:3196–3201. [PubMed: 14963232]

Humbert PO, Grzeschik NA, Brumby AM, Galea R, Elsum I, Richardson HE. Control of tumourigenesis by the Scribble/Dlg/Lgl polarity module. Oncogene. 2008; 27:6888–6907. [PubMed: 19029932]

Imai F, Hirai S, Akimoto K, Koyama H, Miyata T, Ogawa M, Noguchi S, Sasaoka T, Noda T, Ohno S. Inactivation of aPKC{lambda} results in the loss of adherens junctions in neuroepithelial cells without affecting neurogenesis in mouse neocortex. Development. 2006; 133:1735–1744. [PubMed: 16571631]

Insolera R, Chen S, Shi SH. Par proteins and neuronal polarity. Dev Neurobiol. 2010

Jacob J, Maurange C, Gould AP. Temporal control of neuronal diversity: common regulatory principles in insects and vertebrates? Development. 2008; 135:3481–3489. [PubMed: 18849528]

Januschke J, Gonzalez C. The interphase microtubule aster is a determinant of asymmetric division orientation in Drosophila neuroblasts. J Cell Biol. 2010; 188:693–706. [PubMed: 20194641]

Jensen AM, Raff MC. Continuous observation of multipotential retinal progenitors cells in clonal density culture. Developmental Biology. 1997; 188:267–279. [PubMed: 9268574]

Jukam D, Desplan C. Binary fate decisions in differentiating neurons. Current Opinion in Neurobiology. 2010; 20:6–13. [PubMed: 20022236]

Kao CF, Lee T. Birth time/order-dependent neuron type specification. Curr Opin Neurobiol. 2010; 20:14–21. [PubMed: 19944594]

Katayama K, Melendez J, Baumann JM, Leslie JR, Chauhan BK, Nemkul N, Lang RA, Kuan CY, Zheng Y, Yoshida Y. Loss of RhoA in neural progenitor cells causes the disruption of adherens junctions and hyperproliferation. Proc Natl Acad Sci U S A. 2011; 108:7607–7612. [PubMed: 21502507]

Kim S, Lehtinen MK, Sessa A, Zappaterra MW, Cho SH, Gonzalez D, Boggan B, Austin CA, Wijnholds J, Gambello MJ, Malicki J, LaMantia AS, Broccoli V, Walsh CA. The apical complex couples cell fate and cell survival to cerebral cortical development. Neuron. 2010; 66:69–84. [PubMed: 20399730]

Klezovitch O, Fernandez TE, Tapscott SJ, Vasioukhin V. Loss of cell polarity causes severe brain dysplasia in Lgl1 knockout mice. Genes Dev. 2004; 18:559–571. [PubMed: 15037549]

Knoblich JA. Mechanisms of asymmetric stem cell division. Cell. 2008; 132:583–597. [PubMed: 18295577]

Konno D, Shioi G, Shitamukai A, Mori A, Kiyonari H, Miyata T, Matsuzaki F. Neuroepithelial progenitors undergo LGN-dependent planar divisions to maintain self-renewability during mammalian neurogenesis. Nat Cell Biol. 2008; 10:93–101. [PubMed: 18084280]

Kosodo Y, Roper K, Haubensak W, Marzesco AM, Corbeil D, Huttner WB. Asymmetric distribution of the apical plasma membrane during neurogenic divisions of mammalian neuroepithelial cells. Embo J. 2004; 23:2314–2324. [PubMed: 15141162]

Kosodo Y, Suetsugu T, Suda M, Mimori-Kiyosue Y, Toida K, Baba SA, Kimura A, Matsuzaki F. Regulation of interkinetic nuclear migration by cell cycle-coupled active and passive mechanisms in the developing brain. EMBO. 2011:1–15.

Lange C, Calegari F. Cdks and cyclins link G(1) length and differentiation of embryonic, neural and hematopoietic stem cells. Cell Cycle. 2010; 9

Lange C, Huttner WB, Calegari F. Cdk4/cyclinD1 overexpression in neural stem cells shortens G1, delays neurogenesis, and promotes the generation and expansion of basal progenitors. Cell Stem Cell. 2009; 5:320–331. [PubMed: 19733543]

Leber SM, Breedlove SM, Sanes JR. Lineage, arrangement, and death of clonally related motoneurons in the chick spinal cord. J Neurosci. 1990; 10:2451–62. [PubMed: 2376781]

Li M, Sakaguchi DS. Expression patterns of focal adhesion associated proteins in the developing retina. Dev Dyn. 2002; 225:544–553. [PubMed: 12454930]

Lien WH, Klezovitch O, Fernandez TE, Delrow J, Vasioukhin V. alphaE-catenin controls cerebral cortical size by regulating the hedgehog signaling pathway. Science. 2006; 311:1609–1612. [PubMed: 16543460]

Locker M, Agathocleous M, Amato MA, Parain K, Harris WA, Perron M. Hedgehog signaling and the retina: insights into the mechanisms controlling the proliferative properties of neural precursors. Genes Dev. 2006; 20:3036–3048. [PubMed: 17079690]

Lukaszewicz A, Savatier P, Cortay V, Giroud P, Huissoud C, Berland M, Kennedy H, Dehay C. G1 phase regulation, area-specific cell cycle control, and cytoarchitectonics in the primate cortex. Neuron. 2005; 47:353–364. [PubMed: 16055060]

Maitra S, Kulikauskas RM, Gavilan H, Fehon RG. The tumor suppressors Merlin and Expanded function cooperatively to modulate receptor endocytosis and signaling. Curr Biol. 2006; 16:702–709. [PubMed: 16581517]

Malatesta P, Hartfuss E, Gotz M. Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. Development. 2000; 127:5253–63. [PubMed: 11076748]

Marthiens V, ffrench-Constant C. Adherens junction domains are split by asymmetric division of embryonic neural stem cells. EMBO Rep. 2009; 10:515–520. [PubMed: 19373255]

Martinez-Morales JR, Rembold M, Greger K, Simpson JC, Brown KE, Quiring R, Pepperkok R, Martin-Bermudo MD, Himmelbauer H, Wittbrodt J. ojoplano-mediated basal constriction is essential for optic cup morphogenesis. Development. 2009; 136:2165–2175. [PubMed: 19502481]

Matsuzaki F. Asymmetric division of Drosophila neural stem cells: a basis for neural diversity. Curr Opin Neurobiol. 2000; 10:38–44. [PubMed: 10679433]

McConnell SK, Kaznowski CE. Cell cycle dependence of laminar determination in developing neocortex. Science. 1991; 254:282–285. [PubMed: 1925583]

Meyer EJ, Ikmi A, Gibson MC. Interkinetic Nuclear Migration Is a Broadly Conserved Feature of Cell Division in Pseudostratified Epithelia. Curr Biol. 2011

Mione MC, Cavanagh JF, Harris B, Parnavelas JG. Cell fate specification and symmetrical/asymmetrical divisions in the developing cerebral cortex. J Neurosci. 1997; 17:2018–29. [PubMed: 9045730]

Miyata T, Kawaguchi A, Okano H, Ogawa M. Asymmetric inheritance of radial glial fibers by cortical neurons. Neuron. 2001; 31:727–741. [PubMed: 11567613]

Miyata T, Kawaguch A, Saito K, Kawano M, Muto T, Ogawa M. Asymmetric production of surface-dividing and non-surface-dividing cortical progenitor cells. Development. 2004; 131:3133–45. [PubMed: 15175243]

Morin X, Jaouen F, Durbec P. Control of planar divisions by the G-protein regulator LGN maintains progenitors in the chick neuroepithelium. Nat Neurosci. 2007; 10:1440–48. [PubMed: 17934458]

Murciano A, Zamora J, Lopez-Sanchez J, Frade JM. Interkinetic nuclear movement may provide spatial clues to the regulation of neurogenesis. Mol Cell Neurosci. 2002; 21:285–300. [PubMed: 12401448]

Nishimura T, Kaibuchi K. Numb controls integrin endocytosis for directional cell migration with aPKC and PAR-3. Dev Cell. 2007; 13:15–28. [PubMed: 17609107]

Nishizawa Y, Imafuku H, Saito K, Kanda R, Kimura M, Minobe S, Miyazaki F, Kawakatsu S, Masaoka M, Ogawa M, Miyata T. Survey of the morphogenetic dynamics of the ventricular surface of the developing mouse neocortex. Dev Dyn. 2007; 236:3061–3070. [PubMed: 17948308]

Noctor SC, Flint AC, Weissman TA, Dammerman RS, Kriegstein AR. Neurons derived from radial glial cells establish radial units in neocortex. Nature. 2001; 409:714–20. [PubMed: 11217860]

Noctor SC, Martínez-Cerdeño V, Ivic L, Kriegstein AR. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. Nat Neurosci. 2004; 7:136–44. [PubMed: 14703572]

Noctor SC, Martínez-Cerdeño V, Kriegstein AR. Distinct behaviors of neural stem and progenitor cells underlie cortical neurogenesis. J Comp Neurol. 2008; 508:28–44. [PubMed: 18288691]

Norden C, Young S, Link BA, Harris WA. Actomyosin is the main driver of interkinetic nuclear migration in the retina. Cell. 2009; 138:1195–1208. [PubMed: 19766571]

O'Leary DD, Chou SJ, Sahara S. Area patterning of the mammalian cortex. Neuron. 2007; 56:252–269. [PubMed: 17964244]

Oates AC. What's all the noise about developmental stochasticity? Development. 2011; 138:601–607. [PubMed: 21266404]

Ossipova O, Ezan J, Sokol SY. PAR-1 phosphorylates Mind bomb to promote vertebrate neurogenesis. Dev Cell. 2009; 17:222–233. [PubMed: 19686683]

Pilaz LJ, Patti D, Marcy G, Ollier E, Pfister S, Douglas RJ, Betizeau M, Gautier E, Cortay V, Doerflinger N, Kennedy H, Dehay C. Forced G1-phase reduction alters mode of division, neuron number, and laminar phenotype in the cerebral cortex. Proc Natl Acad Sci. 2009; 106:21924–29. [PubMed: 19959663]

Poggi L, Vitorino M, Masai I, Harris WA. Influences on neural lineage and mode of division in the zebrafish retina in vivo. J Cell Biol. 2005; 171:991–999. [PubMed: 16365165]

Qian X, Goderie SK, Shen Q, Stern JH, Temple S. Intrinsic programs of patterned cell lineages in isolated vertebrate CNS ventricular zone cells. Development. 1998; 125:3143–3152. [PubMed: 9671587]

Rasin MR, Gazula VR, Breunig JJ, Kwan KY, Johnson MB, Liu-Chen S, Li HS, Jan LY, Jan YN, Rakic P, Sestan N. Numb and Numbl are required for maintenance of cadherin-based adhesion and polarity of neural progenitors. Nat Neurosci. 2007; 10:819–827. [PubMed: 17589506]

Reillo I, de Juan Romero C, Garcia-Cabezas M, Borrell V. A role for intermediate radial glia in the tangential expansion of the mammalian cerebral cortex. Cereb Cortex. 2010 In press.

Reis T, Edgar BA. Negative regulation of dE2F1 by cyclin-dependent kinases controls cell cycle timing. Cell. 2004; 117:253–264. [PubMed: 15084262]

Roberts RK, Appel B. Apical polarity protein PrkCi is necessary for maintenance of spinal cord precursors in zebrafish. Dev Dyn. 2009; 238:1638–1648. [PubMed: 19449304]

Rusan NM, Peifer M. A role for a novel centrosome cycle in asymmetric cell division. J Cell Biol. 2007; 177:13–20. [PubMed: 17403931]

Sakaue-Sawano A, Kurokawa H, Morimura T, Hanyu A, Hama H, Osawa H, Kashiwagi S, Fukami K, Miyata T, Miyoshi H, Imamura T, Ogawa M, Masai H, Miyawaki A. Visualizing spatiotemporal dynamics of multicellular cell-cycle progression. Cell. 2008; 132:487–498. [PubMed: 18267078]

Salomoni P, Calegari F. Cell cycle control of mammalian neural stem cells: putting a speed limit on G1. Trends Cell Biol. 2010; 20:233–243. [PubMed: 20153966]

Sawa H. Specification of neurons through asymmetric cell divisions. Curr Opin Neurobiol. 2010; 20:44–49. [PubMed: 19896361]

Schenk J, Wilsch-Brauninger M, Calegari F, Huttner WB. Myosin II is required for interkinetic nuclear migration of neural progenitors. Proc Natl Acad Sci U S A. 2009; 106:16487–16492. [PubMed: 19805325]

Schulte D, Bumsted-O'Brien KM. Molecular mechanisms of vertebrate retina development: implications for ganglion cell and photoreceptor patterning. Brain Res. 2008; 1192:151–164. [PubMed: 17553468]

Schwamborn JC, Berezikov E, Knoblich JA. The TRIM-NHL protein TRIM32 activates microRNAs and prevents self-renewal in mouse neural progenitors. Cell. 2009; 136:913–925. [PubMed: 19269368]

Seeley ES, Nachury MV. The perennial organelle: assembly and disassembly of the primary cilium. J Cell Sci. 2010; 123:511–518. [PubMed: 20144999]

Shen Q, Goderie SK, Jin L, Karanth N, Sun Y, Abramova N, Vincent P, Pumiglia K, Temple S. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. Science. 2004; 304:1338–1340. [PubMed: 15060285]

Shen Q, Wang Y, Dimos JT, Fasano CA, Phoenix TN, Lemischka IR, Ivanova NB, Stifani S, Morrisey EE, Temple S. The timing of cortical neurogenesis is encoded within lineages of individual progenitor cells. Nat Neurosci. 2006; 9:743–751. [PubMed: 16680166]

Siegenthaler JA, Ashique AM, Zarbalis K, Patterson KP, Hecht JH, Kane MA, Folias AE, Choe Y, May SR, Kume T, Napoli JL, Peterson AS, Pleasure SJ. Retinoic acid from the meninges regulates cortical neuron generation. Cell. 2009; 139:597–609. [PubMed: 19879845]

Silva AO, Ercole CE, McLoon SC. Plane of cell cleavage and numb distribution during cell division relative to cell differentiation in the developing retina. J Neurosci. 2002; 22:7518–7525. [PubMed: 12196575]

Slater JL, Landman KA, Hughes BD, Shen Q, Temple S. Cell lineage tree models of neurogenesis. J Theor Biol. 2009; 256:164–179. [PubMed: 18977364]

Smith CA, Lau KM, Rahmani Z, Dho SE, Brothers G, She YM, Berry DM, Bonneil E, Thibault P, Schweisguth F, Le Borgne R, McGlade CJ. aPKC-mediated phosphorylation regulates asymmetric membrane localization of the cell fate determinant Numb. Embo J. 2007; 26:468–480. [PubMed: 17203073]

Sottorcornola R, Royer C, Vives V, Tordella L, Zhong S, Wang Y, Ratnayaka I, Shipman M, Cheung A, Gaston-Massuet C, Ferretti P, Molnar Z, Lu X. ASPP2 binds Par-3 and controls the polarity and proliferation of neural progenitors during CNS development. Dev Cell. 2010; 19:126–37. [PubMed: 20619750]

Stegmuller J, Bonni A. Destroy to create: E3 ubiquitin ligases in neurogenesis. F1000 Biol Rep. 2010; 2

Sugiyama M, Sakaue-Sawano A, Iimura T, Fukami K, Kitaguchi T, Kawakami K, Okamoto H, Higashijima S, Miyawaki A. Illuminating cell-cycle progression in the developing zebrafish embryo. Proc Natl Acad Sci U S A. 2009; 106:20812–20817. [PubMed: 19923430]

Sun Y, Goderie SK, Temple S. Asymmetric distribution of EGFR receptor during mitosis generates diverse CNS progenitor cells. Neuron. 2005; 45:873–886. [PubMed: 15797549]

Tanentzapf G, Tepass U. Interactions between the crumbs, lethal giant larvae and bazooka pathways in epithelial polarization. Nat Cell Biol. 2003; 5:46–52. [PubMed: 12510193]

Taverna E, Huttner WB. Neural progenitor nuclei IN motion. Neuron. 2010; 67:906–914. [PubMed: 20869589]

Tien AC, Rajan A, Bellen HJ. A Notch updated. J Cell Biol. 2009; 184:621–629. [PubMed: 19255248]

Tsai JW, Chen Y, Kriegstein AR, Vallee RB. LIS1 RNA interference blocks neural stem cell division, morphogenesis, and motility at multiple stages. J Cell Biol. 2005; 170:935–945. [PubMed: 16144905]

Tsai JW, Lian WN, Kemal S, Kriegstein AR, Vallee RB. Kinesin 3 and cytoplasmic dynein mediate interkinetic nuclear migration in neural stem cells. Nat Neurosci. 2010

Tsuda S, Kitagawa T, Takashima S, Asakawa S, Shimizu N, Mitani H, Shima A, Tsutsumi M, Hori H, Naruse K, Ishikawa Y, Takeda H. FAK-mediated extracellular signals are essential for interkinetic nuclear migration and planar divisions in the neuroepithelium. J Cell Sci. 2010; 123:484–496. [PubMed: 20067997]

Tuoc TC, Stoykova A. Trim11 modulates the function of neurogenic transcription factor Pax6 through ubiquitin-proteosome system. Genes Dev. 2008; 22:1972–1986. [PubMed: 18628401]

Tuoc TC, Stoykova A. Roles of the ubiquitin-proteosome system in neurogenesis. Cell Cycle. 2010; 9:3174–3180. [PubMed: 20852390]

Turner DL, Cepko CL. A common progenitor for neurons and glia persists in the rat retina late in development. Nature. 1987; 328:131–36. [PubMed: 3600789]

Turner DL, Snyder EY, Cepko CL. Lineage-independent determination of cell type in the embryonic mouse retina. Neuron. 1990; 6:833–45. [PubMed: 2163263]

Ueno M, Katayama K, Yamauchi H, Nakayama H, Doi K. Cell cycle progression is required for nuclear migration of neural progenitor cells. Brain Res. 2006; 1088:57–67. [PubMed: 16650835]

Vaccari T, Bilder D. The Drosophila tumor suppressor vps25 prevents nonautonomous overproliferation by regulating notch trafficking. Dev Cell. 2005; 9:687–698. [PubMed: 16256743]

Walsh C, Cepko CL. Cell lineage and cell migration in the developing cerebral cortex. Experientia. 1990; 46:940–7. [PubMed: 2209803]

Walsh C, Cepko CL. Widespread dispersion of neuronal clones across functional regions of the cerebral cortex. Science. 1992; 255:434–40. [PubMed: 1734520]

Wang X, Tsai JW, Imai JH, Lian WN, Vallee RB, Shi SH. Asymmetric centrosome inheritance maintains neural progenitors in the neocortex. Nature. 2009; 461:947–955. [PubMed: 19829375]

Wang Y, Dakubo GD, Thurig S, Mazerolle CJ, Wallace VA. Retinal ganglion cell-derived sonic hedgehog locally controls proliferation and the timing of RGC development in the embryonic mouse retina. Development. 2005; 132:5103–5113. [PubMed: 16236765]

Wang YP, Dakubo G, Howley P, Campsall KD, Mazarolle CJ, Shiga SA, Lewis PM, McMahon AP, Wallace VA. Development of normal retinal organization depends on Sonic hedgehog signaling from ganglion cells. Nat Neurosci. 2002; 5:831–832. [PubMed: 12195432]

Wang X, Tsai JW, LaMonica B, Kriegstein AR. A new subtype of progenitor cell in the mouse embryonic neocortex. Nature Neurosci. 2011; 14:555–62. [PubMed: 21478886]

Ware ML, Tavozoie SF, Reid CB, Walsh CA. Coexistence of widespread clones and large radial clones in early embryonic ferret cortex. Cereb Cortex. 1999; 6:636–45. [PubMed: 10498282]

Westbrook TF, Hu G, Ang XL, Mulligan P, Pavlova NN, Liang A, Leng Y, Maehr R, Shi Y, Harper JW, Elledge SJ. SCFbeta-TRCP controls oncogenic transformation and neural differentiation through REST degradation. Nature. 2008; 452:370–374. [PubMed: 18354483]

Wilcock AC, Swedlow JR, Storey KG. Mitotic spindle orientation distinguishes stem cell and terminal modes of neuron production in the early spinal cord. Development. 2007; 134:1943–1954. [PubMed: 17470968]

Wilson SW, Houart C. Early steps in the development of the forebrain. Dev Cell. 2004; 6:167–181. [PubMed: 14960272]

Wodarz A. Molecular control of cell polarity and asymmetric cell division in Drosophila neuroblasts. Curr Opin Cell Biol. 2005; 17:475–481. [PubMed: 16099639]

Xie Z, Moy LY, Sanada K, Zhou Y, Buchman JJ, Tsai LH. Cep120 and TACCs control interkinetic nuclear migration and the neural progenitor pool. Neuron. 2007; 56:79–93. [PubMed: 17920017]

Yamaguchi M, Imai F, Tonou-Fujimori N, Masai I. Mutations in N-cadherin and a Stardust homolog, Nagie oko, affect cell-cycle exit in zebrafish retina. Mech Dev. 2010; 127:247–264. [PubMed: 20362667]

Yamanaka T, Ohno S. Role of Lgl/Dlg/Scribble in the regulation of epithelial junction, polarity and growth. Front Biosci. 2008; 13:6693–6707. [PubMed: 18508688]

Yamashita YM, Fuller MT. Asymmetric centrosome behavior and the mechanisms of stem cell division. J Cell Biol. 2008; 180:261–266. [PubMed: 18209101]

Yamashita YM, Mahowald AP, Perlin JR, Fuller MT. Asymmetric inheritance of mother versus daughter centrosome in stem cell division. Science. 2007; 315:518–521. [PubMed: 17255513]

Yeo SY, Kim M, Kim HS, Huh TL, Chitnis AB. Fluorescent protein expression driven by her4 regulatory elements reveals the spatiotemporal pattern of Notch signaling in the nervous system of zebrafish embryos. Dev Biol. 2007; 301:555–567. [PubMed: 17134690]

Zernicka-Goetz M, Huang S. Stochasticity vs. determinism in development: a false dichotomy? Nature. 2010; 11:743–4.

Zhang X, Lei K, Yuan X, Wu X, Zhuang Y, Xu T, Xu R, Han M. SUN1/2 and Syne/Nesprin-1/2 complexes connect centrosome to the nucleus during neurogenesis and neuronal migration in mice. Neuron. 2009; 64:173–187. [PubMed: 19874786]

Zhao X, DA D, Lim WK, Brahmachary M, Carro MS, Ludwig T, Cardo CC, Guillemot F, Aldape K, Califano A, Iavarone A, Lasorella A. The N-Myc-DLL3 cascade is suppressed by the ubiquitin ligase Huwe1 to inhibit proliferation and promote neurogenesis in the developing brain. Dev Cell. 2009; 17:210–221. [PubMed: 19686682]

Zhao X, Heng JI, Guardavaccaro D, Jiang R, Pagano M, Guillemot F, Iavarone A, Lasorella A. The HECT-domain ubiquitin ligase Huwe1 controls neural differentiation and proliferation by destabilizing the N-Myc oncoprotein. Nat Cell Biol. 2008; 10:643–653. [PubMed: 18488021]

Zhong W, Chia W. Neurogenesis and asymmetric cell division. Curr Opin Neurobiol. 2008; 18:4–11. [PubMed: 18513950]

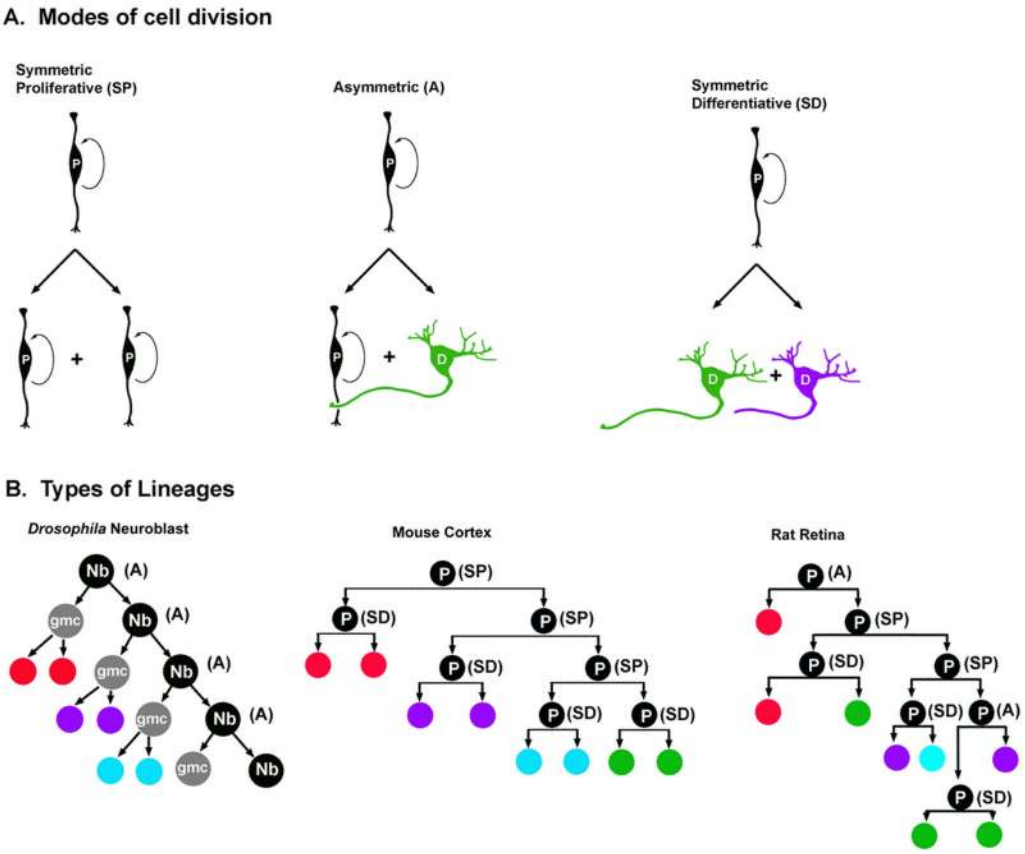

Figure 1.

(A) Modes of cell division for proliferative neuroepithelial cells (*P*). Note that differentiated cells (*D*) may not be of the same differentiated type (purple vs. green). For example differentiated cells may be transit amplifying cells, neurons, glia or different classes for each of these cell types. **(B)** Examples of neuronal lineages. Lineage modeled from *Drosophila* neuroblast precursors (left); Lineage modeled from cortical progenitors (center); Lineage modeled from retinal neuroepithelia (right). The classification for the mode of cell division is shown in parenthesis. Colors represent distinct types of differentiated cells.

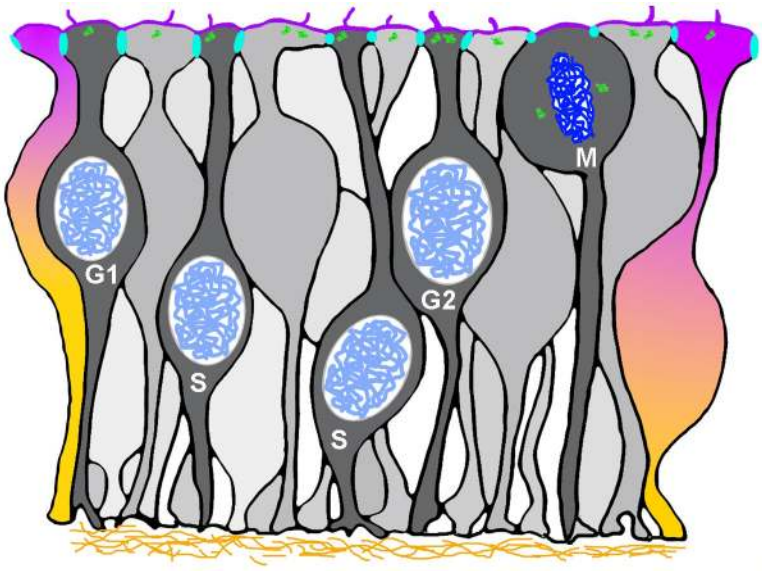

Figure 2.
Schematic of polarized, proliferative neuroepithelium. A dark grey cell progresses through interkinetic nuclear migration, in which the nuclei (blue) oscillates with the cell cycle. Apical features of neuroepithelial cells that are modeled include junctional complexes (aqua blue), primary cilia with apical membrane (purple), and centrosomes (green). The basal lamina (orange) is shown at the bottom. The colored cells on each end represent the intrinsic apicobasal gradients of fate-influencing signals.

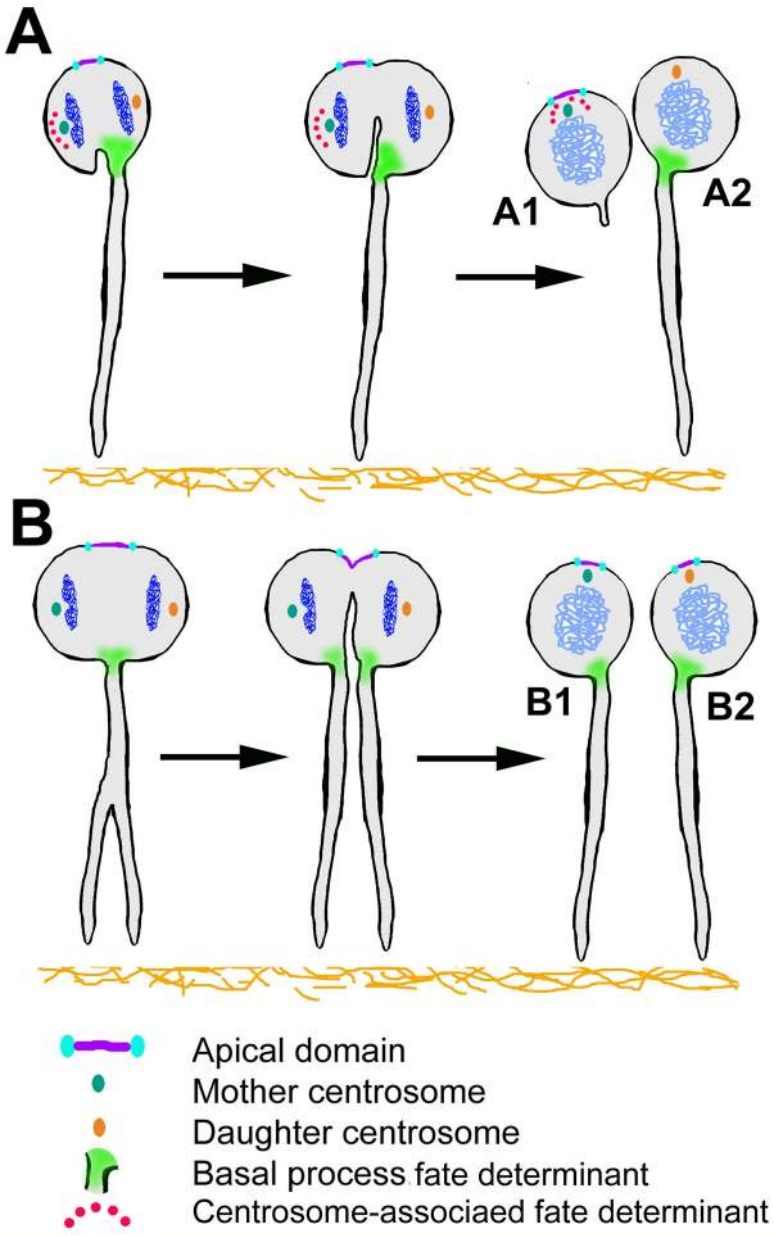

Figure 3.

Examples of asymmetry in cell division. These schematics model segregation of cellular features in mitotic neuroepithelial cells from anaphase (left) through cytokinesis (right) (A) Cell A asymmetrically divides the apical domain (inherited by cell A1) and the basal process (inherited by cell A2). Cell A1 also inherited the mother centrosome (dark green oval) and the associated fate determinants (red dots) (B) Cell B show a more symmetric division in which the apical domain and basal process are divided equally between the B1 and B2 progeny cells. In this example, the only asymmetry is in the division of the mother and daughter centrioles. Note, however, for Cell B the mother centrosomes do not associate with fate determinants as in Cell A (red dots). Cell B also shows a larger apical domain, which has been hypothesize to be more frequently divided equally between the progeny cells. In each cell, fate-influencing proteins are shown associated with the basal process (light green).

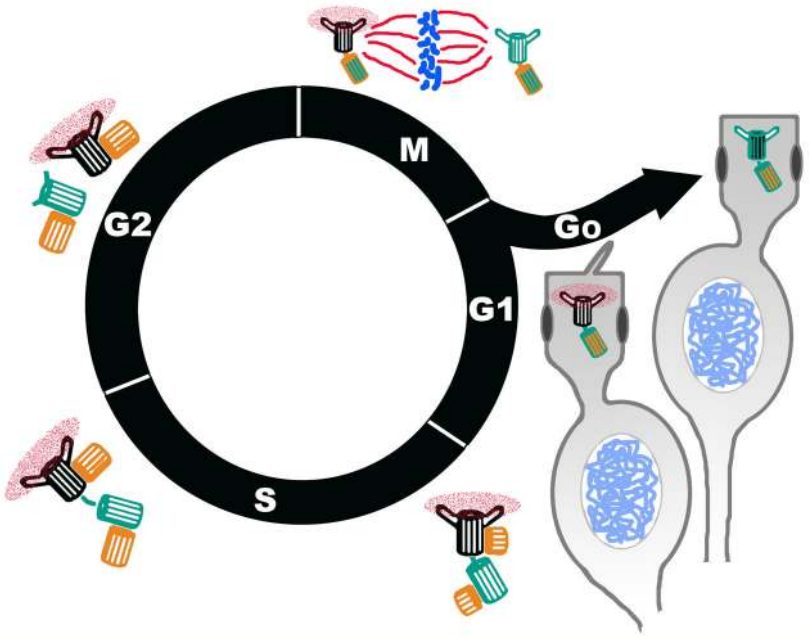

Figure 4.
Schematic of centrosome cycle. The “mother” centrosome, containing the oldest centriole (black with satellite appendages) is shown at M-phase on the left. Note the pericentriolar material and putative fate-influencing factors (red cloud). The younger, “daughter ” centrosome is shown in green. Note satellite appendages do not form until late in the cell cycle. Centrioles undergoing synthesis during duplication at S-phase are shown in orange. At cytokinesis, one cell inherits the mother centrosome (left), while the other cell inherits the daughter centrosome (right), creating asymmetries such as efficiency of primary cilium genesis. Centrosome maturation has already begun at G1/G0 (represented as shifts in colors from either green to black or orange to green).

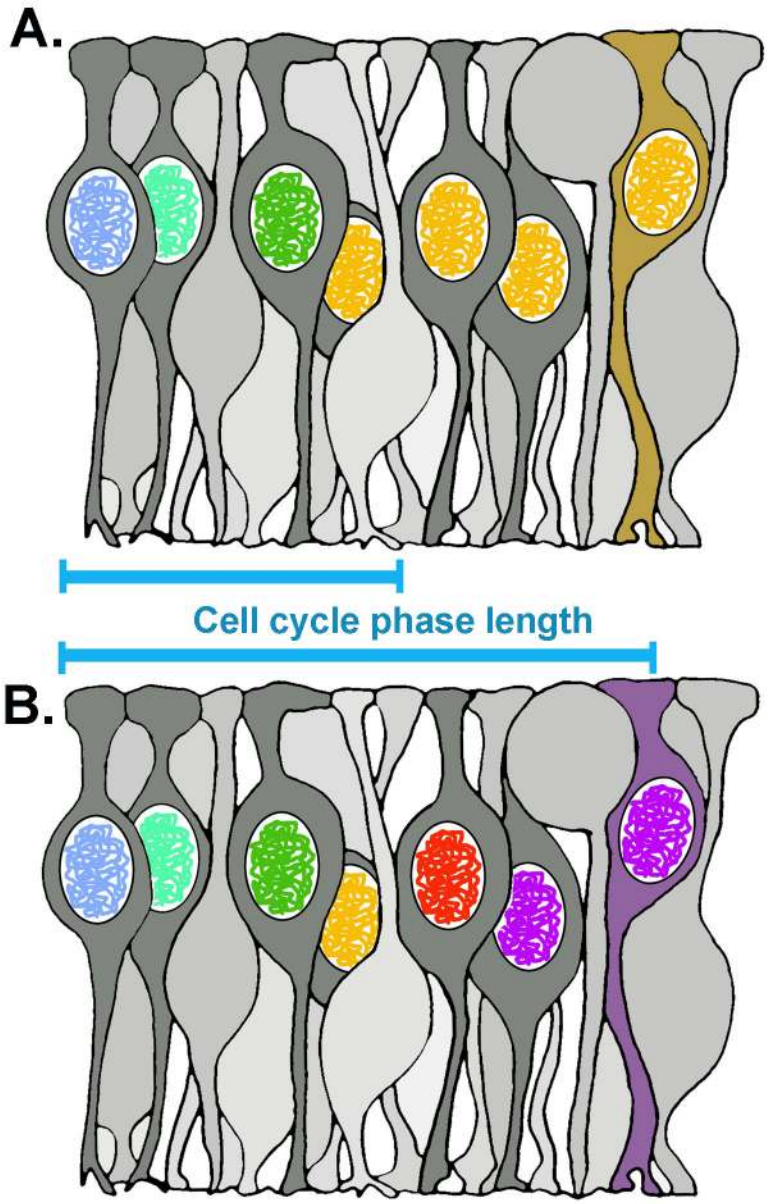

Figure 5.
Schematic of the cell cycle length hypothesis. Neuroepithelial cells progressing through a critical phase of the cell cycle with either **(A)** faster kinetics or **(B)** slower kinetics. In the model, the dark grey neuroepithelial cell is responsive to a fate-influencing factor(s) resulting in progressive transcriptional changes (progression of colors within the nucleus). Because of differences in the duration of the key cell cycle phase, the upper neuroepithelial cell (orange) advances to a different competency state as compared to the lower neuroepithelial cell (purple). For example, one cell may be biased to divide proliferatively, while the other is primed to divide neurogenically.

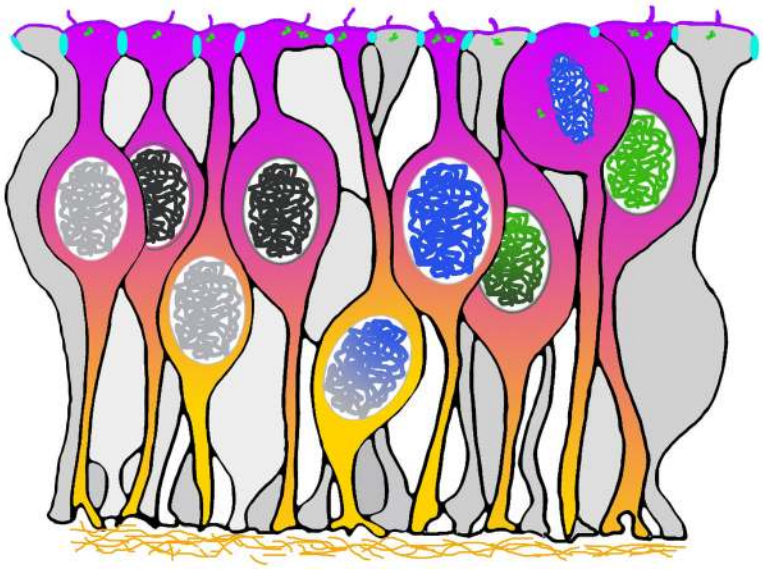

Figure 6.
Polarized signals, interkinetic nuclear migration, and cell fate. Schematic of two cells initiating INM (with grey or black nuclei on left). Through the influence of polarized signals within the cells (purple and orange gradients), nuclei that migrate to different apicobasal positions respond differentially to influence the mode of the next cell division (represented by color changes in the nucleus: grey to blue or black to green).

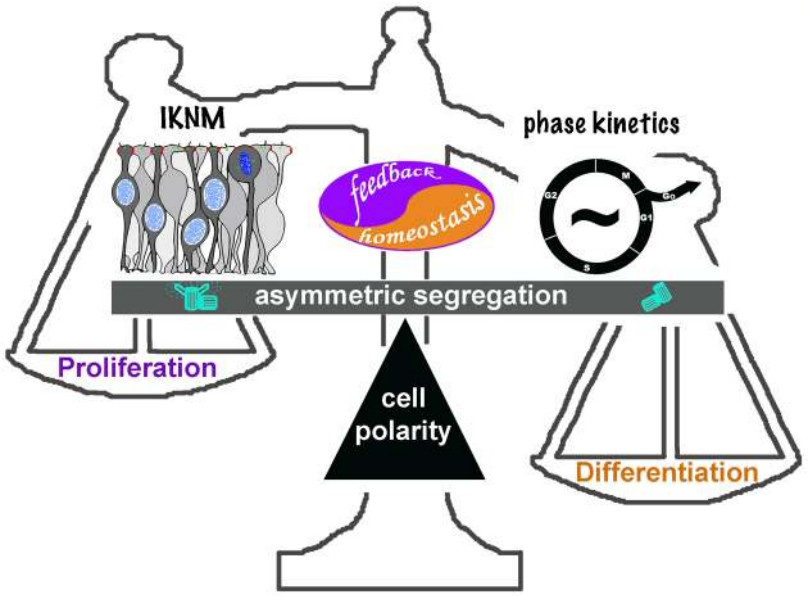

Figure 7.

Schematic emphasizing the potential interactions between the various cell biological influences on neuroepithelial cell fate. Apicobasal cell polarity is essential for inputs such as asymmetric segregation and the degree of polarity may act as a fulcrum to bias partitioning of determinants. Asymmetric segregation establishes initial bias, while interphase parameters such as nuclear position through INM or heterogeneity in cell cycle phase kinetics further influence fate. Feedback and homeostasis act as balancing weights to provide robustness. Ultimately it is the combination of multiple inputs that drive one fate versus another.