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Spindle orientation in mammalian cerebral cortical development

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In any mitotic cell, the orientation of the mitotic spindle determines the orientation of the cleavage plane and therefore the position of the two daughter cells. When combined with polarization of cellular components, spindle orientation is also a well-conserved means of generating daughter cells with asymmetric cell fates, such as progenitors and differentiated cell types. In the mammalian neocortex, the precise planar spindle orientation observed early during development is vital for symmetric proliferative divisions. During later stages, spindles can be oblique or even vertical but the role of this reorientation is somewhat less clear as asymmetric cell fates can arise independently of spindle orientation during this stage. Although decades of work have identified many key conserved regulators of spindle positioning, its precise role in cell fate determination in the mammalian neocortex has been enigmatic. Recent work focused on mInsc and LGN has now revealed an important role for spindle orientation in determination of specific asymmetric cell fates, namely intermediate progenitors and a new progenitor population, termed outer radial glia. In this way, spindle orientation helps determine the neurogenic outcome of asymmetric progenitor divisions, thereby influencing neuron output and cerebral cortical expansion.

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Introduction

During cell division, intracellular components must be partitioned into two daughter cells in a highly regulated manner. For some components this is done symmetrically so that both daughter cells receive an identical set. However, other components, such as cell fate regulators, may be partitioned asymmetrically to result in asymmetric cell fates following division [1]. This cell fate asymmetry contributes to developmental diversification that generates the vast array of different cell types in a fully developed metazoan. Asymmetric localization of subcellular components can be achieved by regulating the distribution of these components and the mitotic spindle relative to one another so that the two daughter cells terminate cytokinesis with distinct sets of these factors [2,3].

Regulated orientation of the spindle has been shown to be an influential factor in cell fate decisions during development of a variety of systems. For example, the *Caenorhabditis elegans* zygote positions the spindle along the anterior–posterior axis through interactions of spindle microtubules with polarity proteins at the cell cortex [2]. Similarly, *Drosophila* neuroblasts orient their spindle along the apicobasal axis through interactions at the cell cortex with apically localized factors [4].

This paradigm of positioning the spindle through interactions at the cell cortex seems to hold true in vertebrate and mammalian asymmetric divisions as well. In particular, in the developing mammalian neocortex, neurons arise from asymmetric divisions of progenitor cells, whereas symmetric divisions drive self-renewal of progenitors [5]. This process is dependent upon spindle orientation, and, like in *C. elegans* and *Drosophila*, involves polarity proteins. Orientation of the spindle has important implications in human brain evolution as well as several developmental disease states [6]. For example, disorders such as lissencephaly (smooth brain) and microcephaly (small brain) can be caused by mutations in genes with specific roles in spindle orientation in the mammalian cerebral cortex, including Lis1, Nde1, and MCPH1 to name a few [7]. In this review, we will focus on mechanisms of spindle orientation in mammals and in particular in the developing cerebral cortex.

Mechanisms of spindle orientation in mammalian cells

Astral microtubule growth and positioning. The mitotic spindle is formed during prophase when the duplicated centrosomes, or microtubule organizing centers (MTOC), nucleate spindle microtubules to position chromosomes, and astral microtubules to position the spindle relative to the cell cortex [8]. Although centrosomes are not required for spindle assembly in all cells (e.g. higher plants [9], planarians [10], and mouse oocytes [11]), there is growing evidence that centrosome function influences spindle positioning [12]. Furthermore, regulation of microtubule polymerization and stability is important not only for spindle assembly, but also for positioning [13].

Astral microtubules elongate from the MTOC and undergo microtubule-capture at the plasma membrane

to position the spindle. This occurs through the concerted effort of dynein–dynactin directed microtubule transport with the help of dynein-associated proteins such as CLASP1, Lis1, and Nde1/Ndel1, thereby pulling the spindle into position [14–17]. One particularly interesting finding is that the micromechanical characteristics of the spindle allow it to move as a whole under spindle positioning forces [18•]. Thus, microtubule anchoring at the cell cortex can position the entire spindle relative to polarity cues.

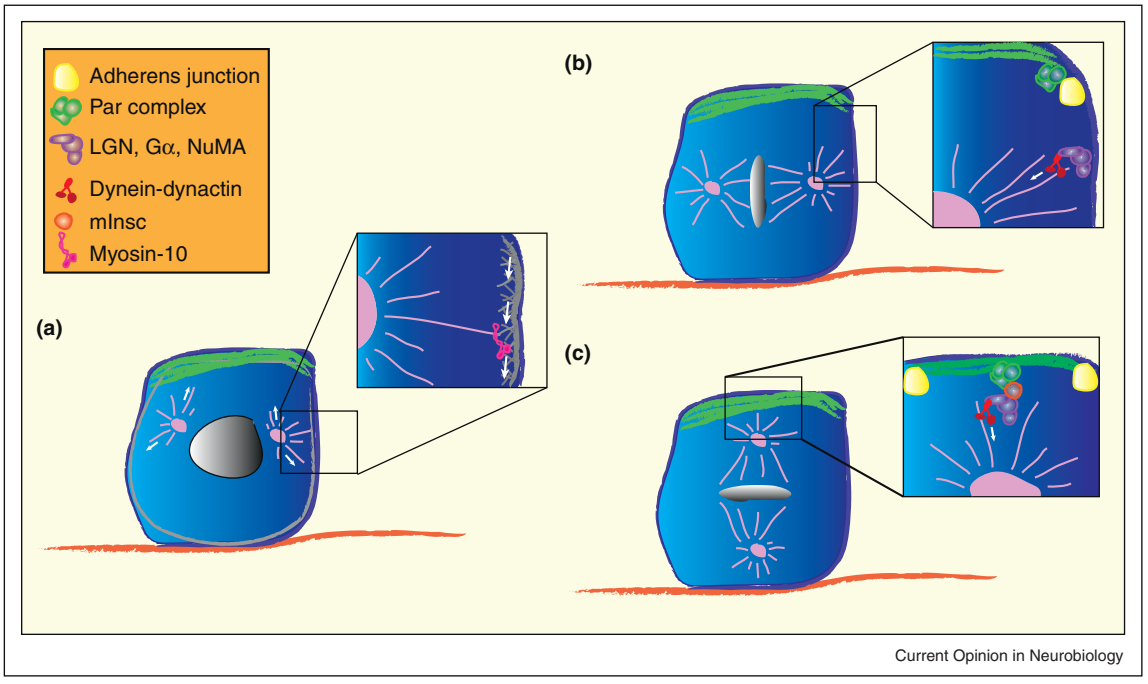
An important player in microtubule anchoring is the actin cytoskeleton. Subcortical F-actin filaments at the cell cortex interact with astral microtubules of the nascent spindle poles [19]. Through myosin transport and cortical flow of F-actin, astral microtubules can be pulled, thereby positioning centrosomes and the entire spindle [20] (Figure 1a). However, since subcortical actin is often uniformly distributed throughout the cell, asymmetry must be conveyed by other factors as well. For example, external forces that influence cell shape can influence spindle orientation through an effect on the actin cytoskeleton [21–23]. Internally, polarity cues, such as apical–basal factors, can influence spindle orientation.

The role of the apical Par complex. Epithelial cells, including the neuroepithelium, exhibit pronounced apicobasal polarity [24]. This polarity can provide an endogenous source of asymmetry to orient the spindle [25]. The apical Par complex containing Par3, Par6, and aPKC, is a master regulator of apicobasal polarity, with Par3 functioning as a scaffold for Par6 and aPKC [26]. These components, with the help of Cdc42, selectively exclude non-apical proteins from the apical domain [27].

In epithelial cells, adherens junctions help to establish and maintain this apical polarity [26]. Adherens junctions, a type of cell–cell contact, are composed of cadherins and catenins, particularly E-cadherin and α-catenin, β-catenin and p120 catenin [28]. These adherens junctions interact with Par-3 to recruit the Par-complex apically, and facilitate apical polarity maintenance by preventing mixing between apical and basolateral domains of the epithelial cell [24]. In addition, adherens junctions can influence the cytoskeleton through α-catenin interaction with actin and p120 catenin interaction with microtubules [28].

Connecting the spindle to polarity cues. Many of the factors involved in orienting the spindle relative to apicobasal

Figure 1



Spindle orientation in mammalian epithelia. **(a)** Spindle orientation begins with spindle microtubule growth from the centrosome (pink). Aster microtubules polymerize and interact with the subcortical actin cytoskeleton (grey), which help position spindle poles through cortical F-actin flow [20] and myosin-10 [100], an unconventional microtubule-binding myosin [101] (inset). **(b)** Planar division occurs when the spindle is positioned perpendicularly to the apicobasal axis (defined by the apical domain, green). This occurs through segregation of the LGN complex (purple) from the apical domain by Par complex proteins (green) and adherens junctions (yellow). Aster microtubules are then positioned through dynein–dynactin (red) association with the LGN complex. **(c)** Vertical orientation (along the apicobasal axis) occurs in the presence of mInsc, which allows association of the LGN complex with the Par complex. This connection pulls the spindle pole toward the apical domain, thereby orienting the spindle vertically. In all panels, the orange line marks the basal surface.

polarity cues have been described in *Drosophila* [2], and, to a large degree, their homologs have been identified to function similarly in mammalian and vertebrate epithelial cells [25]. In particular, a protein complex comprising LGN, NuMA, and Gαi associates tightly with the spindle pole [29,30•]. In planar epithelial divisions, this complex localizes to a restricted belt between apical and basal domains, associating with both spindle poles on either lateral side of the dividing cell [29,31•] (Figure 1b). This localization seems to be maintained through aPKC phosphorylation of LGN to exclude it from the apical domain [32].

In contrast, divisions along the apicobasal axis display association of the LGN complex with only one spindle pole oriented at the apical domain of the cell [30•,33,34•,35] (Figure 1c). With the LGN complex positioned, NuMA acts as the bridge between LGN and dynein–dynactin [36]. Through dynein minus-end directed movement, the spindle pole is positioned adjacent to the LGN complex, either along the lateral axis in the case of planar divisions, or along the apicobasal axis.

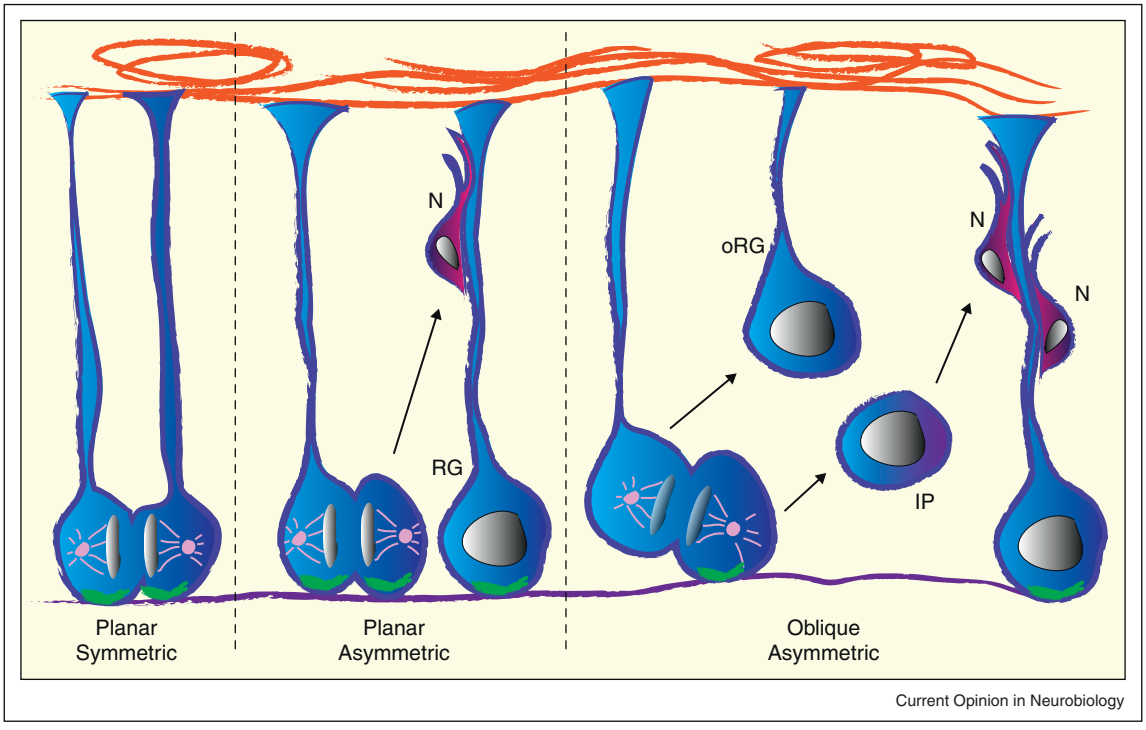
Although LGN is required for directed spindle orientation, it does not define which orientation the cell will adopt during mitosis. In *Drosophila*, that role is fulfilled by Inscuteable (Insc), which functions by coupling the LGN (Pins) complex with the Par complex [37,4,38] to direct LGN apical localization and determine orientation of the spindle. In *Drosophila* embryos, Insc acts as a switch to drive cells toward vertical divisions, whereas cells with inactive Insc drive parallel divisions [37]. As in *Drosophila*, mammalian mInsc interacts with Lgn and Par3 [33], and seems to influence spindle orientation in mammalian epithelia away from planar toward more apicobasal orientation [39,40•,41] (Figure 1c).

Neurogenesis in mammalian cortical development

During mammalian cerebral cortical development, the neuroepithelium initially divides symmetrically and with a planar orientation to expand the progenitor pool [42] (Figure 2). At the start of neurogenesis, the progenitor pool, termed radial glial stem cells (RGs) or apical progenitors, then begin dividing asymmetrically. These asymmetric divisions can result in several outcomes leading to either direct neurogenesis to produce a neuron immediately after division, or indirect neurogenesis giving rise to an intermediate progenitor (IP) (Figure 2). This IP can then divide again to produce two neurons, thereby expanding the neurogenic output.

The asymmetric cell fate resulting from these divisions is likely determined by many factors, such as epigenetic changes and signaling, which we are only just beginning

Figure 2



Spindle orientation in the mammalian neocortex. Planar symmetric divisions (left panel) give rise to two RGs with apical (in green) and basal domains. Planar asymmetric divisions (middle panel) give rise to one RG and a neuron (N) or IP. Oblique or vertical orientation (right panel) gives rise to asymmetric cell fates, tending to generate oRGs and IPs to a greater extent [40•,41]. In all panels, the orange line marks the basal surface.

to identify. In particular, there is now substantial evidence that asymmetric divisions in the cortex give rise to daughter cells with variable Notch activities resulting in daughter cells with greater Notch activity, which tend to remain as RGs, while those with lesser Notch activity become neurons or IPs [43]. Indeed, disruption of Notch signaling in the mammalian neocortex has dramatic consequences to cell fate [44]. For example, inducing Notch activation inhibits neuronal differentiation by maintaining RGs as progenitors [45].

Thus, establishment of differential Notch activities is likely a key event in fate determination following asymmetric division of RGs. Other signaling pathways, such as Shh and Wnt signaling are also vital to acquisition of specific cell fates in the neocortex [46], though their roles

Table 1

Regulators of spindle orientation and their phenotypes in the neocortex

Gene/protein	Function	Effect on spindle	Cortical phenotype (*human*; mouse or rat)
Centrosome/MTOC			
MCPH1	DNA damage repair, chromosome condensation, centrosome function	LOF: increased vertical orientation [48•]	*Microcephaly* [76]; mild microcephaly [48•]
ASPM	Centrosome/spindle pole localization, Wnt signaling	LOF: increased oblique orientation [49]	*Microcephaly, simplified gyri* [77]; mild microcephaly [78]
Cdk5Rap2	Centrosome function, centriole duplication, DNA damage response	LOF: increased vertical orientation [79•]	*Microcephaly* [80]; microcephaly [79•]
Cenpj	Centrosome localization, centriole duplication and elongation	LOF: randomized in HeLa cells [81]	*Microcephaly* [80]
Stil	Spindle pole localization, centriole duplication, Shh signaling	LOF: randomized in HeLa cells [81]	*Microcephaly, simplified gyri* [82]; neural tube defects [83]
Microtubule organization/positioning			
DCX	Microtubule organization, stability	LOF: randomization [13]	*Lissencephaly/Subcortical band heterotopia* [84]; neuronal migration defects [85]
Lis1	Dynein/dynactin complex function	LOF: randomization [51]	*Lissencephaly*; cortical disorganization [86]
Magoh	Splicing, Lis1 expression	LOF: increased vertical and oblique [87•]	Cortical disorganization, microcephaly
Nde1	Lis1–dynein complex	LOF: increased vertical and oblique [17]	*Microlissencephaly*; mild microcephaly [88,89]
Arhgef2	GEF, microtubule associated	LOF: increased planar orientation [90]	Decreased neurons, increased RGs
Tctex1	Dynein light chain, G protein signaling	LOF: decreased planar orientation [90]	Increased neurons, decreased RGs
Htt	Dynein–dynactin complex	LOF: increased vertical and oblique orientation [91•]	*Huntington disease*; decreased RGs, increased neurons [91•]
Apical complex			
Par3	Apicobasal polarity	LOF: increased oblique and vertical in MDCK [32]	Decreased RGs (LOF), increased RGs (GOF) [53,60]
Par6	Apicobasal polarity	LOF: increased oblique in Caco-2 cells [27]	Increased RGs (GOF) [53]
aPKC	Apicobasal polarity	LOF: increased oblique in Caco-2 cells [27]	Normal neurogenesis (aPKClambda)
Cdc42	Apicobasal polarity	LOF: Increased oblique in Caco-2 cells [92], but no change in telencephalon [93]	Decreased RGs, increased IPs [93]
Adherens junctions			
Beta-catenin	Adherens junctions, Wnt signaling	LOF: increased oblique and vertical orientations in midbrain [94]	Decreased RGs (LOF) [95], increased RGs (GOF) [96]
Spindle positioning			
mInsc	Spindle orientation	LOF: increased planar orientation [40•], GOF: increased vertical and oblique orientation [40•,41]	Decreased neurons and IPs (LOF) [40•], increased IPs and oRGs (GOF) [40•,41]
LGN	Spindle orientation	LOF: increased oblique and vertical orientations [41]	Decreased RGs, increased IPs and oRGs [41]
Other			
Lamin-B	Nuclear lamina	LOF: increased oblique orientations [97]	Cortical disorganization [97]
Pax6	Transcription factor, neurogenesis and self-renewal	LOF: increased oblique and vertical orientations [98]	Increased asymmetric fates [98]
Vangl2	Planar cell polarity	LOF: increased planar orientation [99]	Increased early-born neurons, decreased RGs [99]

Not all factors affecting cortical progenitor asymmetric division are shown. This table is limited to those factors where spindle orientation was specifically examined.
LOF = Loss of function, GOF = Gain of function.

in asymmetric fate determination have not been specifically addressed. Importantly, it is still largely unclear how differential signaling activities in daughter cells are established and whether this is influenced by spindle orientation. This is discussed further below.

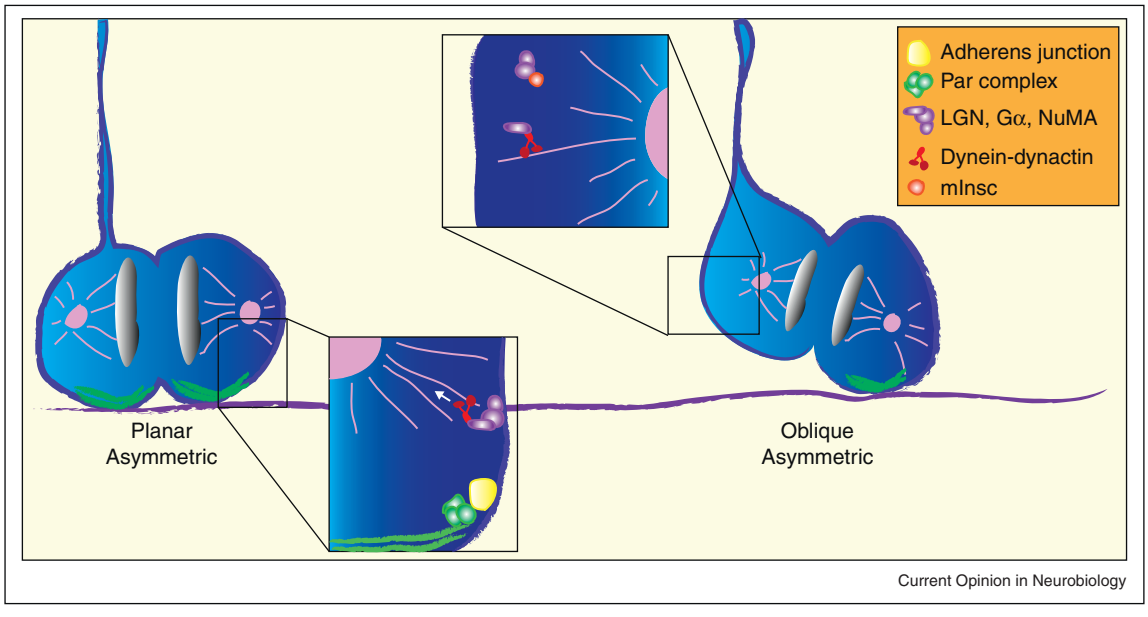
Spindle orientation factors and their phenotypes in the mammalian neocortex

The MTOC and microtubule dynamics. Disruptions in mitotic spindle components, such as the centrosome and astral microtubules, lead to striking phenotypes in the mammalian neocortex. For example, disruption of factors involved in centrosome function leads to misorientation of the mitotic spindle in neural progenitors [47,48•], which results in a depletion of neural progenitors [12,49]. Furthermore, disruption of microtubule dynamics as is seen with loss of Doublecortin (Dcx), a gene mutated in patients with lissencephaly and cortical band heterotopia, leads to a similar depletion of progenitor cells due to randomized spindle orientation [13]. Along these lines, disruption of dynein–dynactin function at the cell cortex, as in the case of Lis1 and Nde1/Ndel1 mutations, similarly leads to depletion of progenitor cells due to randomized spindle orientation (Table 1) [17,50,51].

Apical polarity proteins. Several regulators of the apical Par complex have been shown to regulate asymmetric versus symmetric divisions in the mammalian brain. For example, mutation of ASPP2, a regulator of apical Par3 localization, leads to structural defects as expected with disruption of polarity, but also leads to defects in asymmetric divisions with a decrease in apical RGs [52]. In addition, Par proteins themselves, such as Par3 and Par6, have been shown to promote symmetric, self-renewing divisions (Table 1) [53]. However, inactivation of one of the aPKC isoforms (aPKCλ) did not lead to changes in cell fate despite the striking effect on neuroepithelial architecture [54], although the other isoform remains to be examined in this context.

Spindle orientation machinery. Several of the known orientation regulators that have been examined in other mammalian systems have now been examined in the mammalian neocortex. In particular, LGN has been shown to promote planar orientations in the neocortex and its loss leads to a randomization of spindle orientation with a concomitant increase in IPs and a decrease in apical RGs (Table 1) [41]. Despite the decrease in apical RGs however, the authors describe a population of RGs displaced from the ventricular zone and localized more basally, which is dramatically increased with LGN mutation. These basal RGs likely represent a population of very recently identified RGs of the outer SVZ, termed outer radial glia (oRG) [55•,56•,57•] (Figure 2). Our understanding of these oRGs is still in its infancy, but several studies have revealed that, like apical RGs, oRGs can divide asymmetrically to expand neuronal output. Additionally, although oRGs express identical markers to

Figure 3



Model of spindle orientation in two types of asymmetric divisions. During asymmetric planar divisions (left), LGN associates with NuMA and Gα to direct the spindle pole away from the apical domain along the planar axis. NuMA acts as the bridge between LGN at the lateral poles and dynein/dynactin, which drive spindle pole positioning through directed microtubule transport. During asymmetric oblique or vertical divisions (right), mInsc may compete for binding with LGN and displace NuMA from the LGN complex thereby uncoupling spindle pole positioning and lateral cortex anchoring relative to the apical domain.

apical RGs, they lack an apical process and therefore the apical domain [5]. These are important characteristics as they have major implications for many aspects of asymmetric cell division in the neocortex (discussed below).

In addition, genetic studies of mInsc have now been performed in mouse neocortex and reveal that loss of mInsc leads to a decrease in oblique and vertical divisions, resulting in a decrease in IPs (Table 1) [40•]. On the other hand, overexpression of mInsc leads to a reduction of planar divisions and drives the production of IPs as well as basal RGs [40•,41] (Figure 3). Interestingly, this does not seem to affect the number of apical RGs as seen in other mutants affecting spindle orientation. Furthermore, mInsc seems to specifically affect later neurogenic events, as early dynamics are not affected in mInsc mutants. Thus, mInsc seems to inhibit planar divisions and promote oblique and vertical orientations to drive production of IPs and oRGs.

Spindle orientation and cell fate

Spindle orientation seems to be a key initial factor in acquisition of asymmetric cell fates. Specifically, oblique and vertical (along the apicobasal axis) orientations tend to give rise to asymmetric fate outcomes suggesting these orientations drive asymmetric cell fate. Furthermore, the contribution of these division orientations varies temporally during neurogenesis, with early neuroepithelium dividing primarily with a planar orientation, and oblique orientation arising to a greater extent as neurogenesis increases [51,58]. Vertical orientations are somewhat rare under normal circumstances but can be induced to a greater extent upon genetic manipulation (such as with mInsc overexpression) [40•,41].

Disruption of these orientations has been shown to have consequences for resultant cell fate. For example, early planar orientations seem to be the most sensitive to spindle orientation defects and their disruption leads to depletion of the progenitor pool [51]. Disruption of planar orientations at later stages, by either randomization or induction of vertical and oblique orientations, also leads to a gradual depletion of progenitors due to increased asymmetric neurogenic divisions at the expense of symmetric proliferative divisions. On the other hand, disruption of oblique and vertical orientations leads to a reduction in neurons due to loss of this pool of asymmetric divisions [40•].

It is important to point out that while oblique and vertical divisions promote asymmetric cell fate, the orientation of asymmetric divisions can also be planar [2]. This suggests that while spindle orientation influences cell fate, it is not the only determining factor in generating asymmetric outcomes, leaving the possibility for other factors open for investigation.

One candidate is the apical Par complex. On the basis of the cellular architecture of the developing cortex, one model suggests that oblique or vertical spindle orientation influences the inheritance of the apical domain [59]. Recently, Par3 was shown to localize asymmetrically in dividing RGs where it promotes Notch signaling in cells inheriting greater Par3 levels, thereby promoting retention of RG fate [60]. Par3 was shown to interact with Numb, a well-known fate determinant in *Drosophila* neuroblasts and regulator of Notch signaling [61], and this interaction led to enhanced Notch activity. Numb is also asymmetrically localized in this context [62–64]. Thus, Par3 and Numb localize asymmetrically in dividing RGs to help establish Notch asymmetry post-mitosis.

There are still several open questions here, however. In particular, the link with spindle orientation is not clear since asymmetric distribution of Par3 did not correlate with spindle orientation [60]. Furthermore, Numb and its related Numb-like (Numbl) have additional roles in apicobasal polarity, which may also influence spindle orientation [64]. In addition, numerous studies have examined whether the apical and/or basal domains correlate with daughter cell fate with somewhat contradictory results [54,57•,59,64,65]. Furthermore, the fact that oRGs lack an apical domain suggests that inheritance of the apical domain is not required for RG fate specification per say, but may be involved in oRG versus apical RG fate determination. At the moment, the evidence points to a requirement for both apical and basal domains in maintaining apical RG fate, whereas alternative fates do not correlate with inheritance of these domains [41]. Since these studies are correlative, functional studies to examine apical and basal components in cell fate determination and the role of spindle orientation are still needed.

A new model coming from data from mInsc mutant mice may help explain why oblique and vertical orientations influence asymmetric cell fates but planar divisions also give rise to asymmetric outcomes. The fact that mInsc induces production of IPs and basal RGs suggests that its effect on spindle orientation may specifically regulate indirect versus direct neurogenic asymmetric divisions [40•]. These data point to the intriguing possibility that spindle orientation regulates the type of asymmetric division, rather than whether a division will be asymmetric (Figure 3). This model would suggest that planar asymmetric divisions primarily result in direct neurogenesis while oblique and vertical divisions result in indirect neurogenesis through IPs and basal RGs. It will be important to further test this in the future.

Furthermore, recent structural studies have shed light on a possible competition between mInsc and NuMA for binding to LGN [66•,67•,68•]. This would suggest a potential model whereby spindle orientation machinery

primarily directs planar orientations through the action of LGN and NuMA, but when mInsc is present, the communication between LGN and the spindle via NuMA is disrupted by competition with mInsc (Figure 3). Thus, planar spindle orientation may be an active process of orienting the spindle, while oblique and vertical orientations may reflect a more passive result of inhibiting this orienting machinery. This is in contrast to the switch model seen in *Drosophila*, as mInsc does not drive strictly vertical orientations in the mammalian neocortex.

Spindle orientation in human evolution and developmental disorders

Several human brain diseases have been proposed to stem from defects in asymmetric cell division and spindle orientation [7]. In particular, microcephaly, a condition involving an abnormally small brain and head, has been linked to potential spindle defects. Notably, all the genes so far identified in primary microcephaly encode proteins with roles at the centrosome/MTOC of the spindle [12]. Three of these genes, MCPH1, ASPM, and CDK5RAP2, have been shown to be required for planar oriented divisions in the mouse neocortex [48•,49,69], and two of these (MCPH1 and CDK5RAP2) have been shown to be required for centrosome function and centriole duplication [48•,70]. Furthermore, several of the genes identified in the disorder lissencephaly, which is characterized by a loss of gyri and sulci (the folds and grooves of the cerebral cortex), have also been suggested to have roles in spindle orientation. As mentioned above, LIS1, NDE1, and DCX all regulate spindle orientation [13,17,51], and this has consequences to cell fate specification.

These data from developmental disorders also point to a probable role for spindle orientation in human brain evolution, as this has involved a massive size expansion as well as elaboration of foliation [6]. This may have occurred through genetic changes to factors regulating asymmetric division, and in particular spindle orientation. For example, ASPM and CDK5RAP2 have both been shown to have undergone positive selection along the primate lineage and associate with increased brain size [71–74].

We are only just beginning to understand some of the molecular factors involved in human brain evolution, but regulators of spindle orientation are likely candidates. The identification of oRGs, and the fact that they are dramatically expanded in humans and other animals with large cerebral cortexes, suggests a potential role in evolutionary expansion of neuronal production. Along these lines, it will be important to examine biological processes governing generation of oRGs. Data from LGN and mInsc mutants suggest that oblique oriented divisions give rise to oRGs [40•,41,57•], pointing to the intriguing possibility that oblique spindle orientation may have contributed to evolutionary expansion of the human cerebral cortex.

Concluding remarks

Studies from a diverse array of systems have provided a foundation for understanding the molecular mechanisms of spindle orientation. Many of these mechanisms hold true in the mammalian cerebral cortex as well, and can shed light on asymmetric cell division within this context. Overall, existing data suggest spindle orientation influences asymmetric cell fate though it does not strictly determine whether or not a division will be asymmetric or symmetric. Whether this is due to an inherent stochasticity [75] or an as yet unclear fate determinant, perhaps involving the apical domain, is not yet evident. However, evidence points to a more specific role for spindle orientation in determining the type of asymmetric division in the mammalian neocortex. It will be important to test this model directly as well as whether oblique and vertical divisions reflect a more passive process of disruption of planar orientation as recent interaction evidence suggests.

One of the key remaining questions is how orienting the spindle influences fate determination. Whether this is through asymmetric inheritance of Notch signaling components or other signaling cascade components is still unclear. Now that we have a clearer understanding of the role of spindle orientation, namely in generating IPs and oRGs, we can begin to examine whether factors involved in determination of these progenitor cell types are asymmetrically inherited in a spindle orientation dependent manner.

Finally, an examination of mechanisms of spindle orientation in oRGs would be very exciting, as these seem to undergo asymmetric divisions in the complete absence of an apical domain to help govern the orientation. It may be that the basal domain provides the directional cues responsible for orientation in this context. This would represent quite a divergence from the mechanism used in other systems and should be examined.

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