Mitotic spindle (DIS)orientation and DISease: Cause or consequence?

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Correct alignment of the mitotic spindle during cell division is crucial for cell fate determination, tissue organization, and development. Mutations causing brain diseases and cancer in humans and mice have been associated with spindle orientation defects. These defects are thought to lead to an imbalance between symmetric and asymmetric divisions, causing reduced or excessive cell proliferation. However, most of these disease-linked genes encode proteins that carry out multiple cellular functions. Here, we discuss whether spindle orientation defects are the direct cause for these diseases, or just a correlative side effect.

Introduction

During cell division the orientation of the division plane usually defines the content, the position, and the fate of daughter cells within tissues (Siller and Doe, 2009). As a consequence, it delineates the architecture of the organ, its shape, and function (Castanon and González-Gaitán, 2011). In polarized cells, the division plane orientation determines whether a cell undergoes symmetric or asymmetric cell division (Fig. 1). In symmetric divisions the division plane is parallel to the polarity axis so that cell fate constituents, although polarized, will be equally segregated into daughter cells (Fig. 1 A). By contrast, if the division plane is perpendicular to the polarity axis, daughter cells will inherit different contents and diverge in their development (Fig. 1 B; Siller and Doe, 2009). In certain cases, however, cell fate can be induced regardless of division plane orientation (Clayton et al., 2007; Fleming et al., 2007; Kosodo et al., 2008).

The orientation of the spindle, and the position of centrosomes, determines the orientation of the division plane (Bornens, 2012). Centrosomes are composed of centrioles and the pericentriolar material that nucleates astral and spindle microtubules. Astral microtubules connect the spindle to the cell cortex and control its orientation (Fig. 2). Studies in *Caenorhabditis elegans* and *Drosophila melanogaster* have contributed considerably to our understanding of the molecular mechanisms regulating spindle orientation, which have been recently reviewed (Morin and Bellaïche, 2011; Fig. 2). However, the relevance of spindle orientation control in mammals had remained mostly unexplored. In recent years several studies linked spindle orientation defects to human diseases, in particular brain pathologies (Fish et al., 2006; Yingling et al., 2008; Godin et al., 2010; Lizarraga et al., 2010) and cancer (Pease and Tirnauer, 2011). Here, we explore the connection between human diseases and spindle orientation defects, and discuss to which extent these defects can be considered causative agents of these diseases.

Neurological diseases

In vertebrates the central nervous system arises through a series of symmetric and asymmetric cell divisions (Fig. 3 A; Peyre and Morin, 2012; Shitamukai and Matsuzaki, 2012). At embryogenesis it is composed of a single layer of stem cells, the neuroepithelial stem cells (NESCs), which divide symmetrically. At the onset of neurogenesis, NESCs acquire characteristics of glial cells and are called radial glia cells (RGs). Both NESCs and RGs have apico–basal polarity and are also called apical progenitors. RGs divide asymmetrically to give origin to intermediate progenitors (IPs); IPs do not display apico–basal polarity, they detach from the apical side and divide one time to generate two neurons. Recently, a new kind of progenitor cell was identified, the outer radial glial cells (oRGs; Fietz et al., 2010; Hansen et al., 2010). These cells delaminate from the apical side but maintain an attachment to the basal side. oRGs can divide either asymmetrically, giving origin to an IP and an oRG, or symmetrically, to expand their pool.

Spindles parallel to the apical plane will give rise to planar, symmetric (and proliferative) divisions, whereas vertical or oblique spindles will result in asymmetric (and differentiative) divisions (Fig. 3 B; (Huttner and Brand 1997; Haydar et al., 2003; Kosodo et al., 2004). This implies that interfering with

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Abbreviations used in this paper: IP, intermediate progenitor; MCPH, microcephaly; NESC, neuroepithelial stem cell. oRG, outer radial glia; RG, radial glia.
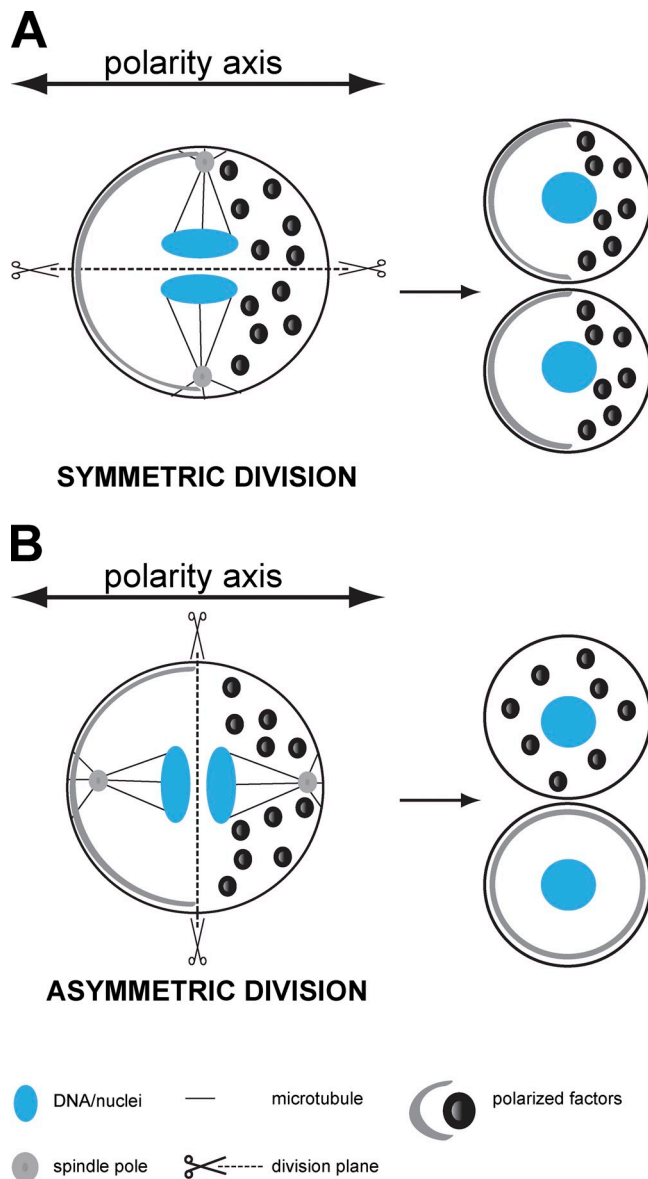
Figure 1. **Orientation of the mitotic spindle: symmetric vs. asymmetric divisions.** In polarized cells, orientation of the spindle perpendicular to the polarity axis causes a symmetric (proliferative) division (A). However, spindle orientation parallel to the polarity axis results in an asymmetric (differentiative) division (B).
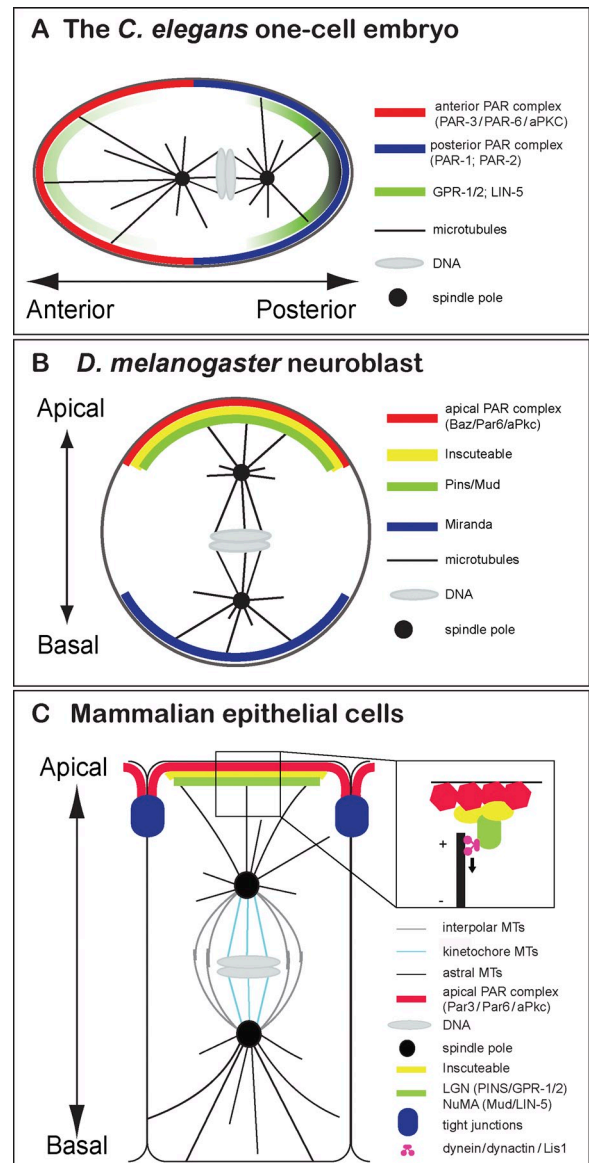

Figure 2. **Spindle orientation is regulated by a conserved set of molecules in metazoans.** (A) The *C. elegans* one-cell embryo is polarized along the anterior–posterior axis and divides asymmetrically in a somatic anterior cell (AB) and a posterior germline precursor cell (P1). The conserved PAR (partitioning defective) proteins are localized asymmetrically at the cortex: PAR-3, PAR-6, and PKC-3 at the anterior and PAR-1 and PAR-2 at the posterior. Spindle positioning is regulated downstream of polarity by GOA-1 and GPA-16 (Gα subunits of heterotrimeric G proteins), which localize around the entire cortex (not depicted), GPR-1 and GPR-2 (receptor-independent activators of G protein signaling), LIN-5 (coil-coiled protein), and the motor dynein (not depicted; Morin and Bellaïche, 2011). GPR-1/2 and LIN-5 are enriched at the posterior cortex in a PAR-dependent manner. The data suggest a model in which the GPR–GαGDP–LIN-5 complex promotes higher activity of dynein at the posterior cortex, resulting in posterior spindle pulling (Morin and Bellaïche, 2011). (B) *D. melanogaster* neuroblasts are stem cell–like precursors that generate the fly's central nervous system. They divide asymmetrically along the apical–basal axis to give rise to a self-renewed neuroblast and a ganglion mother cell. Baz (PAR-3), Par6 (PAR-6), and aPKC (PKC-3) form a complex that localizes at the apical cortex. PINS (GPR-1/2) binds to Gα and localizes to the apical complex by interacting with the Baz-binding protein Inscuteable. (C) The same set of proteins regulates spindle orientation in mammalian cells (Lechler and Fuchs, 2005; Williams et al., 2011; see also Table 1).

spindle orientation to favor oblique, differentiative divisions will favor neurogenesis at the expense of stem cell pool expansion, leading to smaller brains. Consistent with this model, several genes implicated in neuropathologies resulting in small brains have been implicated in the control of spindle orientation. However, this model is controversial because in vivo observation of rodent neurogenesis showed that the choice between an asymmetric and a symmetric cell division does not only rely on the orientation of the spindle axis (Noctor et al., 2008). Moreover, it was shown that randomization of spindle orientation does not necessarily lead to a small brain (Konno et al., 2008). Keeping this controversy in mind, we summarize here the link between spindle orientation defects and three neurological diseases.
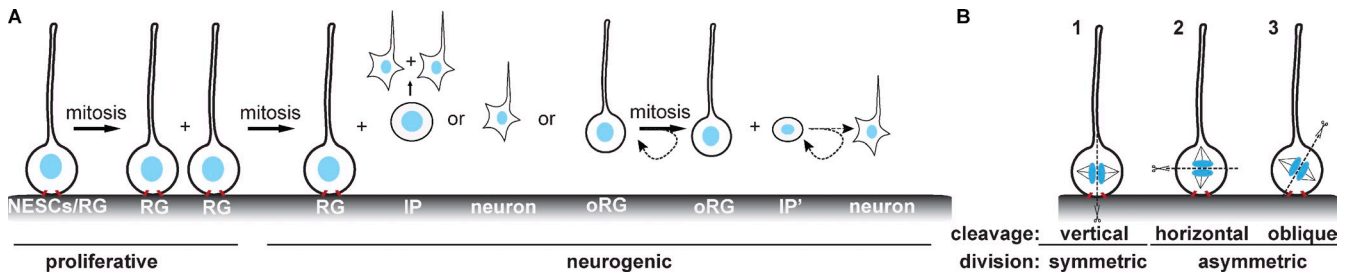
Figure 3. **Mammalian neuronal progenitors and spindle orientation.** (A) Cell subtypes in the developing mammalian brain. NESCs, neuroepithelial stem cells. RG, radial glia. IP, intermediate progenitor. oRG, outer radial glia. IP′, transit amplifying intermediate progenitors. Adherens junctions are in red. (B) A putative role of spindle orientation in the decision of symmetric vs. asymmetric division.

Microcephaly. Primary microcephaly (MCPH) is an autosomal, recessive "small brain" disease. Microcephalic brains are structurally normal but exhibit reduced surface of the neocortex due to a reduced number of cortical neurons (Bond et al., 2002). Patients bearing microcephaly are mentally retarded but do not display other neurological disorders (Thornton and Woods, 2009). Genetically, the pathology is quite heterogeneous. Mutations in nine different genes have been linked with microcephalic brain (Table 1; Thornton and Woods, 2009; Alkuraya et al., 2011; Bakircioglu et al., 2011; Sir et al., 2011).

All of the MCPH proteins can localize to centrosomes and are involved in centriole biogenesis, centrosome maturation, and spindle organization (Table 1; Bettencourt-Dias et al., 2011; Löffler et al., 2011). The most commonly affected gene is *aspm* (abnormal spindle-like microcephaly associated, MCPH5; Thornton and Woods, 2009). In human culture cells, ASPM localizes to centrosomes and spindle poles, similar to its fly and worm orthologue (Table 1; Saunders et al., 1997; Kouprina et al., 2005; van der Voet et al., 2009). Depletion of ASPM by RNAi results in spindle misorientation (Fish et al., 2006). A mutation in ASPM identified in microcephalic patients impairs the ability of ASPM to localize to centrosomes, suggesting that centrosomal localization is crucial for ASPM's role (Higgins et al., 2010).

Mouse *aspm* is highly expressed during early brain development (Bond et al., 2002). Aspm also decorates centrosomes in dividing NESCs (Kouprina et al., 2005; Fish et al., 2006). NESCs depleted of ASPM by RNAi fail to orient the mitotic spindle perpendicular to the ventricular surface of the neuroepithelium, resulting in an asymmetric, differentiative division instead of the symmetric proliferative divisions, therefore reducing the pool of neuronal precursors (Fig. 3; Fish et al., 2006). However, a mutant that encodes a truncated version of ASPM results in microcephaly without interfering with spindle orientation (Pulvers et al., 2010).

How ASPM regulates spindle orientation is not known. In *C. elegans*, ASPM-1 binds to the NuMA homologue LIN-5 and is required to recruit it to meiotic spindle poles. LIN-5 together with dynein promotes meiotic spindle rotation (van der Voet et al., 2009). Therefore, it is possible that ASPM controls spindle orientation in mice and humans by recruiting NuMA to centrosomes.

Two other genes mutated in microcephaly, Microcephalin (MCPH1) and CDK5RAP2 (MCPH3), are required for timely centrosome maturation, which allows centrosomes to nucleate many more microtubules in mitosis (Barr et al., 2010; Gruber et al., 2011). In *mcph1*-deleted mice the checkpoint kinase Chk1 does not localize to centrosomes, resulting in premature mitotic entry in the presence of immature centrosomes. This causes a spindle alignment defect, which increases asymmetric cell divisions of neuroprogenitors at the expense of symmetric, proliferative divisions, and results in smaller brains (Gruber et al., 2011) Similarly, in CDK5RAP2-depleted cells the checkpoint kinase Chk1 is not localized to centrosomes and spindles are misoriented (Barr et al., 2010; Lizarraga et al., 2010).

Depletion of CPAP (MCPH6) and STIL (MCPH7), which are essential for centriole biogenesis, result in spindle orientation defects in culture cells (Kitagawa et al., 2011; Brito et al., 2012), suggesting that impairing centriole biogenesis leads to spindle misalignment. A newly identified mcph gene, *cep63*, is also required for centriole formation (Sir et al., 2011). CEP63 is important to localize CEP152 (MCPH4) to centrioles, while CEP152 recruits CPAP to centrosomes (Cizmecioglu et al., 2010; Sir et al., 2011). However, a role for CEP63 and CEP152 in spindle orientation has not been investigated.

Lissencephaly. Morphologically, lissencephalic brains are small, and have almost a smooth surface and abnormal organization of the neocortex due to neuronal migration defects (lissencephaly means "smooth brain"; Wynshaw-Boris, et al., 2010). Patients are mentally retarded, epileptic, and die during their childhood. Genetic analyses of cases with type 1 lissencephaly identified mutations in mainly one gene, *lis1* (Reiner et al., 1993; Lo Nigro et al., 1997). The role of Lis1 in spindle orientation was first reported in culture epithelial and neuronal cells where Lis1 stabilizes microtubules via interaction with the dynein–dynactin complex (Faulkner et al., 2000; Smith et al., 2000). In vitro and structural studies indicate that Lis1 and its cofactor NudE regulate dynein, and that Lis1 transforms dynein in a processive, high-load microtubule motor protein (McKenney et al., 2010; Huang et al., 2012). Such a role fits with the functions that have been assigned to Lis1, such as transport of nuclei, chromosomes, centrosomes, large vesicles in axons, or in the case of spindle orientation, pulling of the entire spindle at the cell cortex (Table 1 and Fig. 2; Wynshaw-Boris, et al., 2010).

Yingling et al. (2008) have shown that depletion of Lis1 in NESCs results in less stable astral microtubules and loss of dynein cortical localization in mouse. This deflects the mitotic spindle from a horizontal position, leading to premature

Table 1. **Genes regulating spindle orientation and mutated in diseases**

Gene name – species			Cellular function	Associated disease	Molecular characteristics
Vertebrate	**Fly**	**Worm**			
lis1	lis1	lis-1	Dynein-based movement, nucleokinesis (vertebrate, fly, worm), spindle orientation (vertebrate, fly), chromosome alignment (vertebrate), centrosome separation (fly, worm) spindle positioning (worm) (Swan et al., 1999; Dawe et al., 2001; Cockell et al., 2004; Siller and Doe, 2008; Wynshaw-Boris et al., 2010)	Lissencephaly (Reiner et al., 1993; Lo Nigro et al., 1997)	Coiled-coil domain, WD40 repeats
dcx	CG17528[a]	zyg-8	Microtubule polymerization (vertebrate, worm), spindle orientation (vertebrate), spindle positioning (worm) (Gönczy et al., 2001; Pramparo et al., 2010; Wynshaw-Boris et al., 2010)	Lissencephaly (des Portes et al., 1998; Gleeson et al., 1998)	Doublecortin domain, kinase domain
nde1	nudE	nud-2	Centrosome duplication and maturation, chromosome alignment, spindle orientation, nucleokinesis (vertebrate), kinetochore function, chromosome congression, centrosome behavior (fly), nuclear migration (worm) (Wainman et al., 2009; Fridolfsson et al., 2010; Chansard et al., 2011)	Microlissencephaly (Alkuraya et al., 2011; Bakircioglu et al., 2011)	Coiled-coil domain
Gαi1, Gαi2, Gαi3	Gαi1	goa-1, gpa-16	Spindle orientation (vertebrate, fly), ACD (fly, worm), spindle positioning, chromosome segregation (worm) (Srinivasan et al., 2003; Morin and Bellaïche, 2011)	–	GTPase subunit of heterotrimeric G proteins
numa	mud	lin-5	ACD, chromosome segregation (vertebrate, fly, worm), spindle orientation, spindle pole integrity (vertebrate, fly), spindle positioning, cytokinesis (worm) (Lorson et al., 2000; Radulescu and Cleveland, 2010; Capalbo et al., 2011; Morin and Bellaïche, 2011; Kolano et al., 2012)	Leukemia (Wells et al., 1997)	Coiled-coil domain
pins/lgn/ gpsm2/ ags3	pins	gpr-1, gpr-2	ACD (vertebrate, fly, worm), spindle orientation (vertebrate, fly), chromosome segregation (vertebrate, worm), spindle positioning (worm) (Du et al., 2001; Srinivasan et al., 2003; Morin and Bellaïche, 2011)	Non-syndromic deafness (Walsh et al., 2010), brain malformations and deafness in Chudley-McCullough syndrome (Doherty et al., 2012)	GoLoco motif, tetratricopeptide (TPR) domains
insc	insc	–	Spindle orientation (vertebrate, fly), asymmetric cell division (fly) (Morin and Bellaïche, 2011)	–	Armadillo repeats
htt	htt	F21G4.6[a]	Neuronal transport, spindle orientation (vertebrate, fly) (Gunawardena et al., 2003; Godin and Humbert, 2011)	The Huntington's Disease Collaborative Research Group (1993)	Polyglutamine tract, polyproline sequence, HEAT repeats
magoh	mago	mag-1	RNA processing (vertebrate, fly worm), RNA localization (vertebrate, fly), spindle orientation and integrity, genomic stability (vertebrate), cytoskeleton organization (fly) (Li et al., 2000; Kataoka et al., 2001; Palacios, 2002; Le Hir and Andersen, 2008; Silver et al., 2010)	–	Mago nashi domain
apc	apc1, apc2	apr-1	Wnt signaling, ACD, microtubule stability (vertebrate, fly, worm), spindle orientation (vertebrate, fly), chromosome segregation, tumor suppressor (vertebrate) (Yamashita et al., 2003; Mizumoto and Sawa, 2007; McCartney and Näthke, 2008; Bahmanyar et al., 2009)	Familial adenomatous polyposis (FAP), gastrointestinal tumors (Minde et al., 2011)	Armadillo repeats, oligomerization domain, CRM1, β-catenin, microtubule-binding domains,
vegf	pvf1, pvf2, pvf3	pvf-1	Cell migration (vertebrate, fly), growth factor, oncogene, spindle orientation, angiogenesis (vertebrate) (Duchek et al., 2001; Tarsitano et al., 2006; Beck et al., 2011; Sitohy et al., 2012)	Epithelia skin cancer (Beck et al., 2011)	PDGF domain
vhl	vhl	vhl-1	HIF1α regulation (vertebrate, fly, worm), microtubule stability, endocytosis, cell migration (vertebrate, fly), tumor suppressor, spindle orientation, genome integrity (vertebrate) (Thoma et al., 2009; Hsu, 2012)	Renal cell carcinoma (Kaelin, 2008)	Cullin E3 ubiquitin ligase

Table 1. **Genes regulating spindle orientation and mutated in diseases** *(continued)*

Gene name – species			Cellular function	Associated disease	Molecular characteristics
Vertebrate	Fly	Worm			
pten	pten	daf-18	PI3K signaling (vertebrate, fly, worm), tumor suppressor, spindle orientation, genome integrity, cell growth (vertebrate), cell growth, actin cytoskeleton organization, (fly) (Ogg and Ruvkun, 1998; Stocker and Hafen, 2000; von Stein et al., 2005; Toyoshima et al., 2007; Hollander et al., 2011)	PTEN hamartoma tumor syndromes (PHTS) (Hollander et al., 2011)	Protein and lipid phosphatase
mcph1/ micro-cephalin/ brit1	mcph1	–	DNA damage response, centrosome integrity, chromosome segregation (vertebrate, fly), spindle orientation (vertebrate) (Thornton and Woods, 2009; Gruber et al., 2011)	Microcephaly (Jackson et al., 2002)	BRCA1 C-terminal (BRCT) domains
mcph2/ wdr62	–	–	Centrosome integrity, spindle orientation, chromosome alignment (vertebrate) (Bogoyevitch et al., 2012)	Microcephaly, lissencephaly, schizencephaly (Bilgüvar et al., 2010; Nicholas et al., 2010; Yu et al., 2010)	WD40 repeats
mcph3/ cdk5rap2/ cep215	cnn	–	Centrosome assembly, spindle orientation, chromosome segregation (vertebrate, fly), DNA damage response (vertebrate) (Siller and Doe, 2008; Megraw et al., 2011)	Microcephaly (Bond et al., 2005)	Coiled-coil domains, centrosomin motives (CM) 1 and 2
mcph4/ cep152	asl	–	Centriole formation and duplication (vertebrate, fly), genome integrity (vertebrate) (Kalay et al., 2011; Brito et al., 2012)	Microcephaly (Guernsey et al., 2010), Seckel syndrome (Kalay et al., 2011)	Coiled-coil domains
mcph5/ aspm/ calmbp1	asp	aspm-1	Spindle assembly, spindle orientation, cytokinesis (vertebrate, fly), the integrity of spindle poles and the central spindle (fly), meiotic spindle orientation (worm) (Varmark, 2004; van der Voet et al., 2009; Higgins et al., 2010)	Microcephaly (Bond et al., 2002), tumorigenesis (Lin et al., 2008)	Calponin homology (CH) domains, IQ-repeat motifs
mcph6/ cenpj/ cpap	sas4	sas-4	Centriole duplication (vertebrate, fly, worm), spindle orientation (vertebrate), ACD (fly) (Leidel and Gönczy, 2005; Basto et al., 2006; Kitagawa et al., 2011; Brito et al., 2012)	Microcephaly (Bond et al., 2005), Seckel syndrome (Al-Dosari et al., 2010)	Coiled-coil motives, PN2-3 domain, T-complex protein 10 (TCP) domain
mcph7/ stil/sil	ana2	sas-5	Centriole duplication (vertebrate, fly, worm), spindle orientation (vertebrate, fly), ACD (fly) (Leidel and Gönczy, 2005; Wang et al., 2011; Brito et al., 2012)	Microcephaly (Kumar et al., 2009), leukemia (Aplan et al., 1991)	Coiled-coil domain, STIL/ANA2 (STAN) motif
cep63	–	–	Spindle assembly, mitotic entry, genome maintenance, centrosome duplication (vertebrate) (Smith et al., 2009; Löffler et al., 2011)	Microcephaly (Sir et al., 2011)	Coiled-coil domains

In many cases genes mutated in these pathologies control spindle orientation at the cellular level. ACD, asymmetric cell division.
[a]The function of the genes has not been characterized.

asymmetric divisions and finally apoptosis of the arising daughter cells. As a consequence, the pool of brain stem cells is massively diminished early in development, decreasing the number of neurons, causing severe brain abnormalities and eventually embryonic death (Yingling et al., 2008).

Consistent with a role for Lis1 in regulation of spindle orientation in mouse, recent work shows that mutations in the exon junction protein Magoh results in reduced Lis1 levels, spindle orientation defects, and abnormal brain development (Silver et al., 2010). Although expression of Lis1 in these mutants can rescue the brain developmental defects, the authors did not investigate whether the spindle orientation defect was also rescued (Silver et al., 2010). Furthermore, mutations in genes encoding for DCX (doublecortin) and NDE1, both of which function in dynein-dependent processes and physically interact with Lis1, result in spindle orientation defects in *C. elegans* and mice (Gönczy et al., 2001; Feng and Walsh, 2004; Pramparo et al., 2010) and cause lissencephaly in humans (des Portes et al., 1998; Gleeson et al., 1998; Alkuraya et al., 2011; Bakircioglu et al., 2011).

Huntington. Another pathology where spindle orientation may play a role is Huntington's disease. Huntington's disease is a neurodegenerative disorder that manifests in adult life and leads to cognitive defects, dementia, and muscle coordination

defects (Borrell-Pagès et al., 2006). Huntingtin (htt), the protein mutated in Huntington's disease, interacts with microtubules and dynein and mediates neuronal transport (Borrell-Pagès et al., 2006). In cultured cells, depletion of htt results in the loss of dynein, dynactin, and NuMA at centrosomes and in spindle misalignment (Godin et al., 2010). Huntingtin is also required for proper spindle orientation in *D. melanogaster* neuroblasts and mouse cortical progenitors (Godin et al., 2010). As Huntington is a disease that develops later in life, this finding raises the possibility that a defect of neurogenesis during embryonic development contributes to the origin of the disease.

Carcinogenesis

Because the loss of several tumor suppressor genes or overexpression of certain oncogenes results in spindle orientation defects, carcinogenesis is the second disease class that has been associated with defective spindle orientation (Pease and Tirnauer, 2011). Cancer formation results from the uncontrolled proliferation of cells, which impairs tissue function, and from the ability of cells to invade new tissues during metastasis. One prominent hypothesis is that spindle orientation defects increase cell numbers by suppressing the asymmetric, differentiative divisions of stem cells while increasing their symmetric, proliferative divisions (Morrison and Kimble, 2006). Moreover, defective spindle orientation might disorganize tissue architecture, a typical feature of malignant transformation (McAllister and Weinberg, 2010). The best evidence for a defective fate determination of stem cells is found in *D. melanogaster*, where there is a clear distinction between asymmetric differentiative and symmetric proliferative stem cell divisions, and where loss of asymmetric stem cell division results in an uncontrolled invasive cell proliferation (Caussinus and Gonzalez, 2005; Lesage et al., 2010). More recent studies postulated a similar mechanism in mammals, based on experiments performed in mammospheres and mouse models for colon cancer or gliomas (Cicalese et al., 2009; Quyn et al., 2010; Sugiarto et al., 2011). This mechanism could favor the uncontrolled proliferation of stem cells, leading to the formation of cancer stem cells. Indeed, in some cancers, such as papillomas (Driessens et al., 2012), cancer stem cells undergo rapid proliferative divisions, with the ability to be at the origin of an entire tumor cell population. However, there are several caveats to consider. First, there is conflicting evidence as to whether mammalian stem cells undergo asymmetric or symmetric cell divisions (Quyn et al., 2010; Snippert et al., 2010; Bellis et al., 2012); second, the idea of cancer stem cells itself is hotly debated, both as a concept and whether it is applicable to all cancer types (Lobo et al., 2007; Magee et al., 2012); third, cancer stem cells may not necessarily originate from stem cells. Keeping these caveats in mind, we present here the molecular evidence linking spindle orientation to carcinogenesis.

APC: Adenomatous polyposis coli. Mutations in the *apc* gene are found in a vast majority of colon cancers and in familial adenomatous polyposis disease, where they predispose patients to intestinal cancer (Fodde and Smits, 2001; Minde et al., 2011). APC is a tumor suppressor that inhibits canonical Wnt signaling by impairing β-catenin–dependent transcriptional activity (Reya and Clevers, 2005). APC can inhibit β-catenin through direct binding, or by promoting its nuclear export to favor its ubiquitin-dependent degradation. APC also plays a crucial role during mitosis, where it binds the microtubule plus-end scaffold protein EB1 (Su et al., 1995) to promote microtubule stability (Fodde and Smits, 2001; Kaplan et al., 2001). APC mutations or deletions cause spindle orientation and chromosome alignment defects, and lead to chromosomal instability and cytokinesis failure in mammalian cells (Fodde and Smits, 2001; Kaplan et al., 2001; Green and Kaplan, 2003; Tighe et al., 2004; Caldwell et al., 2007). Furthermore, in *D. melanogaster* APC is required for correct spindle orientation and asymmetric cell division in germline stem cells and in the syncytium (McCartney et al., 2001; Yamashita et al., 2003), but not in neuroblasts (Rusan et al., 2008).

The molecular mechanism by which APC controls spindle orientation is still under debate: it could be its ability to stabilize astral microtubules and/or its regulation of cell polarity (Akiyama and Kawasaki, 2006). In vivo APC mutations or loss of APC lead to a rapid cellular transformation, and to cancer formation in the small and large intestine in mice; it correlates with misoriented spindles in both compartments, suggesting that loss of asymmetric divisions promotes tissue overgrowth (Caldwell et al., 2007; Fleming et al., 2009; Quyn et al., 2010). This could occur either through an aberrant distribution of cell fate determinants into daughter cells and/or incorrect placement of the arising daughters within the tissue (Näthke, 2006). However, a recent report challenged this view, showing that APC mutant mice develop colon cancer in the absence of spindle orientation defects (Bellis et al., 2012). Furthermore, the induction of β-catenin signaling alone is sufficient to induce carcinogenesis, implying that the tumor suppressor activity of APC cannot be explained only in terms of spindle orientation control (Harada et al., 1999).

VEGF: Vascular endothelial growth factor. VEGF is an oncogene that promotes angiogenesis in cancer tissues (Ferrara, 2002). Studies investigating the behavior of cancer stem cells in skin papilloma found that inhibition of VEGF results in reduced proliferative symmetric stem cell divisions, reappearance of asymmetric divisions, and tumor regression. These asymmetric divisions correlate with a mitotic spindle oriented perpendicular to the epidermis (Beck et al., 2011), suggesting that high levels of VEGF impair spindle orientation.

VHL: von Hippel-Lindau gene. Mutations in *vhl*, a tumor suppressor gene, predispose patients to cancer formation in multiple tissues, in particular in kidneys (Frew and Krek, 2007; Kaelin, 2008). VHL is an adaptor protein with multiple interactors and functions, one of which is to target the hypoxia-inducible factor 1 α, HIF1α, for ubiquitin-dependent degradation (Kaelin, 2008). Loss of VHL leads to angiogenesis, thus favoring cancer growth. However, VHL also regulates microtubule dynamics both in vertebrates and flies (Hergovich et al., 2003; Thoma et al., 2007, 2009; Duchi et al., 2010), and it plays a crucial role during vertebrate mitosis. VHL depletion or knock-out in culture cells randomizes spindle orientation due to unstable astral microtubules, and weakens the spindle checkpoint, resulting in chromosomal instability (Thoma et al., 2009).
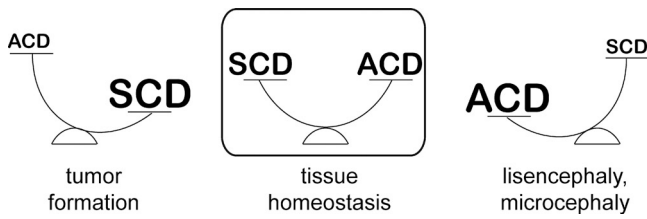
Figure 4. **Equilibrium between symmetric and asymmetric divisions confers proper development and tissue homeostasis.** Schematic representation of the balance between symmetric and asymmetric cell division and its relevance. ACD, asymmetric cell division. SCD, symmetric cell division.

Cancer patients can carry *vhl* mutations affecting only HIF1α stability or only microtubule stability, indicating that both phenotypes are sufficient to induce tumorigenesis (Thoma et al., 2009). One attractive hypothesis is that the elongation of renal tubes requires oriented cell divisions; misregulation of division plane leads to an increase in tube diameter and cyst development, a feature of VHL syndrome (Fischer et al., 2006). However, only very few of those cysts will develop into a carcinoma, suggesting that spindle orientation defects and the ensuing cysts are not sufficient, per se, to induce cancer formation in kidneys. Moreover, loss of VHL may prone cells for aneuploidy, another potential cause of cancer formation (Weaver and Cleveland, 2009).

PTEN: Phosphatase and tensin homologue. PTEN is a lipid phosphatase that controls cell growth by regulating phosphatidylinositol kinase signaling, and it is one of the most frequently mutated tumor suppressor genes (Hollander et al., 2011). PTEN was shown to control spindle orientation in human tissue culture cells (Toyoshima et al., 2007). This study found that phosphatidylinositol-3-phosphate (PIP3) molecules are enriched at the cell equator, and that PIP3 localization directs the correct localization of dynein at the cell cortex. Loss of PTEN or inactivation of PI3-kinase respectively saturate or abolish PIP3 localization in the entire cell cortex, leading to randomization of spindle orientation (Toyoshima et al., 2007). However, as these data were only obtained in cultured cell lines, it will be important to examine whether loss of PTEN also impairs spindle orientation in tissues.

Spindle orientation defects: Cause, aggravating factor, or symptom?

Given the correlation between spindle orientation defects and the appearance of neurological diseases and cancers, it is tempting to postulate that the loss of spindle orientation control is at the origin of these pathologies. Although neurological disorders would be caused by a premature shift from symmetric to asymmetric divisions and consequent reduction in neuron number, cancers would be the results of uncontrolled symmetric and thus proliferative cell divisions (Fig. 4). This would reflect the fact that the controlled balance of symmetric or asymmetric cell divisions is essential for development and tissue homeostasis, and that the consequences of spindle misorientation strongly depend on the biological context. A causal link between spindle orientation defects and carcinogenesis has been made in *D. melanogaster* (Caussinus and Gonzalez, 2005; Castellanos et al., 2008).

In mammals, however, this is only an attractive hypothesis based on correlative evidence. One of the reasons is that all the mutations or gene deletions that we have discussed lead to pleiotropic effects. This ranges from induction of apoptosis (e.g., MCPH1, CDK5RAP2, or Lis1), loss of growth control (e.g., APC, PTEN, VEGF), chromosome segregation defects (e.g., Lis1, APC, VHL, MCPH1, CDK5RAP2), and changes in other microtubule-dependent processes, such as intracellular transport or cell migration (Table 1 and references within). All these processes are implicated in neuropathologies or tumor formation. Moreover, many of those gene products are also present in cilia (e.g., MCPH4, 6, and 7; Bettencourt-Dias et al., 2011) or involved in cilia formation (VHL and PTEN; Frew et al., 2008; Hsu, 2012), which could suggest that cilia defects might be at the origin of some pathologies. Conversely, a number of gene deletions or mutations classically associated with ciliopathies, such as Pkd1 and ITF88, also impair spindle orientation, raising the possibility that spindle orientation defects play an aggravating role in ciliopathies (Fischer et al., 2006; Delaval et al., 2011). Furthermore, it is difficult to establish a direct causality because mutations affecting spindle orientation can have tissue-specific effects. At present it is therefore impossible to determine whether spindle orientation defects are a cause, an aggravating factor, or just a by-product of these diseases.

One way to address this question would be to test whether rescuing spindle orientation defects by reintroducing a separation-of-function mutant suppresses the corresponding pathology. The C-terminal truncation of *aspm* in mice is an example for this approach (Pulvers et al., 2010). This truncation does not disrupt spindle orientation, but still leads to microcephaly, indicating that spindle orientation defects are not essential for primary microcephaly. Another possibility would be to introduce a deletion in a second gene to rescue the spindle orientation defects. For example, to counteract a VHL mutant that cannot stabilize microtubules, one could delete a gene that destabilizes microtubules, like stathmin-1 (Belmont and Mitchison, 1996). Stathmin-1 is an oncogene, but knock-out mice are viable with only minor sociological defects (Schubart et al., 1996; Shumyatsky et al., 2005). Therefore, one could test whether stathmin-1 deletion suppresses both spindle defects and cancerogenesis in such a background. One caveat for the interpretation of this strategy is that the "suppressor" deletion may have other, unwanted effects. Another caveat is that these experiments only reveal whether spindle orientation defects are essential for disease development in a particular genetic background, and not whether spindle orientation defects, per se, can induce a pathological state.

A more direct approach will be to test the effect of a "pure" spindle orientation defect, which has no other side-effects. Two ideal candidates are LGN and Insc, which only affect spindle orientation, and do not impair cell polarity or other aspects of mitotic progression in mammalian systems (Zheng et al., 2010; Postiglione et al., 2011; Williams et al., 2011). Interestingly, both genes have been deleted in mice to study their contribution to brain development (Konno et al., 2008; Postiglione et al., 2011). Loss of LGN randomized mitotic spindle orientation and led to tissue architecture defects but did not result in smaller

brains. On the contrary, loss of Insc led to depletion of vertical and oblique divisions (Fig. 3 B), and this resulted in production of fewer neurons and smaller brains. In the future it will be necessary to closely compare these phenotypes and to combine both mutants for epistasis analysis to investigate the outcome and better understand the role of spindle orientation in this process. Furthermore, it will be interesting to test if mutations in LGN or Insc are ever found in human microcephaly patients.

With regards to carcinogenesis, it is striking that LGN mutant mice have minor developmental defects, but that cancers have not been reported (Konno et al., 2008; Williams et al., 2011). However, before drawing strong conclusions, these mice should be analyzed for spindle orientation defects in other tissues. Furthermore, one should investigate whether some of the LGN functions are taken over by the closely related protein, AGS3 (Sanada and Tsai, 2005; Siller and Doe, 2009).

It will be also important to investigate if spindle orientation defects can play an aggravating role in cancer by combining spindle orientation defects with cancer mutations and testing for synergistic effects. Ideal cancer mutations could be loss of the tumor suppressor p53, or overexpression of the Ras oncogene (Hanahan and Weinberg, 2000). The combinations of mutations will be interesting even if spindle orientation defects, per se, are sufficient to induce tumor formation, as they can reveal whether spindle orientation defects lead to an earlier onset of tumor formation and/or accelerate the progression of the tumor. Overall, such investigations will allow one to test the attractive hypothesis that spindle orientation is a critical process for those diseases, opening up new important paths for possible treatments of these pathologies.

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