Asymmetric centrosome behavior and the mechanisms of stem cell division

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The ability of dividing cells to produce daughters with different fates is an important developmental mechanism conserved from bacteria to fungi, plants, and metazoan animals. Asymmetric outcomes of a cell division can be specified by two general mechanisms: asymmetric segregation of intrinsic fate determinants or asymmetric placement of daughter cells into microenvironments that provide extrinsic signals that direct cells to different states. For both, spindle orientation must be coordinated with the localization of intrinsic determinants or source of extrinsic signals to achieve the proper asymmetric outcome. Recent work on spindle orientation in *Drosophila melanogaster* male germline stem cells and neuroblasts has brought into sharp focus the key role of differential centrosome behavior in developmentally programmed asymmetric division (for reviews see Cabernard, C., and C.Q. Doe. 2007. *Curr. Biol.* 17:R465–R467; Gonzalez, C. 2007. *Nat. Rev. Genet.* 8:462–472). These findings provide new insights and suggest intriguing new models for how cells coordinate spindle orientation with their cellular microenvironment to regulate and direct cell fate decisions within tissues.

The essential stem cell question: to renew or not to renew

Adult stem cells maintain many short-lived but highly differentiated cell types, including cells of the blood, skin, lining of the intestine and colon, and sperm. Although normally specialized to produce particular cell types, adult stem cells are relatively undifferentiated cells that retain their ability to keep dividing and to produce fully differentiated cells throughout adult life. When stem cells divide, their daughters either self-renew stem cell identity or initiate differentiation. The balanced choice between these alternate fates is critical both to maintain stem cell numbers and to rein in their potentially dangerous capacity for long-term proliferation.

A stem cell can divide asymmetrically, producing exactly one stem cell and one differentiating cell to maintain the tissue in a homeostatic state, or symmetrically, producing two stem cells. The latter is an important mechanism for stem cell expansion during embryonic development and replacement of stem cells after injury (for review see Morrison and Kimble, 2006). Recent studies have illuminated the importance of the stem cell microenvironment, or niche, as a source of local extrinsic signals that specify stem cell self-renewal (for reviews see Spradling et al., 2001; Fuchs et al., 2004). In the context of this niche, developmentally regulated orientation of the mitotic spindle directs whether the outcome of a stem cell division is asymmetric or symmetric. When the spindle is oriented perpendicular to the interface with the niche, upon cell cleavage, one daughter can maintain contact with the niche while the other is displaced away and is free to initiate differentiation. In contrast, spindle orientation parallel to the interface with the niche can allow both daughters to inherit attachments to and receive local self-renewal signals from the niche. Such relationships between spindle orientation and asymmetric/symmetric stem cell division have been observed in many systems, including mammalian skin (Lechler and Fuchs, 2005), muscle (Kuang et al., 2007), and neuronal stem cells (Estivill-Torrus et al., 2002), and appear to be broadly used to accomplish asymmetric stem cell divisions.

Spindle reorientation or permanent cell polarity: two routes to an oriented cell division

Cells use two different types of strategies to orient the division plane with respect to intrinsic or extrinsic asymmetry cues. Cells can maintain a fixed orientation throughout the cell cycle so that proper spindle orientation is predetermined before cells enter mitosis. Alternatively, cells can first assemble the mitotic spindle at a different angle and then undergo programmed spindle rotation to acquire the desired orientation by metaphase. The programmed rotation strategy may be especially advantageous in cases in which cells switch between symmetric versus asymmetric divisions (for example, under developmental control or in response to injury). However, with such flexibility, the option for a symmetric outcome must be carefully

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Abbreviations used in this paper: APC, adenomatous polyposis coli; GMC, ganglion mother cell; GSC, germline stem cell; MTOC, microtubule-organizing center; SPB, spindle pole body.

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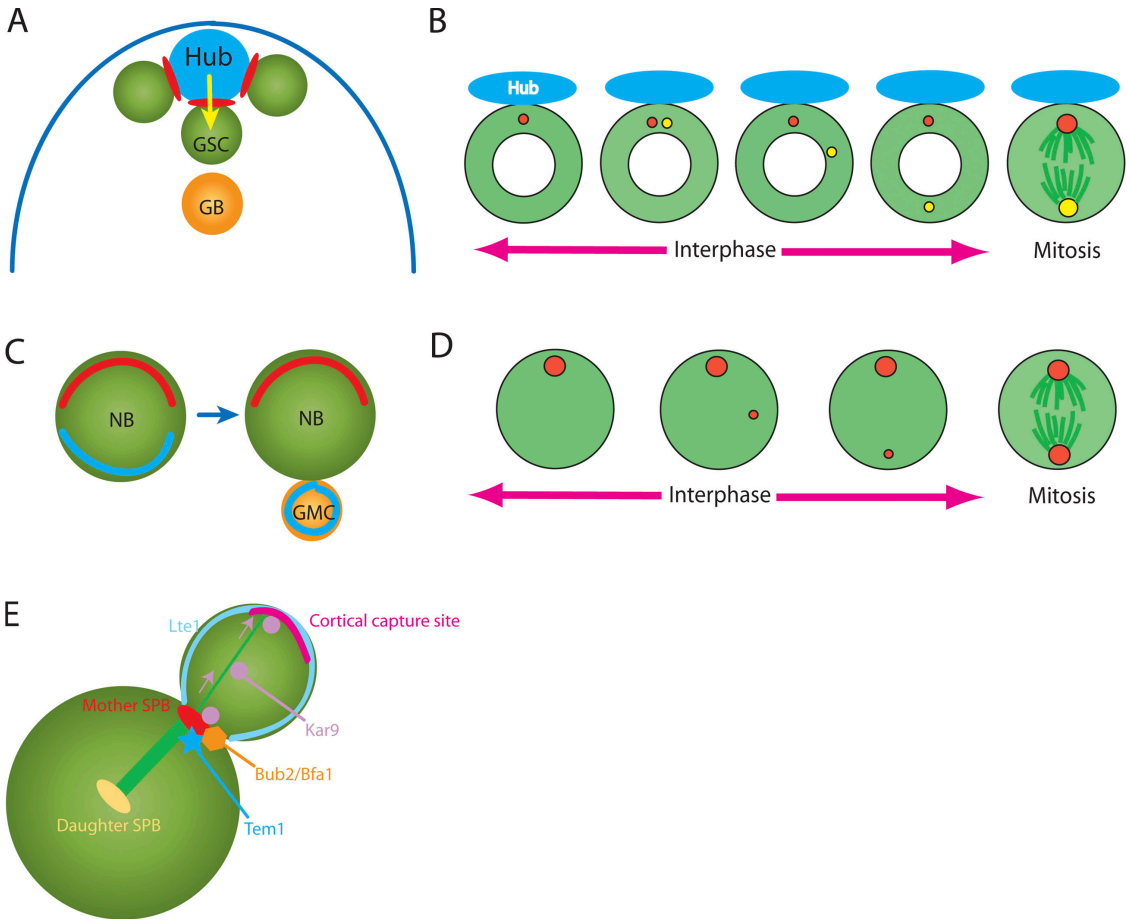

Figure 1. **Asymmetric centrosome/SPB behavior during asymmetric cell divisions.** (A) Structure of the stem cell niche in the *Drosophila* male germline. Somatic hub cells are the major components of the niche for male GSCs. The GSC attaches to the hub via adherens junction (red lines) so that it can receive the signaling ligand, Upd, from the hub (yellow allow) to activate the JAK–STAT (Janus kinase–signal transducer and activator of transcription) pathway. The stem cell daughter that is displaced away from the hub (gonialblast; GB) starts differentiation. (B) Consistent centrosome positioning orients the mitotic spindle in male GSCs. The mother centrosome (red dots) is always located close to the hub, whereas the daughter (yellow dots) migrates toward the opposite side of the cell to set up orientation of the mitotic spindle. (C) Asymmetric division of the *Drosophila* neuroblast (NB). The neuroblast divides asymmetrically by segregating fate determinants. Apical protein complexes (red lines) include Par6, Baz, and atypical PKC, and basal fate determinants (blue lines) include Numb, Miranda, and Prospero (for a more comprehensive set of asymmetrically localized proteins, see the review Yu et al., 2006). (D) Consistent centrosome behavior orients the mitotic spindle in the neuroblast. The apical centrosome (large red dots) retains MTOC activity throughout the cell cycle, whereas the other centrosome (small red dots) becomes active only at the G2-M transition. The inactive centrosome migrates toward the basal side during interphase. Pins might be functioning to provide a cortical cue to anchor active MTOC. (E) Spindle orientation in budding yeast. The mother SPB is normally delivered to the bud cell, where it is captured by the bud tip cortex. This process is mediated by astral microtubules emanating from the mother SPB and Kar9 protein. Cell cycle regulators such as Tem1 and Bub2/Bfa1 are specifically localized to the bud-directed SPB (normally the mother SPB) to coordinate spindle position and cell cycle progression.

controlled lest it allow the undesired proliferation of stem cells, which may perturb orchestrated tissue development/maintenance. In contrast, stem cell systems that use the fixed orientation mechanism may be more resistant to tumorgenesis but more limited in capacity to expand stem cell number for replenishment or repair.

Germline stem cells: oriented division within a stem cell niche

Male and female germline stem cells (GSCs) in *Drosophila melanogaster* provide some of the best-understood examples of asymmetric stem cell divisions in vivo in the context of their niche. *Drosophila* GSCs are physically attached via adherens junctions to somatic niche cells that secrete signaling ligands that specify stem cell identity in the neighboring germ cells. In females, somatic cap cells at the tip of each ovariole secrete TGFβ-class ligands that maintain nearby germ cells in the stem cell state. Activation of the TGFβ signal transduction pathway directly represses transcription of a key differentiation gene, *bam*, in GSCs (Chen and McKearin, 2003a,b). In males, somatic hub cells located at the apical tip of the testis provide the niche by secreting the ligand Upd, which activates the JAK–STAT (Janus kinase–signal transducer and activator of transcription) signal transduction pathway within the GSCs, preventing stem cells from differentiating (Fig. 1 A; Kiger et al., 2001; Tulina and Matunis, 2001).

In both sexes, the mitotic spindle is normally oriented perpendicular to the interface with the niche so that one daughter of each GSC division inherits the adherens junctions and retains close contact with the niche and its sustaining signals,

whereas the other normally loses contact with the niche and initiates differentiation. The mitotic spindle is normally perpendicular to the niche when it is initially set up and does not rotate to acquire the desired orientation. In male GSCs, centrosomes are oriented with respect to the niche throughout the cell cycle, preparing the orientation of mitotic spindle (Fig. 1 B; Yamashita et al., 2003). Female GSCs appear to use the spectrosome, a membrane-rich subcellular organelle, to orient the spindle (Deng and Lin, 1997).

Neuroblasts: asymmetric inheritance of intrinsic determinants

Drosophila neuroblasts provide one of the most well-understood examples of tissue-renewing cells that undergo asymmetric division based on differential segregation of intrinsic fate determinants (Fig. 1 C). In *Drosophila* embryos and larvae, neuroblasts of the central nervous system undergo a series of asymmetric divisions, each generating a new neuroblast and a ganglion mother cell (GMC), which divides once more and then differentiates. Key determinants that regulate differentiation are localized to the basal cortex of the neuroblast before cell division and, as a result of an apicobasally oriented and asymmetrically positioned mitotic spindle, are sequestered into the nascent GMC (for review see Yu et al., 2006).

Asymmetric localization of fate determinants to the basal cortex depends on an evolutionally conserved mechanism based on the Par6, Baz (Par3), and atypical PKC cell polarity complex, which localizes to the apical side of the neuroblast cortex before division. The apical Par complex also serves as a binding platform for proteins that control orientation and positioning of the mitotic spindle. Coordination of the position of cell fate determinants with spindle orientation (which depends on Pins and G protein signaling) means that determinants localized to the basal cortex of the dividing neuroblast are reliably inherited into the GMC, where they promote differentiation. Live cell imaging of embryonic neuroblasts revealed that the cell polarity complex, interphase centrosome, and spindle are all oriented with respect to extrinsic cues from contact with epithelial cells. Although the centrosome maintains position near the interface with the epithelial cells throughout much of interphase, in approximately half of the early embryonic neuroblasts observed, the centrosomes leave this position when they separate and move to the opposite sides of the nucleus in prophase. As a result, when the spindle is initially set up, it is not oriented along the axis of neuroblast asymmetry but reorients to the proper position before the metaphase-anaphase transition (Kaltschmidt et al., 2000; Siegrist and Doe, 2006).

Separate but not equal centrosomes

In contrast to the programmed rotation of the spindle in embryonic neuroblasts, spindles are normally properly oriented at the time that they are set up in larval neuroblasts in the central nervous system as in *Drosophila* GSCs. Larval brain neuroblasts maintain a consistent orientation through many cell cycles so that new GMCs emerge next to those produced during previous cell cycles. In a developmentally programmed specialized centrosome cycle, one of the two centrosomes retains microtubule-organizing center (MTOC) activity and a robust astral microtubule array during interphase and remains close to the apical cortex. Meanwhile, the other centrosome loses MTOC activity and wanders actively throughout the apical half of the cell (Fig. 1 D). Later in the cell cycle, the inactive centrosome moves to the basal side of the cell, where it regains MTOC activity by the onset of mitosis (Rebollo et al., 2007; Rusan and Peifer, 2007).

In a striking parallel, differential behavior of the two centrosomes during interphase also appears to underlie the stereotyped orientation of the spindle in *Drosophila* male GSCs. Early in interphase, the single centrosome in each male GSC is located close to the interface with the stem cell niche. After centrosome duplication, one centrosome maintains a robust array of astral microtubules throughout the cell cycle and stays close to the niche, whereas the other migrates away, setting up the future perpendicular orientation of the mitotic spindle (Yamashita et al., 2007). The centrosome that migrates to the opposite side of the nucleus is associated with few microtubules until late in the cell cycle, when it appears to resume MTOC activity. The separation and migration of centrosomes occurs early in the cell cycle in male GSCs, as centrosomes were already separated in 40% of the male GSCs observed (Yamashita et al., 2003).

Adenomatous polyposis coli 2 (APC2) protein that is localized to the cell cortex where the GSC contacts the niche may link the adherens junctions and astral microtubules emanating from the nearby centrosome, as loss of function mutations in *apc2* result in the misorientation of centrosomes during interphase and spindles during mitosis (Yamashita et al., 2003). This linkage to APC2 and the adherens junction may also help stabilize the astral microtubule array. The centrosome–cortex interaction also appears to be important in neuroblasts because mutant neuroblasts lacking astral microtubules (such as in cnn or asl mutant) cannot correctly orient their mitotic spindles (Megraw et al., 2001; Rusan and Peifer, 2007). Also, proteins required for microtubule–cortex interaction are essential for neuroblast spindle orientation; the NUMA (nuclear mitotic apparatus protein)–related Mud protein, which interacts with centrosomes as well as the cell cortex via Pins, and the dynein complex play an essential role in neuroblast spindle orientation (Siller et al., 2005, 2006; Izumi et al., 2006). Although the mechanism that marks special cortical domains might be different in GSCs and neuroblasts (APC2 vs. Pins), anchoring of centrosomes/spindles to the cortex might be a conserved mechanism to orient the mitotic spindle.

Still in Eden: male GSCs in the niche maintain a centrosomal Eve

Strikingly, differential labeling of mother versus daughter centrosomes in male GSCs revealed that it is the mother centrosome that normally maintains position next to the niche and the daughter centrosome that migrates to the opposite side of the nucleus (Yamashita et al., 2007). The asymmetric behavior of mother and daughter centrosomes ensures the stereotyped positioning of centrosomes within the GSC, which, in turn, sets up the perpendicular orientation of the spindle once the GSC enters mitosis. In turn, the oriented spindle programs the normally

asymmetric outcome of the stem cell division, retaining one daughter cell attached to the niche and its self-renewal signals, whereas the other is displaced away from the niche and is free to differentiate. As a result, it is the mother centrosome containing the oldest centriole that is consistently inherited by the stem cell. Thus, male GSCs maintain a "centrosomal Eve," a very old centrosome that contains a centriole assembled many cell generations earlier (Yamashita et al., 2007). It will be interesting to examine whether it is also the mother centrosome that maintains a robust microtubule array and maintains apical position in larval neuroblasts. The similarities between male GSCs and larval neuroblasts raise the possibility that a novel, developmentally programmed centrosome cycle with differential regulation of two centrosomes within a single cell may be a general mechanism in stem cells or tissue progenitors by which a stereotyped spindle orientation is set up before spindle assembly.

Why the centrosome? Hints from other systems

Studies on centrosome behavior in other systems may shed light on how the asymmetric behavior of centrosomes in asymmetric stem cell divisions may be programmed. Observations in mammalian cultured cells suggest that structural differences between older and younger centrioles can be used to confer differential behavior on mother and daughter centrosomes. Mature and young centrioles have different structural features, including subdistal appendages that appear to allow mature centrioles to better anchor and maintain microtubules nucleated from centrosomes (for reviews see Urbani and Stearns, 1999; Delattre and Gonczy, 2004). Perhaps as a result, mother and daughter centrioles have been observed to behave differently during early interphase in mammalian cultured cells. Mother centrioles had a more robust microtubule array and remained relatively stationary during interphase, whereas daughter centrioles had fewer microtubules and tended to move actively around the cell (Piel et al., 2000, 2001).

It takes 1.5 to two cell cycles for centrioles to mature (for review see Delattre and Gonczy, 2004). Although the reason why it takes this long for centrioles to mature is not fully understood, this extended maturation time might be exploited to confer different properties on centrosomes in the same cell. The mother centrosome contains the oldest centriole (the grandmother centriole) and a newly born centriole, whereas the daughter centrosome contains a centriole assembled during the previous cell cycle and a newly born centriole. Thus, the mother centrosome may have a higher capacity to maintain microtubules as a result of the more mature structural state of its oldest centriole. If the gradual maturation of microtubule anchoring capacity is also true for *Drosophila* centrioles, the unusually early separation of duplicated centrosomes in *Drosophila* male GSCs may help the daughter centrosome move away before it matures enough to anchor many microtubules and be trapped near the niche-GSC interface. Although there are as yet no known structural differences between *Drosophila* mother and daughter centrioles, such as the distal appendage observed in mammalian centrioles, the daughter centriole is shorter than the mother centriole for most of the cell cycle in *Drosophila* cells, which may confer qualitative differences between mother and daughter centrioles (Vidwans et al., 2003).

Presumably as a result of the asymmetric centrosome behavior in *Drosophila* male GSCs, the mother centrosome is normally segregated into the cell that maintains stem cell identity (Yamashita et al., 2007). It is tempting to speculate that one or the other centrosome may harbor fate determinants, which are then differentially inherited either by the stem cell or the daughter cell that initiates differentiation. Indeed, asymmetric inheritance of a fate-determining mRNA that associates with only one centrosome during early embryonic development has been reported in a mollusk (Lambert and Nagy, 2002). It remains to be established whether asymmetrically inherited centrosomes in stem cells are carriers of developmental information or innocent bystanders that are differentially segregated because of their role in spindle orientation during the preceding mitosis.

Centrosomes as integrators of cell cycle events

In budding yeast, differences between the mother and daughter spindle pole bodies (SPBs), the functional equivalent of centrosomes, appear to be used in establishing the stereotyped orientation of the mitotic spindle and, thus, successful cell division. Because bud production and growth occur before nuclear division, spindle orientation must be correlated with the nascent bud such that one nucleus is reliably sent off into the bud. In unperturbed budding yeast cells, the mother SPB, which has a more robust astral microtubule array as in *Drosophila* male GSCs, is normally directed toward the bud (Fig. 1 E). These astral microtubules are captured and stabilized by the bud tip cortex in a Kar9-dependent manner, guiding the mother SPB to the bud tip (Liakopoulos et al., 2003; Maekawa et al., 2003). Kar9 may be an orthologue of APC in higher organisms, raising a potential conserved link between the centrosome (SPB)-astral microtubule-APC2 (Kar9) cell cortex (Bienz, 2001). The fact that the mother centrosome is inherited by the stem cell in male GSCs but that the mother SPB is normally inherited by the bud in *Saccharomyces cerevisiae* raises the question of whether the bud might be considered the primitive stem cell equivalent in yeast. Indeed the mother yeast cell can only divide up to $\sim$50 times, thus displaying some attributes of a transit-amplifying cell, whereas the division number–counting system seems to be reset in the bud, which can keep dividing.

In addition to possible fate determinants, centrosomes may harbor mechanisms that sense the state of the cell and regulate cell cycle progression. Components of the mitotic exit network such as Tem1, Bub2, and Bfa1 are asymmetrically localized to the mother but not the daughter SPB (Fig. 1 E; Pereira et al., 2000, 2001, 2002; for review see Pereira and Schiebel, 2001). Interaction between the GTPase Tem1 and Lte1, the guanine nucleotide exchange factor for Tem1, which localizes specifically to the bud cortex, appears to be a part of the spindle position/orientation checkpoint. When the mother SPB enters the bud, localized Lte1 activates Tem1, which activates the mitotic exit network, allowing cell cycle progression (Pereira et al., 2000, 2001, 2002; Pereira and Schiebel, 2005). One wonders

whether adult stem cells in multicellular organisms might use a similar orientation checkpoint mechanism to ensure the asymmetric outcome of stem cell division in the context of the niche microenvironment. In budding yeast, inheritance of the mother SPB to the bud appears to depend on the ability of the mother SPB to harbor more astral microtubules because transient destabilization of astral microtubules by nocodazole resulted in the randomization of mother-daughter SPB inheritance. Thus, it may be that it is the asymmetric loading of checkpoint components rather than intrinsic, asymmetric differences between mother and daughter SPBs that is important for spindle orientation and its coordination with cell cycle progression. There are striking parallels between *Drosophila* male GSCs and budding yeast: (1) the centrosome (SPB)-astral microtubule-APC2 (Kar9) cell cortex link, (2) spindle orientation with respect to tissue/cell polarity (niche or preformed bud), and (3) the mother-daughter centrosome (SPB).

Concluding remarks

The developmental programs that establish male GSC fate or larval neuroblast identity are able to reprogram the behavior of a fundamental cytoskeletal organelle, the centrosome. In the resulting novel centrosomal cycle, one of the two centrosomes retains a robust microtubule array and can be anchored through it to a specific pericortical site. In contrast, the other centrosome loses MTOC activity and is free to migrate. The asymmetric behavior of the two centrosomes, which is perhaps based on different capacities of mature versus newly assembled centrioles, can then be used to set up a stereotyped orientation of the spindle with respect to either an external niche or localized intrinsic determinants, providing for a reliably asymmetric outcome of the stem cell division. Thus, the stem cell program is able to impose an extra layer of regulation to modify general cell division machinery such as the mitotic spindle and the centrosome to orchestrate cell division within the context of tissue architecture.

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