Stem Cell Self-Renewal: 
Centrosomes on the Move

Three recent studies show that centrosome asymmetry correlates with self-renewal of Drosophila neural and germline stem cells and that equalizing centrosomes disrupts asymmetric cell division.

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Stem cells need to balance self-renewal with differentiation to maintain tissue homeostasis. One mechanism to ensure stem cell self-renewal is asymmetric cell division, in which one sibling self-renews while the other sibling initiates differentiation. It is thus important to identify stem cell polarity cues that direct the daughter cells to self-renew or differentiate. Now three recent papers show that centrosome asymmetry correlates with — and is required for — proper asymmetric cell division in two model stem cell systems, Drosophila larval neuroblasts and Drosophila male germline stem cells [1–3].

Previous work from the Fuller lab and others has shown that male germline stem cells undergo asymmetric cell division: one daughter cell remains connected by adherens junctions to somatic ‘hub cells’ and self-renews as a germline stem cell, and the other loses contact with the hub and begins to differentiate (the gonialblast) [4]. A new study by Yamashita et al. [1] provides evidence that centrosome asymmetry contributes to spindle orientation in the germline stem cell, and hence to reliable self-renewal of these stem cells. Using an elegant pulse–chase method to follow centriole segregation using a GFP-tagged version of the centriole protein PACT, they found that the oldest centrioles accumulate more pericentriolar material (PCM) and maintain a more robust microtubule array compared with the newly formed centrioles, and this may help anchor the older centrosomes to the germline stem cell cortex (and possibly the adherens junctions at the hub cell contact). If this model is correct, then reducing centrosomal microtubules should release the older centrosome from the site of contact between the germline stem cell and the hub. Indeed, mutations in centrosomin (which encodes a PCM protein required for efficient microtubule nucleation) randomized the distribution of mother or daughter centrosomes relative to the hub–germline stem cell axis. Interestingly, Yamashita et al. [4] previously observed that centrosomin mutants show a 20–30% increase in germline stem cells, perhaps due to altered centrosome asymmetry or spindle orientation. In the future, it will be vital to test the precise role of centrosome asymmetry in the establishment of germline stem cell or gonialblast cell fate.

How does this finding relate to other stem cells? Satisfyingly, two recent papers report centrosome asymmetry in Drosophila larval neural stem cells, called neuroblasts [2,3]. Larval neuroblasts divide asymmetrically to generate a larger self-renewing apical neuroblast and a smaller basal ganglion mother cell (GMC), which is committed to neural differentiation. Now Rebollo et al. [2] and Rusan et al. [3] show that one neuroblast centrosome remains associated with the neuroblast cortex throughout the cell cycle; this ‘apical’ centrosome maintains its PCM and microtubule nucleation potential. In contrast, during prophase the other centriole pair moves dynamically around the neuroblast cytoplasm without recruiting PCM or nucleating stable microtubules. At metaphase, this centriole pair ceases motion, accumulates the PCM components γ-tubulin and Polo kinase, nucleates spindle microtubules, and is segregated into the basal GMC [2,3] (Figure 1, right). Although Rebollo et al. [2] used individual neuroblasts cultured in vitro, whereas Rusan et al. [3] used whole brain explant cultures, both studies reached essentially the same conclusion.

How is centrosome asymmetry achieved in larval neuroblasts? It is easy to imagine that the mother centrosome is maintained in the static, PCM-rich apical neuroblast centrosome and the newly formed daughter centrosomes are partitioned into the ganglion mother cell, similar to male germline stem cell division, but this mechanism remains to be tested. Rebollo et al. [2] test a different hypothesis — that neuroblast cortical polarity regulates centrosomal asymmetry. The Pins protein is normally localized to the neuroblast cortex overlying the static apical centrosome; Pins is thought to anchor this centrosome via Mud, a centrosomal and cortical Drosophila NuMA homolog [5–7]. Rebollo et al. [2] find that in pins mutants initial centrosome asymmetry is properly established: one centrosome is anchored at the neuroblast cortex whereas the second centriole pair migrates away. Subsequently, the apical centrosome begins to wander through the cytoplasm, similar to the basal centrosome. This suggests that Pins contributes to the differences in apical and basal centrosome behavior or to linkage of apical microtubules to the cortex; it is unlikely that Pins is required to establish structural asymmetry between centrosomes.

What is the function of centrosome asymmetry in neuroblasts? Rusan et al. [3] studied asterless (asl) mutants, which lack functional centrosomes [8]. Surprisingly, asl mutant neuroblasts frequently divide with
normal spindle orientation (one spindle pole centered on the site of contact between the neuroblast and the ganglion mother cell), although a low frequency of symmetric divisions are observed [3]. Similar results were previously observed for centrosomin mutants [9]. These results suggest that centrosomes are required for reliable spindle orientation, but that a mechanism independent of centrosomes or astral microtubules also contributes to spindle orientation. The function of centrosome asymmetry remains to be tested. Rebollo et al. [2] show that neuroblast polarity (i.e. Pins function) maintains centrosome asymmetry; perhaps there is a feedback loop in which centrosome asymmetry contributes to neuroblast polarity. This would be consistent with a recent finding that only one spindle pole is able to induce Pins cortical polarity in embryonic neuroblasts [10].

In conclusion, these three papers provide complementary data on the role of centrosome asymmetry in stem cell division. In both male germline stem cells and neuroblasts, the static PCM-rich centrosome is segregated into the stem cell, and perturbation of centrosome asymmetry disrupts reliable asymmetric cell division. It would be interesting to know whether the young centriole zooms around the germline stem cell similar to its behavior in neuroblasts; likewise it would be good to know if maternal centrioles are exclusively segregated into self-renewing neuroblasts as they are in germline stem cells. These answers should come soon. It will be more important to address the mechanisms establishing centrosome asymmetry and the function of centrosome asymmetry in stem cell self-renewal. For example, does the older centrosome act solely to ensure reliable spindle alignment along the cell polarity axis? Or might old and young centrioles/centrosomes contribute distinct factors to each sibling cell, helping to maintain one as a stem cell and push the other towards differentiation? The foundation has been laid for exploring the role of centrosome asymmetry in fly neural and germline stem cells — can other stem cells be far behind?

References
Mitochondrial Fission: A Non-Nuclear Role for Num1p

It is an established assumption that the inheritance of intracellular organelles into daughter cells is not left to chance. A recent study by Rob Jensen and coworkers provides a new link between a protein required for the inheritance of nuclei in yeast with the positioning and morphology of the mitochondria.

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The mitochondria and the nucleus both contain DNA, but the machinery that governs their inheritance is distinct. The inheritance of nuclear DNA in both yeast and higher eukaryotes is tightly regulated and has been the subject of intense investigation for many years. In contrast, although the segregation of the DNA-containing mitochondria in yeast requires cytoskeletal elements for directed transport into the bud, the regulation of mitochondrial segregation in higher eukaryotes is poorly understood. It is thought that the positioning of the cleavage furrow during cytokinesis provides a physical barrier that passively confines two populations of mitochondria within each daughter cell. However, a recent study by the group of Rob Jensen [1] has uncovered an unexpected link between the regulation of nuclear segregation and mitochondrial morphology and inheritance.

Num1p (nuclear migration 1) plays a critical role in co-ordinating nuclear movement into the yeast daughter bud. It is a large, 313 kDa protein that is anchored through its carboxy-terminal pleckstrin homology (PH) domain to domains enriched in phosphatidylinositol (3,4) bisphosphate (PI(3,4)P2) at the cell cortex in the yeast Saccharomyces cerevisiae [2,3]. Num1p binds to dynein (Pac11p) and tubulin (Tub3p), interactions that are required for microtubule sliding, a process essential for the movement of the nuclei across the bud neck [2,4,5]. Num1p also binds to the formin Bni1p, which is recruited to the plasma membrane through active Rho GTPases [6]. Bni1p promotes the growth of new actin filaments from its cortical position at the bud tip [6] and is required for the localization of Num1p at the bud tip, since its loss leads to a relocation of Num1p to the bud neck [2]. Although a function for Num1p in nuclear segregation has been well established, its role in the mother cell has been less clear. Num1p was identified in an early genetic screen for proteins required to maintain mitochondrial morphology, a process unrelated to nuclear segregation [7]. The recent work by Rob Jensen and coworkers [1] has now independently identified Num1p from a suppressor screen where the expression of a truncated form of Num1p rescued the fused, net-like phenotype of a mitochondrial dynamin mutant, DNM1-109p. This genetic interaction was further verified using a TAP-tagging approach which showed that 10–30% of the total cellular Num1p protein is bound to Dnm1p. This new role of Num1p in organelle inheritance highlights a potentially important link between mitochondrial inheritance and fission.

Although Num1p is a core component of nuclear segregation, this recent work revealed that the loss of Num1p did not affect mitochondrial inheritance into the bud, suggesting that it is not a primary determinant in the retention or delivery of mitochondria during mitosis [1]. However, when both Dnm1p and Num1p were deleted, then the fused, net-like mitochondrial reticulum was seen to migrate entirely into the daughter bud in around 20% of the cells. The contribution of Num1p in the retention of mitochondria in the mother must be considered within the context of the other known determinants of mitochondrial segregation in yeast. Work by Liza Pon and others has shown that the movement of mitochondria along actin cables requires the actin-nucleating Arp2/3 complex, which is recruited to mitochondria by the PUF family member Jsn1p [8]. Mitochondrial-associated Arp2/3 triggers polymerization of new actin filaments, providing the force for anterograde movement into the bud. Retrograde movement of mitochondria towards the mother pole is due to the mitochondrion-dependent anchoring of the mitochondria upon an actin cable that is actively growing from the bud tip [9]. The Bni1p-dependent growth of the actin cable initiated from the bud tip effectively pushes the cable backwards and carries the associated mitochondria in a retrograde direction towards the mother pole (Figure 1A).

Although it is localized throughout the cell, Bni1p is specifically targeted to the bud tips during mitosis where it recruits...