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Control of asymmetric cell division

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Asymmetric cell division (ACD) is a mechanism to generate cellular diversity and used by prokaryotes and eukaryotes alike. Stem cells in particular rely on ACD to self-renew the stem cell while simultaneously generating a differentiating sibling. It is well established that the differential partitioning of cell fate determinants in the form of RNA and proteins between sibling cells induces changes in cell behavior and fate. Recently, insight into molecular mechanisms has been gained that could explain how centrosomes and centrosome-associated structures such as histones, chromosomes or the primary cilium, segregate asymmetrically. Similarly, many cell types also generate physical asymmetry in the form of sibling cell size differences. Emerging data suggests that spindle-induced cleavage furrow positioning through regulated spindle placement and spindle geometry is insufficient to explain all occurrence of cell-size asymmetry. Instead, asymmetric membrane extension based on asymmetric Myosin localization and cortical remodeling could be a driving force for the generation of physical asymmetry.

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Introduction

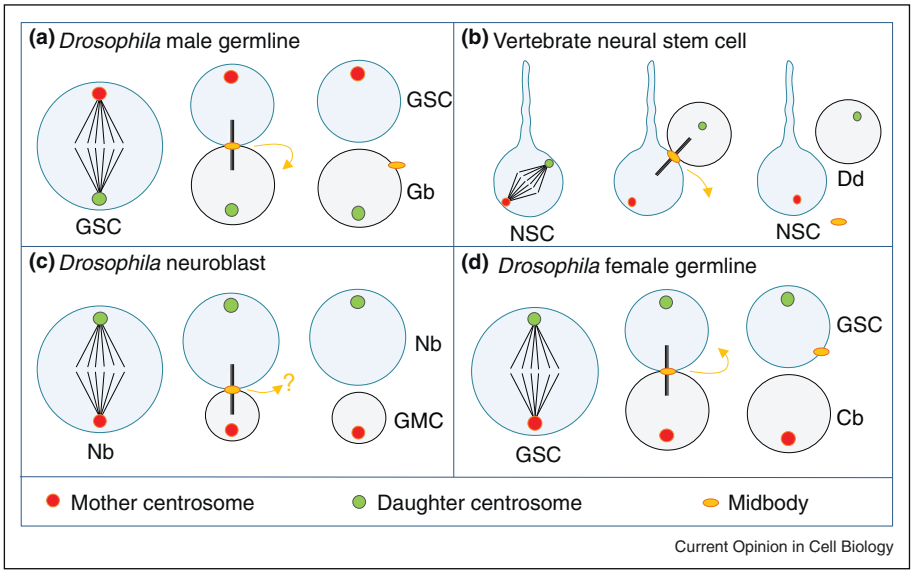
Asymmetric cell division (ACD) generates cellular diversity by differentially segregating RNA and protein determinants into the two sibling cells [1]. ACD is utilized by both prokaryotes and eukaryotes to generate sibling cells with a different molecular identity, cell fate and behavior. Stem cells rely on ACD to generate differentiating siblings while regenerating the stem cell through self-renewal [2–5]. Many of the key players and mechanisms controlling ACD are conserved between invertebrates and vertebrates [1,2]. A unifying principle that has emerged in the last years is that cell polarity controls several aspects of asymmetric cell division, such as cell fate determinant segregation and spindle orientation. Many excellent reviews have already been written on this topic [1,3,4,6,7]. Here, we will first discuss new data concerning centrosome asymmetry, biased chromosome segregation and asymmetric inheritance of centrosome-associated structures. In the second part, we will also review recent insight into the generation and function of sibling cell size asymmetry.

Centrosomes are inherently asymmetric and segregate non-randomly

Centrosomes are the microtubule organizing centers (MTOCs) of animal cells, consisting of a pair of centrioles surrounded by pericentriolar material (PCM) [8]. Centrioles replicate semi conservatively; the old 'mother' centriole serves as a template for the generation of a young 'daughter' centriole, both of which go on to reform the PCM cloud and generate a new centrosome after separating. Several stem cell types have been reported to contain physically and molecularly asymmetric centrosomes, segregating non-randomly, leading to the hypothesis that centrosomes provide instructive cues to influence cell fate decisions [9–12,13•]. For instance, *Drosophila* male germline stem cells and vertebrate neural stem cells inherit the older mother centrosome, whereas the younger daughter centriole is obtained by the differentiating sibling cell [9,12] (Figure 1a,b). However, *Drosophila* neural stem cells, called neuroblasts [2], or female germline stem cells (GSCs) inherit the younger daughter centrosome after cell division [10,11,13•], indicating that stemness is not always associated with centriole age (Figure 1c,d).

The mechanism for biased centrosome segregation seems to be rooted in MTOC activity. For instance, *Drosophila* neuroblast centrosomes undergo an elaborate centrosome dematuration and rematuration cycle, in which the mother centriole sheds PCM right after centrosome separation and, as a consequence, loses its position on the apical cortex. It remains PCM-free during interphase, only regaining PCM and MTOC activity from prophase onwards. The daughter centriole, however, remains stationed in the apical half of the neuroblast because it retains PCM and MTOC activity throughout interphase [10,14,15]. Recently it was found that asymmetrically localized factors such as Centrobin (Cnb), the mitotic kinase Polo and Pericentrin (PCNT)-like protein (Plp) control PCM retention and thus asymmetric MTOC activity, ultimately affecting centrosome positioning and spindle orientation [11,16••,17••]. For instance, Cnb specifically localizes to the neuroblast daughter

Figure 1



Asymmetric centrosome and midbody inheritance. Segregation pattern of mother centrosome (red), daughter centrosome (green) and midbody (orange) in **(a)** *Drosophila* male germline stem cells (GSCs), **(b)** Vertebrate neural stem cells (NSCs), **(c)** *Drosophila* neuroblasts (Nbs) and **(d)** *Drosophila* female germline stem cells (GSCs). In NSCs, the midbody is released into the extracellular space and in Nbs, its fate is currently unknown. GMC; ganglion mother cells, Gb; gonialblast, Dd; differentiating daughter, CB; cystoblast.

centriole and is necessary and sufficient to retain PCM on the apical daughter centriole [11,16••]. Polo is localized on the apical daughter centrosome throughout interphase and phosphorylates Cnb, which is required for PCM retention [14,16••,18]. The mother centriole-containing centrosome does not localize Cnb and downregulates Polo after centrosomes separate and remains free of Polo during interphase. Only from prophase onwards, Polo returns to the basal centrosome, initiating its maturation [11,14,19•]. How Polo localization is controlled is not clear but it was recently suggested that Plp, which localizes to both centrosomes albeit enriched on the mother, prevents premature Polo localization [17••]. Furthermore, the centriolar protein Bld10 (Cep135 in vertebrates) is required to generate interphase centrosome asymmetry through shedding of Polo and subsequently PCM [19•]. The molecular mechanism and function of centrosome asymmetry is incompletely understood, but it is clear that correct centrosome positioning is an important step in setting up spindle orientation [9,15,18]. During asymmetric cell division, the correct orientation of the mitotic spindle is very important to accurately segregate cell fate determinants, influencing stem cell homeostasis and differentiation [20]. Also, asymmetric centrosome segregation seems to be an evolutionary conserved mechanism since yeast spindle pole bodies are also distributed in a non-random fashion [21,22].

Non-random sister chromatid segregation

Centrosomes are not the only subcellular components to segregate non-randomly. In yeast, mouse embryonic stem (ES) cells and *Drosophila* female GSCs, sister chromatids segregate in a biased fashion [23–27]. Surprisingly, a recent report showed that in male GSCs, only the X and Y chromosomes segregate non-randomly, whereas autosomes are inherited randomly [28••]. Biased X and Y chromosome segregation could be connected to the immortal strand hypothesis, which proposes that stem cells reduce the accumulation of replication-induced mutations by retaining the older template DNA strands [29]. However, GCSs do not retain the non-mortal strand [28••].

The molecular mechanism underlying biased DNA segregation is still unclear but centrosome asymmetry could be connected with biased sister chromatid segregation. For instance, Centrosomin (Cnn), a major organizer of the pericentriolar matrix (PCM) [30], the SUN domain protein Klaroid (KOI) and the KASH domain protein Klarsicht (Klar) are all required for biased chromosome segregation [28••,31]. SUN-domain and KASH-domain proteins are members of the LINC complex (linker of nucleoskeleton and cytoskeleton), tethering the nucleus via the nuclear envelope to cytoskeletal components such as microtubules and thus centrosomes. Since DNA is physically connected to centrosomes via kinetochores, it has been speculated that epigenetic marks and asymmetric kinetochore protein assembly could form a biased centrosome-DNA connection via microtubules, leading to non-random chromatid segregation [32]. Indeed, it was found that Dnmt2, a potential methyltransferase, contributes to biased X and Y sister chromatid segregation