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# Centrosomes in asymmetric cell division.

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| **Author Comments:** | |

# Centrosomes in asymmetric cell division.

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## Abstract

Asymmetric cell division (ACD) is a strategy for achieving cell diversity. Research carried out over the last two decades has shown that in some cell types that divide asymmetrically, mother and daughter centrosomes are noticeably different from one another in structure, behaviour, and fate, and that robust ACD depends upon centrosome function. Here, I review the latest advances in this field with special emphasis on the complex structure-function relationship of centrosomes with regards to ACD and on mechanistic insight derived from cell types that divide symmetrically but is likely to be relevant in ACD. I also include a comment arguing for the need to investigate the centrosome cycle in other cell types that divide asymmetrically.

## Introduction

This short piece is intended to offer a concise view of the most recent articles published on "centrosomes in asymmetric cell division". It is therefore not suitable as an introduction to this subject, which can be obtained from previous, comprehensive reviews on asymmetric cell division or centrosomes in general [1-5] and others on the specific subject of centrosomes in asymmetric cell division [6-9].

Pioneer work on diving grasshopper neuroblats showing that unequal asters bring about unequally sized daughter cells was probably the first hint that centrosome activity may be tailored to the specific needs of cells that divide asymmetrically [10]. This was solidly substantiated two decades later by the discovery that mother and daughter centrosomes segregate according to cell fate and have different roles in ACD in Drosophila germline stem cells (GSCs) and neuroblasts as well as neural progenitors in vertebrates (NBs) [11-15].

Although belonging to different lineages from different species these cells share four traits that altogether make them distinct: (i) they undergo a particular type of ACD in which one of the daughters is a renewed version of the mother and can go through repeated rounds of such a "self-renewing" ACD; (ii) during interphase the centrosome is close to the cell membrane, away from the nucleus; (iii) the interaction between centrosome and plasma membrane takes place at the apical side, which is fated to remain in the daughter cell that becomes the renewed stem/progenitor; and (iv) the fate of each centrosome correlates tightly with centrosome age.

**Relevant news from "symmetric" divisions.**

The last few years have seen a great deal of new insight on centriole duplication, basal body function, PCM assembly, etc that derive from cell types that divide symmetrically but may eventually help to understand centrosome asymmetry in the context of ACD [16-23]. A remarkable example is the new concept of PCM as a molecular assembly formed via liquid–liquid phase separation [24]. This exciting conceptual revolution is a paradigm change that is already exerting a strong influence on centrosome biology [25] and ACD (reviewed in [26]) and may be specially relevant in asymmetric centrosome cycles where mother and daughter centrosomes become conspicuously unequal as far as PCM recruitment is concerned. The reader is also referred to an interesting article adding a pertinent note of caution [27].

Another one is targeted co-translation. In different zebrafish and human cell types Pericentrin (PCNT), Abnormal Spindle Microcephaly-related (ASPM), Hyaluronan Mediated Motility Receptor (HMMR), and Nuclear Mitotic Apparatus Protein 1 (NUMA1) mRNAs have been found to localize to the centrosome where they are translated during mitosis [28, 29]. In situ translation of key scaffold proteins may optimise centrosome maturation not only by speeding up their arrival at the destination but also by facilitating specific protein interactions that may help folding and protein-complex assembly. Moreover, targeted translation minimises the chances of assembly of ectopic PCM aggregates. It is tempting to speculate that such supramolecular ribonucleoprotein aggregates made of mRNAs, ribosomes and nascent peptides may also have a significant role in PCM phase separation. Co-translational targeting may add a further layer of regulation of centrosome asymmetry in ACD. Indeed, mutations in PCNT and ASPM cause primary microcephaly phenotypes that are thought to arise from proliferation defects in neural progenitors [8].

**Form follows function.**

Advance in the last few years on the fundamental question of how centrosome asymmetry contributes to ACD has been significant in the case of neural stem cells in chickens and mice

where functions specifically attributable to either the mother or the daughter centrosomes have been identified.

In chickens, daughter centrosome-specific satellites serve as a platform for the asymmetric delivery of the regulator of Notch ligands Mindbomb1 (Mib1) to the differentiating cell that is thereby capable of signalling its sibling to retain neural stem identity through Notch trans-activation [30].

In mice and chickens, the mother centrosome organises a distinct ring-like microtubule structure juxtaposed to the cell junctions that sets the mechanical properties of the cell membrane around the centrosome-to-membrane anchoring site [31, 32]. In mice, upon inactivation of the distal appendage-specific protein CEP83 the mother centrosome remains close the apical endfoot, but is no longer anchored to the membrane [31]. This small displacement of centrosome position disrupts the microtubule ring-structure, resulting in expansion and increased stiffness of the apical surface and activation of mechanically sensitive YAP signaling [33], which in turn promotes overproliferation of neural progenitors and cortex overgrowth [31]. The role of the mechanical properties of the cortex in the balance between proliferative and neurogenic activity had previously been suggested by the decrease in stiffness of the ventricular zone that occurs along the decline in neurogenic potential during development as well as by the stiffer ventricular surface of gyrated animals compared to that of rodents [34, 35].

Another key mother centriole protein, the microtubule organization protein AKNA, which has been found to be enriched at the mother centriole's subdistal appendages, orchestrates destabilisation of microtubules at the adherens junctions and constriction of the apical endfoot that are required for timely delamination from the ventral zone [36]. Also related to centrosome maturation-linked functions, the role of Rbfox proteins in promoting neuronal differentiation by switching from a centrosomal splice form of Ninein in neural progenitor cells to a non-centrosomal isoform in neurons [37] further substantiates earlier results showing the key role of Ninein in neural stemness in rodents [15, 38].

The functional relevance of the unequal behaviour of mother and daughter centrosomes in ACD of neural stem cells is also underpinned by the discovery of centrosome asymmetries that must be overridden for symmetric proliferative divisions to occur. In chickens, a Golgi resident pool of Mib1 is released at mitosis onset to overcome centrosome-dependent Mib1 asymmetry [30]. In motor neuron progenitors in the developing chick spinal cord, SHH signalling upregulates PCNT, thus bringing PCNT and PCNT-bound A-kinase anchoring protein PKA levels in mother and daughter centrosomes even. The regulatory activity that PKA has on SHH signalling closes a positive feedback loop that confers robustness to this process [39].

A remarkable conclusion from these data and others published before is that loss of function of proteins that localise at PCM, appendages, satellites, and centriole proximal sites brings about very different phenotypes, including unscheduled differentiation, delamination

defects, cell death, and overproliferation or depletion of neural progenitors. This conclusion underscores the complex structure-function relationship of centrosomes and suggests that different centrosome domains may play dedicated roles in ACD.

Also in vertebrates and as a counterpoint, a recent article reports that neuron progenitors in the developing cerebellum that divide asymmetrically present conspicuously different mother and daughter centrosomes, but daughter cell fate and centrosome age do not correlate [40].

Drosophila germline and neural stem cells were instrumental in the discovery of asymmetric centrosome cycles [11-14, 41-43]. The ease of experimental manipulation and genetic tractability of Drosophila facilitated the relatively fast identification of main regulators of centrosome asymmetry, and functional assays to establish the contribution of centrosome asymmetry to ACD in these cells followed suit. In short, loss of centrosome asymmetry, centrosome dysfunction, or lack of centrosomes altogether can alter cell fate and, in some instances, result in tumour growth. However, the actual fraction of cases of faulty daughter cell fate determination is surprisingly small. The two-sided conclusion is that robust, faultless ACD is totally dependent upon the corresponding asymmetric centrosome cycle, but still GSCs and NBs can fulfil their developmental programmes rather effectively without centrosomes. Similarly, neurogenesis in mice can be sustained by ectopic acentriolar $p53^{-/-}$ progenitors [44]. However, unlike neural progenitors in vertebrates, the quest for centrosome maturation-dependent cell fate determinants in Drosophila is still open.

Perhaps as a trade-off of such early discoveries, the main lines of thought on centrosome asymmetry and the role of centrosomes in ACD in flies remain largely as described in early reviews on the subject [45-48] and results published in the last few years, informative as they are, are incremental. In NBs, recent additions to the centrosome asymmetry network are the newly discovered role of Plk4 in shedding off the PCM from the mother centriole by phosphorylating mother centriole-bound Spd2/Cep192 [49], as well as ALIX, ADP-ribosylation factor-like 2 (arl2), and tubulin-binding cofactor D (TBCD) that function together to regulate microtubule nucleation and growth [50, 51]. Very recent 3D-structured illumination microscopy and live-cell imaging data [52] add further detail to the established role of Polo-dependent Centrobin function in centrosome asymmetry in NBs. In mGSCs, last advances include the identification of new components of the centrosome orientation checkpoint and regulators of Apc2 enrichment at the cell cortex [53-56]; the finding that Klp10A restrains mother centrosomes from overgrowth that would result in unequally sized daughters [57]; and the discovery that contrary to most Drosophila cells, daughter and mother centrioles present some interesting maturation-specific structural traits in mGSCs [58]. Very recent work on mGSCs has led to the identification of the Drosophila homologue of human ciliopathy gene Alstrom syndrome alms1a as the first stem cell-specific regulator of centriole duplication [59].

The resilience of ACD in GSCs and NBs to centrosome loss unveils the activity of parallel, centrosome-independent mechanism. In mGSCs one such a mechanism may be migration of the spectrosome to the hub-GSC interface where it seems to help maintain proper spindle orientation [60]. In NBs, the position of the last-born daughter works in parallel with centrosomes to set polarity orientation [61].

**The need for more experimental models.**

We have learned that centrosome age and fate correlate tightly in all but one case [40], and that the mother centrosome is fated to the renewed stem in some lineages and to the differentiating daughter in others. However, given the small number of cell types that have been investigated in detail, generalisations are out of order. Thus, for instance, we do not know if the case of granule neuron progenitors in the developing cerebellum in which daughter cell fate and centrosome age do not correlate [40] is exceptional, nor do we know if daughter centrosome retention by the renewed stem cell is an oddity only to be found in flies. The same goes for the so far unique case of NBs where, adding further evidence towards defeating the concept of general principles in biology, for most of the interphase each centrosome contains a single centriole rather than a diplosome, and PCM and MTOC activity are organised by the daughter centriole only [41, 42]. Moreover, because the few cases analysed in detail so far correspond to ACD in stem cells, we have no clue as to the possible relevance of centrosome asymmetry in ACD in other cell types.

Answers to these questions can only come from a systematic evaluation of the centrosome cycle in as many ACD types from as many species as possible. Obvious choices are model systems where such experiments are easier to perform like Drosophila intestinal stem cells (ISCs) and sensory organ precursors (SOPs), as well as C. elegans' ACDs. In ISCs, recent results confirm a tight correlation between supernumerary centrosomes and overproliferation, but cause-effect relation has not been established [62, 63]. In SOPs, the predictable asynchronous movement towards the midbody of the centrosomes that are fated to each daughter hints at some extent of centrosome asymmetry [64]. In C. elegans' first zygotic division, very recent results show that anterior-posterior axis specification is guided by both a centrosome-dependent mechanism that requires Aurora A kinase and a centrosome-independent back up mechanism [65, 66] (reviewed in [67]). There are no mother/daughter specific markers for centrioles in C. elegans, but a recent technical note reporting the use of centriolar proteins fused to photo-switchable Dendra2 suggests that mother and daughter centrioles segregate randomly in a particular cell that divides through ACD at a late stage of development [68]. Technologies like Dendra2, or others like EosFP and SNAP-tagging that circumvent the need for maturation-specific markers [42, 69] should also be applicable at least to those cell types in vertebrates that are more amenable to experimental manipulation like for instance basal epidermal, hematopoietic, and skeletal muscle stem cells.

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**Conflicts of Interest.**

The author declares that he has no competing interests.

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