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Centrosomes, chromosome instability (CIN) and aneuploidy

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Abstract

Each time a cell divides its chromosome content must be equally segregated into the two daughter cells. This critical process is mediated by a complex microtubule based apparatus, the mitotic spindle. In most animal cells the centrosomes contribute to the formation and the proper function of the mitotic spindle by anchoring and nucleating microtubules and by establishing its functional bipolar organization. Aberrant expression of proteins involved in centrosome biogenesis can drive centrosome dysfunction or abnormal centrosome number, leading ultimately to improper mitotic spindle formation and chromosome missegregation. Here we review recent work focusing on the importance of the centrosome for mitotic spindle formation and the relation between the centrosome status and the mechanisms controlling faithful chromosome inheritance.

Introduction

The main function of mitosis is to achieve the faithful segregation of one copy of each chromosome into each daughter cell. The physical apparatus responsible for this fundamental cellular process, the mitotic spindle, is assembled of microtubules and hundreds of proteins that are involved in its morphogenesis, the regulation of its dynamic properties, and the assembly of the microtubule attachment site on the chromosome, the kinetochore [1]. In most animal cells the poles of the spindle contain centrosomes which function to mediate microtubule nucleation and anchoring and to facilitate the organization of the overall structure. Those complex organelles are made of two barreled shaped, orthogonally-assembled structures, the centrioles, embedded in an amorphous proteinacious material called the pericentriolar material (PCM). The PCM contains proteins which are directly involved in microtubule nucleation, including the γ-tubulin ring complex and pericentrin [2,3].

Similar to the chromosomes, the centrosome at each spindle pole is delivered into the corresponding daughter cell at cell division and then is duplicated in the following S phase. Each centriole pair so produced is used to nucleate microtubules to form a spindle pole in the next mitosis. Despite their similar overall organization, the two centrioles in each centrosome are not equivalent, with a mother centriole that is one cell cycle older (and characterized, in mammals, by the presence of distal and sub-distal appendages involved in microtubule anchoring) and a more newly born daughter centriole [4].

The centrosome duplication cycle and the cell cycle share common key regulators. Active Cdks (Cyclin-dependent kinases) have been shown to be essential to initiate centriole duplication in S phase [5,6] and to allow centrosome maturation and separation, together with Plk1 and Aurora A in late S/G2, G2 and M phases [7-10]. Although the sequence of events is not entirely understood, it has been proposed that CDK2 activates the proteins

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NPM, MPS1 and CP110 at the onset of S phase. Those proteins in turn trigger the sequential recruitment of the five core centriolar components SPD2/CEP192, ZYG1/Plk4, SAS5/STIL, SAS6/hSAS6 and SAS4/CPAP in the vicinity of the mother centriole so as to enable daughter centriole formation [4,11,12]. Both cell cycle regulator and centriolar protein levels are tightly controlled and disruption of their expression levels or their enzymatic activities results in abnormal centrosome number or microtubule nucleation, conditions which are often associated with abnormal mitotic spindle activity.

In this review, we describe the importance of centrosome homeostasis for the accuracy of chromosome segregation and the maintenance of cell ploidy and we discuss the cellular pathways that prevent cell division in the presence of centrosome anomalies.

Chromosome instability (CIN) and centrosome abnormalities

Genome stability is dependent on the accuracy of chromosome segregation by the mitotic spindle. Errors produce aneuploidy, a state in which a cell possesses a chromosome content other than a multiple of the haploid number. More than 90% of human solid tumors (and the majority of haemotopoietic cancers) are aneuploid [13]. In contrast to simple aneuploidy – from missegregation of one or a handful of chromosomes – many tumor cells acquire chromosomal instability (CIN), a condition in which the cells have a continuously changing aneuploidy arising from continuing segregation errors. Various defects in mitotic processes can be responsible for CIN and the first suspected one was a defective mitotic checkpoint (also known as the spindle assembly checkpoint). This checkpoint is the major cell cycle control mechanism governing advance from metaphase to anaphase. A “wait anaphase” inhibitor is produced by unattached kinetochores so that anaphase onset is delayed until the centromere of each chromosome has made stable attachment to the mitotic spindle. The linkage of mitotic checkpoint components to CIN was initially proposed from an apparent high rate of mutation in a core component of the checkpoint (Bub1) in CIN cancer cells [14]. However, most CIN cells subsequently reported have an intact mitotic checkpoint despite an elevated rate of chromosome missegregation. This has been described for a variety of chromosomally unstable cancer cell lines harboring an active checkpoint in presence of unaligned chromosomes [15] or in presence of defective spindle activity following treatment with spindle poisons [16•].

It has become increasingly recognized that perturbation of other mitotic elements can be responsible for CIN. One of these is defective cohesion between sister chromatids, which has been recently demonstrated to be responsible for CIN in various cancer cell lines [17••]. Here, the authors clearly demonstrated the necessity of intact cohesion: normally stable cell lines were converted to unstable ones after depletion of the cohesin subunit STAG2. Even more remarkably, chromosomal stability was rescued in highly unstable aneuploid glioblastoma cell lines by substituting a non-mutated form of STAG2 in place of the previously mutated one.

But the most prominent cause of CIN is probably the presence of abnormally high numbers of centrosomes. Indeed, this state - called centrosome amplification - is repeatedly observed in cancer cells lines which also harbor a CIN phenotype [18-20]. Cells can acquire extra centrosomes by diverse mechanisms including cell fusion, failure in completion of cytokinesis, and the deregulation of centrosome biogenesis, i.e., the overduplication of centrosomes or the *de novo* assembly of extra centrosomes. Production of multiple centrosomes by cell fusion is a mechanism used during development, especially by skeletal muscle as a means to produce multi-nucleated, multi-centrosome containing cells. Such fusion events, of course, are unlikely drivers of chromosome missegregation since terminally differentiated muscle cells do not continue to divide. It should be noted as well

that the multiple centrosomes in these cells do not nucleate microtubules [21], suggesting the presence of mechanisms to suppress nucleation activity as a means to prevent any potential deleterious effects from the extra centrosomes.

Skipping mitosis altogether [22] and failure to complete cytokinesis [23-25] have both been shown to induce centrosome amplification in transformed cells. However, the potential of cytokinesis failure to generate cells with stable centrosome amplification has been questioned [26]. In this work, Krzywicka-Racka and Sluder tested if multiple rounds of chemically-induced cytokinesis failure in transformed and non-transformed cells can drive centrosome amplification. In two of the cell types tested (RPE1 and HCT116 cells), cells failing cytokinesis did not accumulate extra centrosomes. In the third cell type (CHO cells), cells did accumulate modest levels of extra centrosomes, but the cells did not continue to proliferate as a consequence of a p53-p21 dependent cell cycle arrest in the subsequent interphase [26].

Cells can also acquire multiple centrosomes by amplification through perturbation in centrosome biogenesis when the levels, timing, or localization of proteins involved in centriole formation are missregulated. Recent studies have described how Plk4, a kinase essential for centrosome duplication, is very tightly autoregulated: its self-phosphorylation within a 24 amino acid phospho-degron makes it a substrate for ubiquitination by the SKP1-CUL1-F-Box (SCF) complex in order to regulate its cellular levels (and kinase activity) through subsequent proteosomal degradation [27••]. Furthermore, in Drosophilla, stabilization of Plk4 can be achieved during mitosis through the dephosphorylation of Plk4 by PP2A, an activity necessary to promote normal centriole duplication [28•]. Other work in Drosophilla embryos and in human cells has revealed the importance of the recruitment of core centriolar proteins CPAP and Plk4 to the centrosome by CEP152 to support normal centrosome biogenesis [29]. Finally, recent work has described another level of complexity in centrosome biogenesis. Using an RNA interference approach in human cells, an indispensable recruitment of STIL by CPAP at the G1/S transition has been reported to enable the initiation of procentriole formation [12,30-32]. Altogether, these studies underlined the importance of tight control of synthesis and accumulation of centriolar components in order to maintain normal centrosome homeostasis.

Mechanisms of chromosomal instability induced by centrosome amplification

The correlation between centrosome amplification and aneuploidy was described more than a century ago by Theodor Boveri, but only recently were detailed mechanisms proposed to explain this relationship. Centrosome amplification can predispose cells to CIN in a two-step mechanism: 1) the formation of a multipolar spindle and 2) the resolution of this aberrant mitotic configuration into a bipolar spindle (Figure 1). This transition from a multipolar to a bipolar spindle promotes the formation of incorrect kinetochore microtubule attachment that then provokes subsequent chromosome segregation errors during anaphase and that are maintained at cytokinesis. Cells arising from multipolar divisions are often inviable [33•,34]. This was especially highlighted by use of live cell imaging to demonstrate that multipolar division is lethal and that transient multipolar spindles in the presence of extra centrosomes do promote segregation errors [33•]. Despite this, there are notable exceptions, such as liver, where multipolarity has been proposed [35] to be beneficial by generating genetic diversity in hepatocytes.

Coalescence of centrosomes nucleating a multipolar spindle into a bipolar spindle requires the minus end directed motor dynein, as demonstrated by Quintyne and coauthors [36]. Studies using genome wide RNA interference approaches (in squamous cell carcinoma cells

[34] and in Drosophilla S2 cells [37]) subsequently highlighted the importance of the actin cytoskeleton and functional kinetochore-microtubule interface in mediating proper centrosome clustering in cells with a multipolar spindle. In parallel with the mechanical forces involved, work in cells [37,38] and fly [39] models has demonstrated that the delay in kinetochore attachment or production of aberrant attachments leads to failure to silence the mitotic checkpoint with normal timing, thus delaying advance to anaphase in cells with extra centrosomes. This delay facilitatescentrosome clustering that can mitigate the deleterious consequences of multipolar division.

The transition from a multipolar spindle to a bipolar spindle also enables an increased frequency of abnormal kinetochore/microtubule configurations. In cells initially forming bipolar mitotic spindles, the kinetochores of each duplicated sister chromatid normally bi-orient, with the two kinetochores of each pair attaching to microtubules nucleated by opposite spindle poles, thereby generating a configuration called amphitelic attachment. In cells with an initial multipolar spindle, however, each kinetochore has an elevated chance of capturing microtubules emanating from more than one pole. If in subsequent centrosome clustering those poles end up coalescing into different composite poles, the kinetochore will now be attached to microtubules from both spindle poles, a configuration called merotely. As the both mitotic and meiotic checkpoints in vertebrate mitosis [40,41] and female meiosis [42••], respectively, are silenced by microtubule attachment, merotelic attachments go unrecognized as attachment errors. At anaphase entry, the merotelically attached chromosome is pulled toward both spindle poles, thereby producing a lagging chromosome with a high potential for missegregation.

This sequence of events has been clearly described to be responsible for CIN in a human cancer cell line (U2OS) where centrosome amplification - induced by Plk4 overexpression - was shown to be directly linked to chromosome missegragation [33•]. However, in a further study where the fate of lagging chromosomes was followed using a LacI-GFP to target a LacO array integrated at a specific chromosomal locus, it was reported that the merotelically attached chromosomes were actually segregating toward the correct daughter cell in a majority of the anaphases [43] suggesting that lagging anaphase chromosome may not be the sole mechanism responsible for CIN. In line with this idea, recent work using live imaging of a cancer cell line (a Wilm's tumor kidney cancer cell line) along with analysis of tumor chromosome content has offered support for the combination of an initial tripolar mitosis followed - without centrosome clustering - by cytokinesis failure between two of three nascent daughter cells as a mechanism for inducing the missegregation of multiple chromosomes in a single mitotic event [44••].

Centrosomes, p53, and the cell cycle: a continuing controversy

The contribution of centrosome amplification to CIN and to the establishment of ananeuploid chromosome content raises the question of the existence of mechanisms controlling centrosome number. Can cells monitor or detect the presence of extra centrosomes? Evidence emerging over the past two decades has provided contradictory answers to this question.

On the one hand, work a decade ago originally proposed that specific cell types depleted of centrosomes can go through mitosis normally but then arrest in the following interphase without replicating their DNA, thus implicating a requirement of centrosomes in cell cycle advance in interphase [45,46]. However, a following study opposed this proposition, reporting that non-transformed human cells were able to sustained normal cell cycle progression after laser ablation of their centrosomes [47]. Furthermore, the evidence of Fukasawa *et al* lead to the initial proposal that mouse embryonic fibroblasts lacking p53

accumulate an abnormal number of centrosomes [48]. Hence, this work suggested that p53 opposes cell cycle progression in cells with ***extra*** centrosomes.

Additional work following cells with too many centrosomes lead to an even more direct proposal of a p53-dependent G1/S arrest in response to centrosome amplification and has been referred to as a tetraploidy checkpoint [49]. The existence of such a checkpoint responsible for arresting cell cycle progression following cytokinesis failure and doubling of the DNA and centrosome content remains highly controversial. The notion of a tetraploidy checkpoint was quickly challenged, with the observed p53-dependent G1/S arrest after cytokinesis failure linked to direct DNA damage [50,51] or consequences of damage to the spindle machinery arising from the drug treatment used to generate the tetraploid cells [52].

Another possible linkage of p53 activation to centrosome amplification has recently emerged from efforts proposing that in otherwise unperturbed U2OS cells in which centrosome amplification was induced - by overexpressing a CDK6 activator (a D-type cyclin encoded by a Kaposis's sarcoma herpes virus) - a proapoptotic signal dependent on p53 was triggered [53]. Additionally, depletion of p53 by shRNA in an unperturbed immortalized diploid human cell line (RPE1) was reported to lead to a mild level of centrosome amplification [54•], an observation which can either support the idea of a direct role of p53 in centrosome duplication or the possibility that the p53 arrests cell cycle progression in response to spontaneously acquired extra centrosomes.

Support for the proposal that the absence of p53 might be directly responsible for driving centrosome amplification has come from two lines of evidence. First, the absence of activation of the CDK inhibitor p21 by p53 may trigger high CDK activity to drive multiple rounds of centrosome duplication in G1/S arrested cells [55]. Alternatively, p53 may be directly required at the centrosome to mediate its duplication at the G1/S transition [56].

Furthermore, evidence for the recruitment of cyclinE/Cdk2 to the centrosome led to the proposal that this was necessary to allow the initiation of DNA replication in S phase [57]. This study, along with another describing the activation of a p38-p53-p21 dependent G1/S arrest in RPE1 cells depleted of centriolar components [58], provided additional evidence to support the idea that cell cycle progression was sensitive to centrosome integrity.

Consequences of centrosome amplification on aneuploidy and cell proliferation

In light of the contradictory evidence linking p53 and cell cycle advance to centrosome number, our view is that the most plausible explanation for a G1/S arrest observed in cells with extra centrosomes is the result of DNA damage caused by an aberrant event in the previous mitosis (Figure 1). For cells with extra centrosomes and the corresponding erroneous kinetochore/microtubule attachments, lagging chromosomes (as described above) are frequent and those chromosomes are likely to be damaged. This can happen because of trapping the lagging chromosome into DNA bridges during cytokinesis (as first suggested 30 years ago by the evidence of Mullins and Biesele [59]) with the direct result of DNA damage and activation of a DNA damage response involving p53 [60••].

Lagging chromosomes arising from aberrant spindles can also be included into micronuclei, and work from Pellman and colleagues [61••] has recently shown that the micronuclear environment so produced is partially dissociated from the cell cycle (at least in part because of a paucity of nuclear pores). As a consequence, in the subsequent interphase, DNA replication in a micronucleus can be delayed, but not recognized, and mitotic entry ensues before DNA replication has been completed within the micronucleus. This situation

produces massive DNA damage and chromosome rearrangements (known as chromothripsis) that are restricted to the chromosome(s) encapsulated within the micronucleus. A final possible cause for acquiring DNA damage in cells with extra centrosomes is the long mitotic delay required for clustering centrosomes, as prolonged mitotic delays have been shown recently to induce telomere deprotection, telomere damage and a p53-dependent arrest at the next G1 to S phase transition [62•,63].

Conclusion

Aneuploidy is a common feature of cancer cells, and it is now well established that centrosome amplification can strongly contribute to the establishment of this state by favoring chromosome segregation errors during mitosis. Although the mechanisms linking centrosome amplification to chromosome instability are well understood, it is uncertain if centrosome amplification by itself can be sufficient to drive tumor formation. It is possible that to be able to drive cell transformation and tumor formation centrosome amplification may need to be added to other defects, such as mutation or loss of a tumor suppressor. To establish the sequence of events leading to tumor formation in presence of extra centrosome and to understand the importance of centrosome amplification in this process, it is now essential to develop mouse models where this state can be induced independently of any other factors as a means to test how it contributes to neoplasia.

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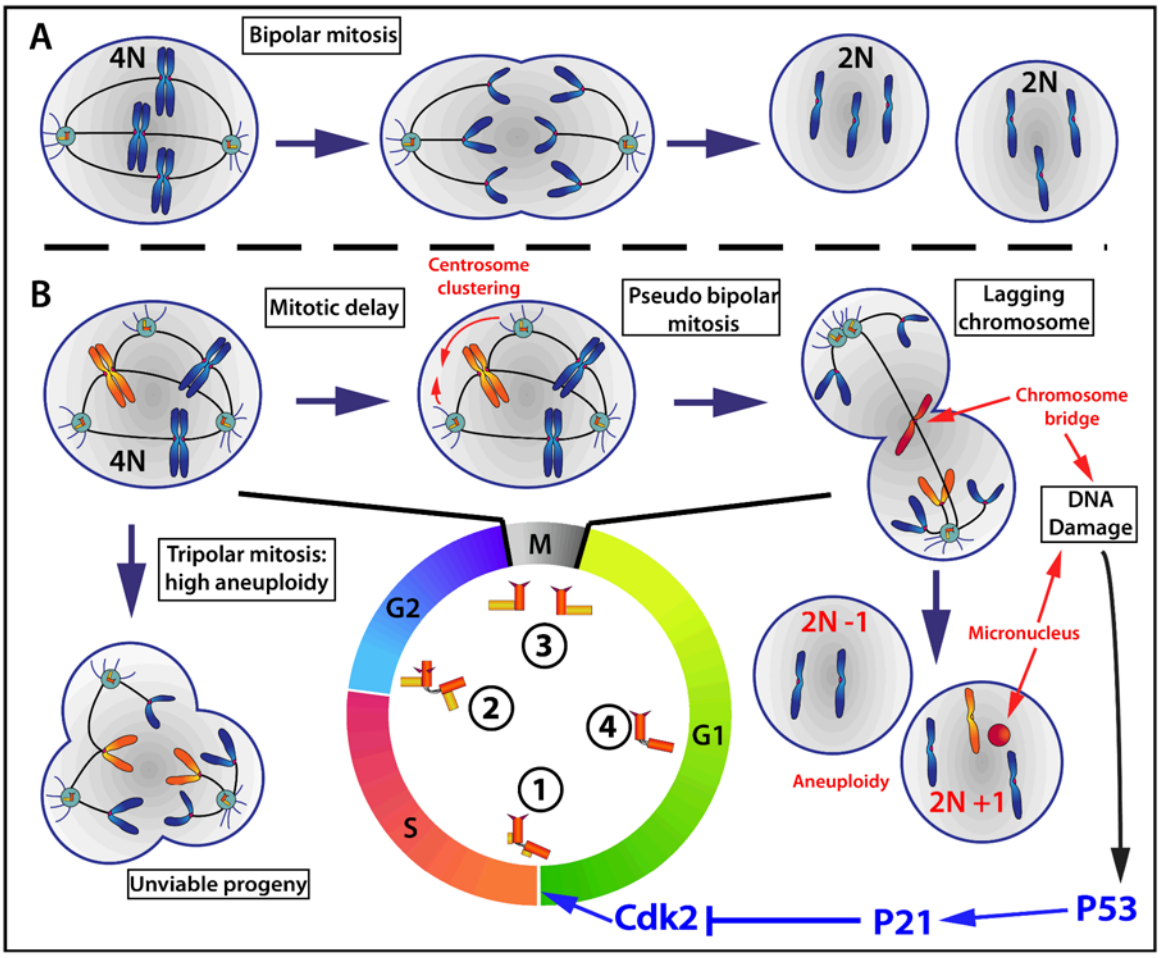

Figure 1. Chromosomes segregation in presence of extra centrosomes

Centrosome duplication starts at the G1/S transition with procentriole formation (1). Centrosomes are matured throughout the G2 phase (2) and they are separated to form the poles of the mitotic spindle in M phase (3). In G1, the centrosomes lose their orthogonal configuration in preparation for their duplication (4). **A.** Cells with two centrosomes form a bipolar spindle and chromosomes are usually accurately segregated. Cellular ploidy is maintained and cell proliferation is sustained. **B.** Cells entering mitosis with more than two centrosomes can either go through a multipolar mitosis or cluster their centrosomes to form a bipolar spindle. Progeny of multipolar divisions are highly aneuploid and are usually inviable. Centrosome clustering favors the formation of merotelic kinetochore/microtubule attachments resulting in lagging chromosomes. Lagging chromosomes can be included in DNA bridges or micronuclei during cell cleavage to produce daughter cells. These phenomena induce p53- dependent activation of p21, which inhibits Cdk2 and produces cell cycle arrest at the G1/S transition.