Minireview

The centrosome cycle

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Abstract The centrosome is the major microtubule-organizing center of animal cells. It influences cell shape and polarity and directs the formation of the bipolar mitotic spindle. Numerical and structural centrosome aberrations have been implicated in disease, notably cancer. In dividing cells, centrosomes need to be duplicated and segregated in synchrony with chromosomes. This centrosome cycle requires a series of structural and functional transitions that are regulated by both phosphorylation and proteolysis. Here we summarize recent information on the regulation of the centrosome cycle and its coordination with the chromosomal cell cycle.

Key words: Centrosome duplication; Centrosome maturation; Centrosome separation; Centriole disorientation; Protein phosphorylation; Proteolysis

1. Introduction

In animal cells, the centrosome is the major microtubule-organizing center (MTOC). Thus, it influences all microtubule (MT)-dependent processes, including organelle transport, cell shape, polarity and motility. Centrosomes also play a critical role during mitosis when they contribute to control spindle bipolarity, spindle positioning and cytokinesis. Although bipolar spindles can form in the absence of centrosomes, these organelles exert a dominant influence on the number of spindle poles (for review see [1,2]). Any aberration in centrosome numbers can interfere with bipolar spindle formation and chromosome segregation. Therefore, centrosome duplication and segregation need to be tightly coordinated with the duplication and segregation of the genome.

Vertebrate centrosomes comprise two barrel-shaped centrioles, each made up of nine triplets of short MTs, which are embedded within a protein-dense matrix known as the pericentriolar matrix (PCM) (Fig. 1). Intriguingly, the two centrioles are not equal. Tracing the fate of an individual centriole in fact reveals that approximately 1.5 cell cycles elapse between the first emergence of a new (pro-) centriole and its complete structural maturation ([3]; see also Fig. 1). The PCM harbors γ-tubulin ring complexes (γ-TuRCs) that are essential for MT nucleation [4], as well as several coiled-coil proteins. As shown by electron microscopy, centrosomes undergo a series of morphological changes throughout the cell cycle [3]. On the basis of morphological observations, the centrosome cycle has been subdivided into a series of discrete events (summarized schematically in Fig. 1). These are commonly referred to as *centrosome duplication*, *centrosome maturation*, *centrosome separation* and *centriole disorientation*.

Recent studies indicate that the centrosome cycle is regulated by both reversible phosphorylation and proteolysis. In particular, the identification of several centrosome-associated protein kinases and phosphatases (e.g. [5–7]) has afforded new insights into the regulation of centrosome structure and function (summarized in Table 1). Furthermore, the establishment of centrosome duplication assays both in *Xenopus* egg extracts [8] and cultured mammalian cells [9,10] has markedly improved our prospects for dissecting the centrosome cycle. Here we review recent findings that begin to uncover the regulation of the centrosome cycle and its integration with the chromosomal cell cycle (see also [11–13]). The article is focused on the centrosome cycle in animal cells. The properties of the spindle pole body (SPB), the yeast equivalent of the centrosome, have been expertly reviewed elsewhere [14–16].

2. Centrosome duplication

A first important link between DNA replication and centrosome duplication has emerged from studies demonstrating that cyclin-dependent kinase 2 (Cdk2) is required for both of these key S phase events [8–10,17]. Whereas cyclin E was identified as the binding partner of Cdk2 regulating centrosome duplication in *Xenopus* embryos [8,17], studies in mammalian somatic cells attribute a predominant role to the Cdk2/cyclin A complex [10,18]. This may reflect the fact that Cdk2 associates with different cyclins, depending on developmental context. Alternatively, cyclins E and A might act sequentially during centrosome duplication in somatic cells. Little definitive evidence is presently available on the targets of Cdk2 that are relevant to centrosome duplication, but two candidate substrates have been proposed: one is the protein kinase mMps1p [19], whose homolog in *Saccharomyces cerevisiae* is required for both the duplication of the SPB and the spindle assembly checkpoint [16]. However, although murine Mps1 was reported to be required downstream of Cdk2 for centrosome duplication [19], this conclusion was challenged by a subsequent study on human Mps1 [20]. Thus, whereas the data implicating budding yeast Mps1p in the duplication of the SPB appear compelling, an involvement of this kinase in the mammalian centrosome cycle remains controversial. The other proposed Cdk2 substrate is the putative chaperone nu-

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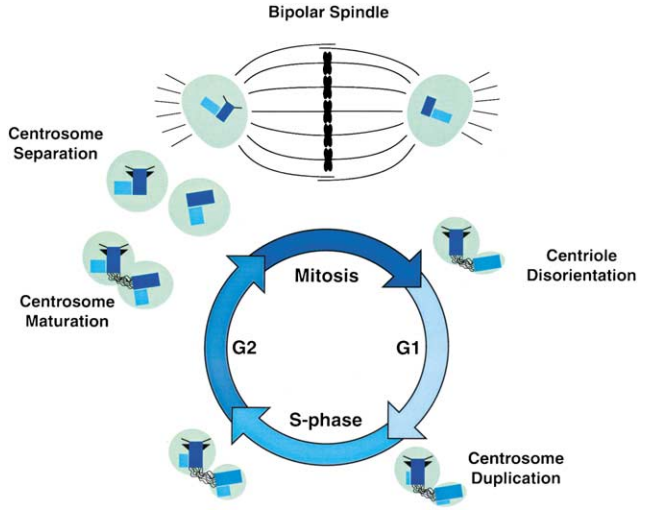

Fig. 1. Schematic view of the centrosome cycle in relation to the cell cycle. Mature centrioles are shown in dark blue, immature centrioles in blue, pro-centrioles in light blue and the PCM in green. Black triangles symbolize the subdistal appendages and black lines the distal appendages. The wavy lines indicate a hypothetical proteinaceous linker connecting parental centrioles. The immature centriole recruits γ-TuRCs and maturation markers in late G2, thereby acquiring competence for MT nucleation [27,29–31]. It subsequently acquires the distal and subdistal appendages at the end of mitosis (for detailed description see [3]). The exact role of appendages remains unclear but probably relates to MT anchoring (for review see [67])

cleophosmin/B23 [21]. However, the bulk of this protein clearly localizes to the nucleolus and the nucleoplasm, implicating it in ribosome biogenesis. Thus, the role of nucleophosmin/B23 in centrosome duplication awaits clarification.

Two other protein kinases, in addition to Cdk2, have also been implicated in centrosome duplication. In the nematode *Caenorhabditis elegans*, the *ZYG-1* kinase was shown to be essential for centrosome duplication but, remarkably, not for cell cycle progression [6]. *Zyg-1* mutant embryos arrested with single, unpaired centrioles in monopolar spindles, indicating that ZYG-1 is required specifically for pro-centriole formation. The kinase could not be detected at interphase centrosomes, but transiently localized to spindle poles during late mitosis. What kinase(s) may functionally resemble ZYG-1

Table 1

Enzyme	Substrate	Reference
Centrosome duplication		
Cdk2/cyclin E or cyclin A	Mps1? Nucleophosmin/B23	[8–10,17,19–21]
Zyg-1	?	[6]
CaMKII	?	[22]
SCF (slimb)	?	[23,24]
Centrosome maturation		
Plk1	Asp?	[33,34,39]
Aurora-A	?	[32]
Nek2	?	[35,36,44]
PP4	?	[37,38]
Centrosome separation		
Nek2/PP1α	C-Nap1	[42–44,46,47]
PKA?	Centrin	[45]
Aurora-A	Eg5	[49]
Cdk1	Eg5	[48,50,51]
Centriole disorientation		
SCF	?	[23]

in other organisms is an interesting unresolved question. The other kinase recently implicated in centrosome duplication is calcium–calmodulin kinase II (CaMKII) [22]. In an assay based on *Xenopus* egg extracts [8], inhibition of this kinase completely abolished centrosome duplication [22]. Considering that calmodulin and the calcium-binding protein, centrin/Cdc31, have also been implicated in SPB duplication in *S. cerevisiae* [14], these findings hint at a conserved mechanism for MTOC duplication that relies on calcium-regulated proteins.

Increasing evidence suggests that ubiquitin-dependent proteolysis also plays an important role in the centrosome cycle. Inhibitors of protein degradation were shown to block centrosome duplication in *Xenopus* [23], and mutations in the F-box protein *slimb*, a putative component of a Skp1–cullin-F-box (SCF) complex, cause centrosome amplification in *Drosophila* [24]. Furthermore, certain components of the SCF complex have been localized to centrosomes [23,25]. The precise role of proteolysis in the regulation of the centrosome cycle remains to be determined, but one attractive possibility is that certain proteins need to be degraded in order to allow centrosome disorientation, which in turn may represent a prerequisite for centrosome duplication (see also below).

It is not presently known how many pathways contribute to the coordination of centrosome duplication and DNA replication. With Cdk2 one important link has been identified (see above). In addition, it is clear that in somatic cells centrosome duplication and DNA replication are connected through a common requirement for phosphorylation of the retinoblastoma gene product pRb and the liberation of E2F transcription factors [10]. It is possible that the E2F requirement for centrosome duplication reflects the fact that both cyclins E and A are E2F target genes. But a more interesting possibility is that E2F also controls the transcription of additional, as yet unidentified genes required for centrosome duplication.

In spite of the impressive progress described above, the actual mechanisms that underlie centrosome duplication remain unknown. From the perspective of the entire centrosome, the process is clearly of a semi-conservative nature: each centrosome in a G2 cell contains one centriole present already in G1 and one synthesized during S phase [26]. From the perspective of the centriole, however, the process is conservative, in that none of the structural components of the G1 centriole appears to redistribute into the new pro-centriole. What template directs the synthesis of a pro-centriole in orthogonal orientation to a pre-existing parental centriole remains one of the most fascinating unresolved mysteries in cell biology.

3. Centrosome maturation

Centrosome maturation refers to the recruitment of additional PCM proteins, particularly γ-TuRCs, that occurs shortly before mitosis (for review see [27]). The amount of γ-tubulin at vertebrate centrosomes increases about three- to five-fold [28], and this accompanies a striking increase in MT nucleating activity at the centrosome. At about the same time, the immature parental centriole acquires maturation markers such as ninein and cenexin/Odf2 [29–31]. Phosphorylation undoubtedly plays a key role in centrosome maturation. Both Polo-like kinases (Plks) and A-type Aurora kinases have been directly implicated in this process by genetic analyses, anti-

body injection and RNA-mediated interference [32–34]. Furthermore, there is evidence for regulation of centrosome integrity, and perhaps maturation, by Nek2, a member of the Nek/NIMA family of kinases [35,36], and protein phosphatase 4 was shown to be required for the recruitment of γ-TuRCs in both *Drosophila* and *C. elegans* [37,38]. To better understand the apparently complex events that occur at the centrosome at the onset of mitosis, it would obviously be critical to identify the substrates of these various enzymes. One Polo substrate identified in *Drosophila* is the protein Asp (abnormal spindle) [39]. This protein, when phosphorylated by Polo, restores the ability of salt-stripped centrosomes to form MT-asters, but it is not clear whether Asp functions directly in MT nucleation. Instead, it may play an important role both in tethering MTs to spindle poles and in the formation of the central spindle [40,41].

4. Centrosome separation

The separation of the duplicated centrosomes into two clearly distinct MTOCs occurs at the G2/M transition, apparently in two distinct steps. In a first step, which is independent of MTs, cohesion between the two parental centrioles is disrupted. In a second step, the two centrosomes are then separated through the action of MT-dependent motor proteins. Throughout most of the cell cycle, parental centrioles appear to be connected through a proteinaceous structure for which the centriole-associated coiled-coil protein C-Nap1 (also known as Cep250) may function as a docking site [42,43]. The centrosome association of C-Nap1, and presumably that of other proteins, is clearly regulated through phosphorylation [42,44–47]. One particularly attractive model proposes that the phosphorylation state of C-Nap1 is determined by the relative activities of the Nek2 kinase and a member of the type I phosphatase (PP1) family. As long as Nek2 activity is held in check by PP1, cohesion between parental centrioles persists. However, at the onset of mitosis PP1 is inactivated, perhaps as a consequence of phosphorylation by Cdk1. As a result, Nek2 activity prevails and cohesion is lost, so that the two centrosomes are available for separation through MT-dependent motors. Prominent among the latter is Eg5, a centrosome and spindle-associated kinesin-related motor that is itself regulated by at least two kinases, Cdk1 and Aurora-A [48,49]. Whereas the functional consequences of Eg5 phosphorylation by Aurora-A are not yet understood, phosphorylation by Cdk1 is clearly required for Eg5 binding to the spindle [48,50], perhaps via the dynactin complex [51].

5. Centrosome disorientation

Centrosome disorientation occurs during late mitosis/early G1 and refers to a striking loss of orthogonal orientation between the two centrioles. Observed by electron microscopy a long time ago, its significance remains uncertain, although several intriguing proposals have recently been put forward. One possibility is that centriole disorientation is related to the re-establishment of a linker structure between parental centrioles [43]. As this linker was disassembled at the preceding G2/M transition, it clearly needs to be re-established at the beginning of the new cell cycle and for this, the intimate connection between centriole and (former) pro-centriole needs to be broken. Another possibility is that centriole disorientation represents a prerequisite for centriole duplication, and, considering that pro-centrioles assemble close to the proximal ends of parental centrioles, this also seems plausible [17,23]. Finally, spectacular live cell imaging studies revealed an astonishingly dynamic behavior of centrosomes throughout the cell cycle [29]. From these studies, centriole disorientation and a subsequent movement of the mature centriole towards the cleavage furrow were proposed to constitute a key step in abscission, the terminal phase of cell division [52]. These provocative proposals are by no means mutually exclusive, and the continued investigation of centriole disorientation may well reveal yet other unexpected function.

6. Old and new cell cycle functions for centrosomes

Centrosomes have long been implicated in both spindle assembly and spindle positioning, but recent studies have emphasized centrosome-independent pathways for spindle assembly. It is now well established that bipolar spindles can assemble in the absence of centrosomes, and that the corresponding mechanisms exist not only in plants and specialized animal cells (i.e. eggs), but also in somatic animal cells [53–55]. This should not distract from the fact, however, that most animal cell divisions do occur in the presence of centrosomes, and this probably enhances both the speed and precision of spindle assembly and the fidelity of chromosome segregation. Furthermore, recent studies are not only attracting renewed attention to the role of centrosomes in cytokinesis [52,53,55], but point to yet other, previously unexpected functions for this organelle. In particular, when centrosomes were removed from somatic vertebrate cells, by either microsurgery or laser ablation, a significant proportion of cells completed cell division but then failed to undergo the next round of DNA synthesis. Taken at face value, this suggests a critical role for the centrosome in regulating the G1 to S transition [53,55]. What this role could be is currently unknown but clearly worthy of careful scrutiny.

7. Deregulation of the centrosome cycle

It has long been proposed that centrosomal aberrations could contribute to aneuploidy and cancer formation [56]. This old idea has recently attracted renewed interest, and several studies report frequent aberrations in centrosome numbers, shape and functional capacity in a variety of cancer tissues [57–60]. These studies indicate a strong correlation between centrosomal anomalies and aneuploidy [61], but with regard to the role of centrosomes in tumor progression, it remains difficult to distinguish cause from consequence [62]. Several genes have been shown to cause a centrosome amplification phenotype when deregulated [12,60,63–65], but how they influence centrosome numbers remains poorly understood. Some of these genes are implicated in the recognition of DNA damage (BRCA1, BRCA2 and ATR), others in the response to such damage (p53 itself, p21, GADD45 and Mdm2), in ubiquitin-dependent protein degradation (Skp2 and TSG101) or in mitotic progression (Aurora-A and survivin). How all these genes could regulate centrosome duplication is not immediately obvious.

A priori a centrosome amplification phenotype could arise through mechanisms that deregulate centrosome duplication during S phase [10,66]. However, a recent study based on the

overexpression of Aurora-A and other mitotic kinases in cultured cells shows that extra copies of centrosomes may also frequently arise as a result of failed cell division rather than deregulated duplication, particularly in cells that are defective for p53 function [63]. This strongly suggests that errors during cell division, combined with an inability to detect the ensuing tetraploidization in the absence of p53, could represent a major pathway for centrosome amplification in tumor cells. Finally, it is important to bear in mind that tumor cells exhibit not only numerical but also structural centrosome anomalies. This suggests that deregulation of yet other aspects of the centrosome cycle, e.g. a premature centrosome maturation [57], could cause anomalies in MT nucleation. These in turn could influence cell shape, polarity and motility, and thus be relevant to the problem of tissue invasion and metastasis [62].

8. Conclusions

To proliferate successfully, cells need to coordinate both the duplication and segregation of centrosomes with the propagation of the genome. It is not surprising, therefore, that the centrosome responds to many cell cycle cues, and in turn, contributes to promote cell cycle transitions. Much remains to be learned about the integration of the centrosome cycle and the chromosome cycle, and this promises to be a fertile field for future studies. Many bona fide centrosomal components undoubtedly await identification. On the other hand, for several proteins that have already been localized to the centrosome, it is not yet clear whether they regulate centrosome function, or instead, rather use the centrosome as a platform for favoring signaling processes through proximity. Thus, the centrosome remains an enigmatic organelle and almost certainly holds additional surprises in store.

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