Review

CellPress

Centrosome dynamics as a source of chromosomal instability

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Accurate segregation of duplicated chromosomes between two daughter cells depends on bipolar spindle formation, a metaphase state in which sister kinetochores are attached to microtubules emanating from opposite spindle poles. To ensure bi-orientation, cells possess surveillance systems that safeguard against microtubule-kinetochore attachment defects, including the spindle assembly checkpoint and the error correction machinery. However, recent developments have identified centrosome dynamics – that is, centrosome disjunction and poleward movement of duplicated centrosomes – as a central target for deregulation of bi-orientation in cancer cells. In this review, we discuss novel insights into the mechanisms that underlie centrosome dynamics and discuss how these mechanisms are perturbed in cancer cells to drive chromosome mis-segregation and advance neoplastic transformation.

A Clinical perspective on centrosome dynamics

Whole chromosome instability (W-CIN), the inability to faithfully segregate duplicated chromosomes between two daughter cells, can result in cells with abnormal numbers of chromosomes, a condition referred to as aneuploidy [1]. Although a causal relationship between aneuploidy and cancer remains a topic of debate, aneuploidy is a common feature of human cancers, and one of several mechanisms by which aneuploidy is thought to drive tumorigenesis is through loss of whole chromosomes that contain key tumor suppressor genes [1,2]. Nonetheless, the molecular and genetic bases of W-CIN in human cancer cells remain poorly understood. While much attention has been focused on the role of mitotic checkpoint signaling, attachment error correction, and centrosome duplication, mutations in key regulators of these mitotic processes are rarely observed in human cancer [3]. Recently, improper timing of centrosome separation has been appreciated as a new and potentially frequent source of aneuploidization in human cancers [4–7]. In this review, we highlight novel insights into normal centrosome biology and explain how abnormal centrosome dynamics are thought to drive chromosome segregation errors and promote cancer.

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Keywords: centrosome disjunction; centrosome movement; centrosome dynamics; chromosomal instability; cancer.
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0962-8924/
 http://dx.doi.org/10.1016/j.tcb.2014.10.002

Centrosome structure

In animal cells, the centrosome is the primary microtubule-organizing center [8,9]. In nondividing cells, centrosomes are located in close proximity to the nucleus where they organize microtubules to help establish cell shape, polarity, and proper positioning of subcellular organelles [10]. In dividing cells, centrosomes duplicate to form a bipolar mitotic spindle that separates chromosomal content evenly between two daughter cells. [9]. One centrosome consists of two orthogonally positioned cylindrical organelles called centrioles that are joined by fibers connecting their proximal ends. Centrioles are surrounded by an unstructured mass of proteins referred to as the pericentriolar material (PCM) [11]. Each centriole consists of nine sets of microtubule triplets assembled into a cartwheel structure. Paired centrioles differ from each other in that one is the mother centriole with appendages at its distal ends and the other is the daughter centriole, which lacks these structures. The PCM contains γ-tubulin ring complexes (γ-TuRCs) as well as several large coiled-coil proteins including pericentrin, ninein, and Cep135, which together function in nucleating, anchoring, and positioning microtubules [12].

The centrosome cycle

The centrosome is duplicated and separated once per cell cycle and proceeds in a timely fashion that is coordinated with the cell cycle. For the purposes of this review, we will divide the centrosome cycle into two parts: centrosome duplication and centrosome dynamics, which encompasses centrosome splitting (disjunction) and movement. Centrosome duplication takes place between the late G1 and early G2 phase and is characterized by four stages: centriole disengagement; centriole duplication; centriole elongation; and centrosome maturation. The key events and molecular drivers of each of the four stages are summarized in Box 1. Additional background on centrosome duplication can be found in several recent in-depth reviews [13–16]. Part two of the centrosome cycle, centrosome dynamics, takes place between the late G2 and early M phase and will be reviewed in detail below.

Centrosome dynamics

Centrosome dynamics can be subdivided into two stages: centrosome disjunction in late G2 phase, and microtubule motor protein-mediated centrosome movement toward opposite poles in prophase or prometaphase.

Box 1. The four stages of centrosome duplication

Centriole disengagement

During late mitosis and the early G1 phase, the perpendicular orientation of centriole pairs is lost as the daughter centriole begins to dissociate and remains attached to the mother centriole merely through flexible fibers (Figure I). This process, termed centriole disengagement, is essential for limiting centriole duplication to one round per cell cycle and for recruiting PCM [58]. Separase and Plk1 have been identified as key regulators of centriole disengagement [59]. Separase is thought to drive disengagement by removing cohesin rings that hold mother and daughter centrioles together through proteolytic cleavage of the cohesin subunit Scc1 [60]. However, subsequent publications have argued against a need for cleavage of centriole-associated cohesin in disengagement [61,62]. Plk1 regulates centriole disengagement through its interaction with a centrosomal splice variant of Sgo1 known as shorter shugoshin 1 (sSgo1). sSgo1 protects centriolar cohesin from untimely separase-mediated cleavage through a direct interaction with Plk1 [63]. Astrin and Akt kinase interacting protein 1 (Aki1 kinase) also regulate centromeric and centriolar cohesin dissolution through a largely unresolved mechanism [64,65].

Centriole duplication

Following disengagement, the cell contains one centrosome comprised of two structurally and functionally dissimilar centrioles. The mother centriole, which originates from the mother cell, nucleates and organizes microtubules, whereas the daughter centriole, which is replicated from the mother centriole as a procentriole, only nucleates microtubules and is relatively mobile [14]. Synthesis of the daughter centriole from a pre-existing mother centriole, termed centriole duplication, takes place in the early S phase. Centriole duplication is incompletely understood, but involves at least five key proteins: CEP192, SAS-4 (CPAP), SAS-5 (STIL), SAS-6, and Plk4 [66]. The latter two are particularly important as their overexpression is associated with increased centriole synthesis, centrosome amplification, and chromosomal instability [67–75].

Centriole elongation

Newly generated daughter centrioles (also called procentrioles) that emerge near the proximal ends of mature centrioles during the early S phase elongate and reach full length by the late G2 or early M phase (Figure I). Elongation requires several proteins, including POC5, OFD1, SAS-4, and CP110 [14], with the latter two being best understood at a molecular level [76–78].

Centrosome maturation

In the late G2 phase, the PCM dramatically increases γ-TuRCs and its associated proteins, a process referred to as centrosome maturation (Figure I) [79]. Both Plk1 and Aurora A are recruited to the centrosomes in G2 to mediate maturation [80,81]. Recruitment of Aurora A to centrosomes is dependent on Plk1 activity, while activation of centrosome-associated Plk1 is dependent on Aurora A kinase activity [82]. The microtubule-binding protein TPX2 is also involved in centrosome maturation, presumably by interacting with, and activating Aurora A [83–85]. Other Plk1 substrates implicated in maturation are pericentrin, NEDD1, CEP192, and CEP215 [86]. Centrosome maturation is initiated when Plk1 phosphorylates pericentrin and NEDD1, which properly targets γ-TuRC to the PCM [87,88]. Aurora A then localizes to the centrosome and is activated by Plk1 and the LIM kinase protein Ajuba to complete centrosome maturation by recruiting large tumor suppressor kinase 2 (LATS2), nuclear distribution protein nudE-like 1 (NDEL1), and transforming, acidic coiled-coil containing protein 3 (TACC3) to the centrosome via phosphorylation [82].

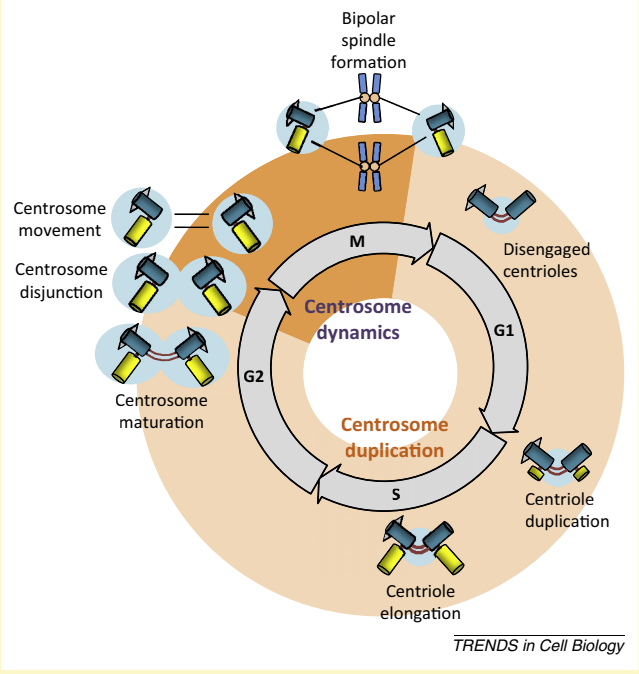

Figure I. The centrosome cycle. The centrosome cycle is divided into two parts: centrosome duplication, which encompasses centriole disengagement, duplication, elongation, and maturation; and centrosome dynamics, which includes centrosome disjunction and movement. In late mitosis, the daughter centriole disengages from the mother centriole and the two centrioles lose their orthogonal configuration (centriole disengagement). At the G1/S transition, one new daughter centriole is synthesized per mother centriole to form a new centrosome (centriole duplication and elongation). In the late G2 phase, both centrosomes recruit PCM components in order to prepare for mitosis (centrosome maturation). At the G2/M transition, centrosomal cohesion is gradually lost (centrosome disjunction) and centrosomes move toward opposite poles to form a bipolar spindle (centrosome movement) [9–11].

Centrosome disjunction

Until the late G2 phase, centrosomes are joined by centrosomal cohesin complexes, which include C-Nap1 and rootletin [17]. C-Nap1 is a large coiled-coil protein that localizes rootletin to the proximal end of centrioles, which physically links the two centrioles via fibrous polymers [17]. Late in G2, C-Nap1 and rootletin are phosphorylated by the never in mitosis A (NIMA)-related Ser/Thr kinase Nek2A, causing centrosome disjunction (Figure 1A) [18,19]. Accumulation of Nek2A to centrosomes is regulated by two components of the Hippo pathway, human Salvador homolog 1 (hSav1) and the Ser/Thr protein kinase Mst2, the latter of which activates Nek2A through phosphorylation (Figure 1A) [20]. In turn, polo-like kinase 1 (Plk1) activates Mst2 through phosphorylation. This particular post-translational modification also promotes centrosome disjunction by preventing Nek2A binding to the Ser/Thr protein phosphatase 1γ (PP1 γ) which antagonizes Nek2A (Figure 1A).

Recently, it was discovered that cyclin B2/cyclin-dependent kinase 1 (Cdk1) is an upstream regulator of the Nek2-dependent centrosome disjunction pathway [5]. Cyclin B2 is a member of the B-type cyclin family and activates Cdk1 through direct binding [21]. Prior to this study, little was known about cyclin B2 other than it localized to centriolar satellites in somatic cells and had an undefined role in spindle formation in *Xenopus* oocytes [22,23]. In experiments using gain- and loss-of-function models, cyclin B2 was found to play a critical role in centrosome separation during G2 by promoting Aurora A activity at centrosomes (Figure 1A). Aurora A is required for the activation of Plk1 [24], which, as mentioned, regulates centrosome separation by Nek2A-dependent phosphorylation of the centrosome linker proteins C-Nap1 and rootletin [13,25]. Overexpression