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REVIEW

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Regulation of the centrosome cycle

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ABSTRACT

The centrosome, consisting of mother and daughter centrioles surrounded by the pericentriolar matrix (PCM), functions primarily as a microtubule organizing center (MTOC) in most animal cells. In dividing cells the centrosome duplicates once per cell cycle and its number and structure are highly regulated during each cell cycle to organize an effective bipolar spindle in the mitotic phase. Defects in the regulation of centrosome duplication lead to a variety of human diseases, including cancer, through abnormal cell division and inappropriate chromosome segregation. At the end of mitosis the daughter centriole disengages from the mother centriole. This centriole disengagement is an important licensing step for centrosome duplication. In S phase, one new daughter centriole forms perpendicular to each centriole. The centrosome recruits further PCM proteins in the late G2 phase and the two centrosomes separate at mitotic entry to form a bipolar spindle. Here, we summarize research findings in the field of centrosome biology, focusing on the mechanisms of regulation of the centrosome cycle in human cells.

Abbreviation: Anaphase promoting complex/cyclosome (APC/C), microtubule organizing center (MTOC), microtubules (MTs), pericentriolar matrix (PCM), polo-like kinase (Plk), γ-tubulin ring complexes (γ-TuRCs)

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Introduction

Centrosomes are the microtubule organizing centers (MTOCs) of most animal cells and play a critical role in mitotic spindle orientation. The centrosome consists of a pair of centrioles, namely mother and daughter centrioles, embedded in the pericentriolar matrix (PCM). The PCM contains γ-tubulin ring complexes (γ-TuRCs), which play important roles in nucleating, anchoring, and positioning microtubules. Centrioles are characterized by a nine-fold radical symmetry of microtubules (MTs) and also function as basal bodies for the formation of cilia and flagella. The mother centriole harbors subdistal and distal appendages that play important roles in anchoring MTs and in docking centrioles to the membrane during flagellum or cilium formation.

In G1/S phase a single centrosome is located in close apposition to the nuclear envelope. Centrosome duplication is controlled by centriole replication. The mother and daughter centrioles are disengaged at the end of mitosis. After centriole disengagement, a proteinaceous linker is established between the 2 centrioles and physically connects them during interphase until mitosis. Building of the new centriole begins in early S phase with the formation of a procentriole at each centriole. One new daughter centriole forms perpendicular to each mother centriole during S phase, and the new daughter centriole gradually elongates during S and G2 phases. In late G2 phase, the amount of PCM proteins surrounding the centrioles increases, and the 2 centrosomes separate by dissolution of the linker that connects the 2 centrosomes. The separated centrosomes then move to opposite sides of the cell to form the spindle poles. Many of the proteins involved in the centrosome cycle have been identified and characterized (Figure 1). In this review we summarize research findings related to the centrosome cycle.

Centriole disengagement

Centriole disengagement involves the disorientation and physical separation of mother and daughter centrioles at the end of mitosis. Disengagement is an important licensing step for the next round of centrosome replication, preventing reduplication within one cell cycle.[1] Engagement is thought to be a critical block to reduplication inherent to centrioles. Consistent with this, physical removal of the daughter centriole by laser ablation induces reduplication of the daughter on the mother centriole.[2]

The mechanism of centriole disengagement is similar to that of sister chromatid separation at anaphase. Sister chromatids are held together by the ring cohesin complex, which consists of the 4 subunits Scc1, Smc1, Smc3, and SA1/SA2; dissociation of this complex by separase-mediated cleavage of Scc1 allows segregation of sister chromatids. The cohesin complex also localizes to the junction of engaged centrioles and is cleaved there by separase-mediated Scc1 proteolysis.[3,4] Separase is activated when its inhibitor securin is targeted for degradation by the E3 ligase anaphase promoting complex/cyclosome (APC/C)–Cdc20 and thus contributes to centriole disengagement.[5]

The serine/threonine protein kinase polo-like kinase 1 (Plk1) functions in cooperation with separase to trigger centriole

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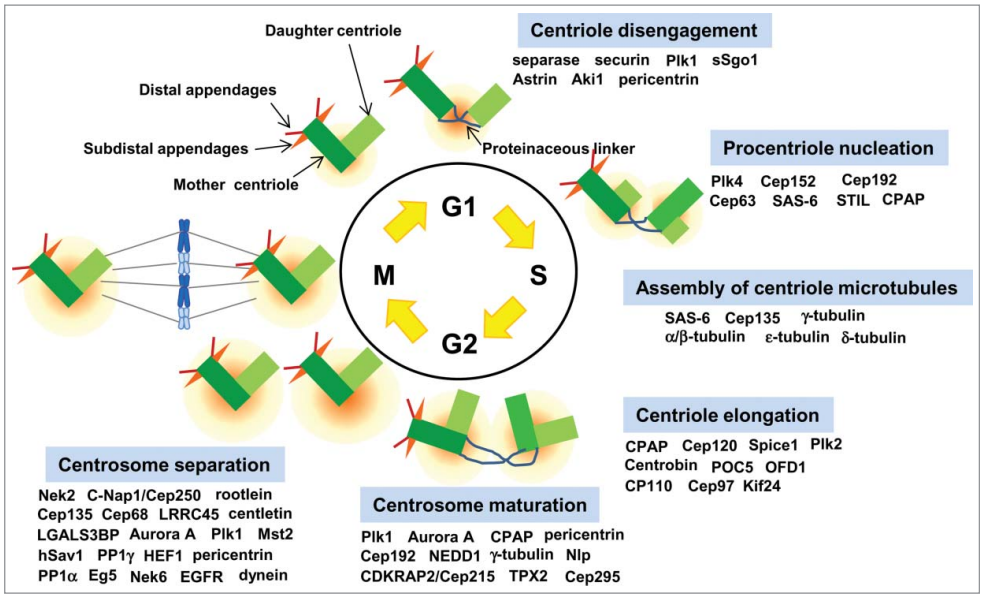

Figure 1. The centrosome cycle. Engagement of mother and daughter centrioles blocks centriole duplication. Disengagement of 2 centrioles occurs at the end of mitosis, and construction of the procentriole at the proximal end of the mother centriole is initiated at the G1-S transition. The 9-fold symmetry of the centriole is established by the formation of a cartwheel structure through the oligomerization of SAS-6. During the S and G2 phases, centriole elongation is promoted by CPAP. Later on in G2 phase, Plk1 and Aurora A kinase induce centrosome maturation and accumulation of PCM proteins. Centrosome separation takes place in late G2 phase to form the spindle poles. Proteins that function in each process are shown.

disengagement,[3] and also mediates an APC/C–Cdc20-independent pathway of disengagement.[5,6] Plk1 interacts with the smaller of 2 splice variants of Shugoshin 1 (Sgo1), sSgo1, which localizes to the centrosome in a Plk1-dependent manner and functions in the protection of centriole cohesion.[4,7] In addition, the microtubule and kinetochore-associated protein Astrin functions as an inhibitor of centrosomal separase.[8] Akt kinase-interacting protein 1 (Aki1) interacts with cohesin in the centrosome and this interaction prevents premature cleavage and is important for centriole cohesion.[9] Furthermore, cleavage of cohesin is insufficient for centriole disengagement in *Drosophila*.[10] In addition to cohesin, pericentrin/kendrin, a scaffolding element of the PCM, is a crucial target of separase at the centrosome and is important for centriole disengagement as it protects the engaged centrioles from premature disengagement.[11,12] Recent studies in *Caenorhabditis elegans* showed that MT-dependent forces also promote centriole disengagement.[13] In addition to disengagement, Plk1-dependent modification of daughter centrioles in early mitosis is also a licensing step for centriole duplication in the next cell cycle; the modified centrioles become competent to duplicate in the following S phase.[14 15,16]

After centriole disengagement, a proteinaceous linker composed of C-Nap1/Cep250 and the filamentous protein rootletin is established between the 2 centrioles and physically connects them during interphase until entry into mitosis.[17] This proteinaceous linker is referred to as centrosome cohesion[18] or the G1-G2 tether.[19]

Procentriole nucleation

Centrosome replication begins at the G1/S transition with nucleation of a procentriole at the base of the pre-existing centrioles. Plk4 is thought to be the key kinase responsible for the initiation of centriole duplication.[20-22] Centrosomal localization of Plk4 is regulated in time and space by the ordered interaction with 2 scaffolds, Cep192 and Cep152. Plk4 is recruited to the centrioles together with Cep152 through interaction with Cep192.[23,24] The centrosomal localization of Cep152 depends on Cep192.[23] Cep192 and Cep152 localize around the centriole barrel as the inner Cep192 ring and the outer Cep152 ring.[25] Crystal structure analyses revealed that Plk4 competitively binds to Cep192 and Cep152 in opposite orientations and in a mutually exclusive manner. Plk4 is repositioned from the inner Cep192 ring to the outer Cep152 ring as Cep152 is recruited around the Cep192-enriched daughter centriole.[26] Cep63 also functions together with Cep152 to promote efficient centriole duplication; Cep63 colocalizes with Cep152 to the proximal end of the mother centriole wall and Cep63–Cep152 direct interaction is required for centrosomal localization of both proteins.[27-29] Plk4 then dynamically moves from the surroundings of mother and daughter centrioles to the sites of procentriole assembly.[24] Plk4 recruits STIL and SAS-6 to each mother centriole, and these proteins subsequently recruit CPAP to trigger the assembly of procentriolar MTs.[20,30,31] STIL is phosphorylated by Plk4, and this phosphorylation facilitates the STIL–SAS-6 interaction to trigger SAS-6 recruitment.[32,33]

Building the cartwheel

The initial visible sign of procentriole formation is the emergence of a cartwheel-like structure with 9-fold symmetry.[34] The cartwheel consists of a central hub surrounded by 9 radical spokes. SAS-6 localizes to the cartwheel center and is a key molecule in cartwheel assembly.[35] Structural analysis of the SAS-6 protein provided crucial insight into the mechanism underlying the 9-fold radical symmetry of centrioles.[36,37] The SAS-6 molecule has a conserved amino-terminal domain, a coiled-coil domain, and a poorly conserved C-terminal domain. SAS-6 homodimerizes in parallel via the coiled-coil domain, resulting in a rod-shaped structure that oligomerizes via the N-

terminal domain. SAS-6 oligomers form a ring-like structure that resembles a central hub composed of 9 amino-terminal dimers, and 9 radical spokes formed by 9 coiled-coil dimers. These structures within the proximal part of the centrioles play pivotal roles in centriole assembly and elongation. A recent report described a model of SAS-6 recruitment to the mother centriole.[38] In S phase, SAS-6 is transiently recruited to the lumen of the mother centriole, where it is assembled into a structure with 9-fold symmetry structure through interactions with the luminal wall. The assembled SAS-6 oligomer is then repositioned to the luminal wall of the mother centriole for procentriole formation. This repositioning of SAS-6 is dependent on STIL and Plk4.

During mitosis, SAS-6 and STIL dissociate from centrioles and are subsequently degraded.[39] The cartwheel is removed from nascent centrioles at the end of mitosis. Centriole-to-centrosome conversion mediated by a newly generated centriole-enriched protein, Cep295, is required for stabilization of the centrioles lacking cartwheels.[40]

Assembly of centriole microtubules

In most animal cells, the daughter centriole is composed of 9 radically arranged MT triplets that form a cylinder built around the cartwheel. Starting from the inside, each triplet contains A-tubules, B-tubules, and C-tubules. The A-tubule of one triplet is connected to the C-tubule of the next triplet via an A-C linker. The A-tubule is nucleated by a conical structure resembling the γ-tubulin ring complex (γ-TuRC) structure, whereas B- and C-tubules are formed from the wall of A- and B-tubules, respectively.[41] ε-tubulin is required for the addition of B-tubules and C-tubules, and δ-tubulin is required for the addition of C-tubules.[42]

Cep135 is a highly conserved centrosomal protein that is involved in cartwheel assembly. The SAS-6 coiled-coil length is shorter than the distance between the cartwheel hub and the A-tubule of MT triplets. Cep135 directly interacts with SAS-6 via its C-terminal region and with MTs via its N-terminal region, acting as the physical link between SAS-6 and MTs.[43] Depletion of Cep135 results in the formation of abnormal centriole structures with altered MT triplet numbers and short centrioles.

Centriole elongation

After the formation of procentrioles, new centrioles start elongating in S phase, followed by elongation of the distal region during G2 phase. A number of conserved molecules are involved in the regulation of centriole elongation. CPAP stabilizes the cartwheel structure and plays an important role in recruiting MTs to the cartwheel structure during centriole elongation.[44-46] Overexpression of CPAP results in elongated centrioles.

The interaction of STIL with CPAP and formation of a complex with SAS-6 are required events for centriole elongation.[30,47-49] Cep135 interacts with CPAP via its N-terminal region and is involved in CPAP-induced centriole elongation.[43] Cep120 localizes to daughter centrioles and is essential for centriole assembly,[50] and also interacts with CPAP and Spice1 to positively regulate centriole elongation.[51,52] In addition, Plk2 phosphorylation is critical for the role of CPAP in procentriole formation and centriole elongation.[53] A daughter centriole protein, centrobin, is recruited to the centrosome early during centriole duplication, where it interacts with CPAP and α/β-tubulin dimers and promotes the elongation and stability of centrioles.[54,55] A recent report revealed that centrobin interacts with the ubiquitinated form of CPAP and prevents CPAP degradation for centriole elongation.[56]

Distinct proximal and distal elongation steps have been identified. The centrin-binding protein, POC5, and mouse orofaciodigital syndrome 1 (OFD1) localize to the distal portion of centrioles and are required for distal elongation.[57,58] Expression levels of POC1 protein play a role in the early steps of centriole duplication and the later step of elongation.[59]

CP110 and its interacting proteins act as capping structures that determine the final length of centrioles. CP110 localizes to the distal end of the centrioles and its depletion impairs the regulation of centriole length, resulting in long centrioles.[44,45] CP110 interacts with Cep97 and the kinesin-13 homolog Kif24. Cep97 recruits CP110 to the centrosome; depletion of Cep97 also results in centriole elongation.[60] Loss of Kif24 leads to the disappearance of CP110 from mother centrioles but not from abnormally long centrioles.[61] The level of CP110 is regulated by the $SCF^{cyclinF}$ ubiquitin ligase complex, which targets it for degradation, and this process is antagonized by the deubiquinating enzyme USP33.[62,63]

Centrosome maturation

This step is characterized by the acquisition of PCM proteins γ-TuRC and associated proteins. Recently, studies using 3D-structured illumination microscopy revealed that PCM proteins are organized in concentric toroids around mother centrioles in interphase and that the centrosome acquires additional PCM proteins that surround the toroidal PCM during mitosis.[25]

CPAP localizes to the PCM in addition to the proximal region of the centriole and plays a role in PCM recruitment independent of its role in centriole duplication.[64,65] CPAP interacts with, and forms a scaffolding complex with, PCM proteins, thus tethering them to the centrosome. A guanine nucleotide that binds to the α/β-tubulin dimer attached to CPAP regulates CPAP-dependent PCM recruitment to the centrosome.[66]

The centrosome shows an increased ability to nucleate and anchor microtubules towards the end of G2 phase and during mitosis. Plk1 and Aurora A kinases are required for this process. Plk1 plays crucial roles in the initiation of centrosome maturation. Plk1 phosphorylates the PCM proteins, pericentrin, Cep192, NEDD1, and CDKRAP2/Cep215.[67] Phosphorylation of pericentrin by Plk1 is required for the recruitment of Cep192, NEDD1, γ-tubulin, Aurora A, and Plk1 itself.[68] Pericentrin and Cep192 are mutually interdependent for their localization to the centrosome, and both proteins are required for the recruitment of NEDD1 and γ-tubulin.[69,70] CDKRAP2/Cep215 is associated with γ-TuRC and stimulates microtubule nucleation.[71,72]

In addition to the recruitment of PCM proteins to the centrosome, displacement of ninein-like protein (Nlp) from the centrosome is also important for centrosome maturation. Nlp binds to γ-TuRCs and stimulates microtubule nucleation

during interphase. Plk1 phosphorylates Nlp and displaces it from the centrosome.[73,74]

Plk1 promotes the recruitment of Aurora A to the centrosome. During G2 phase, Aurora A kinase functions in the initial activation of Plk1 together with Bora and contributes to centrosome maturation.[75-77] Once Plk1 is activated in G2 phase, continuous Plk1 activity is required during mitosis to maintain the PCM structure of the centrosome.[78] Plk1-dependent modification of daughter centrioles renders the centrosomes competent for recruiting PCM proteins involved in MT nucleation during the G2/M transition.[15] Plk1 is involved in the degradation of Bora in mitosis.[79] Minimal amounts of the Aurora A-Bora complex are sufficient to sustain Plk1 activity during mitosis.[80] The microtubule binding protein TPX2 is also involved in centrosome maturation through the activation of Aurora A.[81]

Centrosome separation

In the G2 phase, centrosome separation occurs through a 2-step process that consists of phosphorylation-dependent dissolution of the proteinaceous linker that connects 2 mother centrioles by Nek2 kinase and force-dependent separation of the centrosome by Eg5 to form spindle poles.[17]

C-Nap1/Cep250 localizes to the proximal ends of the mother centriole,[82] whereas rootletin is found in the proteinaceous linker between the 2 centrioles.[83] C-Nap1/Cep250 functions as a docking site for rootletin. The centriolar protein Cep135 interacts with C-Nap1/Cep250 and functions as a docking site for C-Nap1/Cep250.[84] Cep68 is also involved in the proteinaceous linker.[18] Cep68 forms fibers that attach to the proximal end of mother centrioles and functions in cooperation with rootletin and C-Nap1/Cep250 in centrosome cohesion.

Nek2 is a NIMA-related kinase that localizes to the centrosome during the S and G2 phases. Centrosome separation is triggered by Nek2-dependent phosphorylation of the centrosome linker proteins, including C-Nap1/Cep250 and rootletin, at the G2/M transition. Recently, multisite phosphorylation of C-Nap1/Cep250 by Nek2 was shown to disrupt the interaction of C-Nap1/Cep250 with Cep135.[85] Cep68 is also phosphorylated by Nek2.[86] Cep68 dissociates from centrosomes during mitosis and phosphorylation of Cep68 appears to promote its degradation in mitosis.[87]

A recent report showed that LRRC45, centletin, and LGALS3BP are also components of the proteinaceous linker.[86,88,89] LRRC45 localizes to the proximal ends of centrioles and forms a fiber-like structure between centrioles. LRRC45 is associated with C-Nap1/Cep250 and rootletin and is phosphorylated by Nek2 during mitosis. Centletin localizes to the proximal ends of centrioles, directly binds to C-Nap1/Cep250 and Cep68, and is also phosphorylated by Nek2. LGALS3BP functions at the connecting region between the 2 parental centrioles.

Regulation of Nek2 kinase activity is crucial for proper dissolution of the proteinaceous linker. Aurora A activates Plk1, which binds to and phosphorylates the Hippo pathway effector kinase Mst2.[90] Mst2 and hSav1, Hippo pathway scaffold proteins, directly bind to Nek2 and regulate the localization of Nek2 and the phosphorylation of C-Nap1/Cep250 and rootletin by Nek2.[91] Phosphorylation of Mst2 by Plk1 prevents binding of protein phosphatase 1γ (PP1γ) to Mst2-Nek2 and reduces the levels of PP1γ in the Mst2-Nek2-PP1γ complex, resulting in increased Nek2-dependent phosphorylation of C-Nap1/Cep250.[90] Furthermore, Nek2 associates with the negative regulators, HEF1 and pericentrin. The focal adhesion scaffolding protein HEF1 prevents Nek2 accumulation and inhibits its activity at the centrosomes.[92] Pericentrin seems to anchor Nek2 at the centrosome and suppresses its kinase activity.[93] In addition, protein phosphatase 1α (PP1α) dephosphorylates and inactivates Nek2.[94]

After their separation caused by dissolution of the linker proteins, the 2 centrosomes move to opposite directions to form bipolar spindles that are generated by the organization of motor proteins. The kinesin Eg5 generates the principal force necessary for centrosome separation.[17] Plk1 and intact MTs are required for the targeting of Eg5 to the centrosome.[90,95,96] Phosphorylation of Eg5 by Nek6, a NIMA kinase family protein, is important for Plk1-mediated targeting of Eg5.[96] Nuclear envelope-associated dynein anchored to the nuclear pores during prophase and the sliding of 2 antiparallel oriented MTs by dynein in (pro)metaphase function together with Eg5 to coordinate proper centrosome separation.[97,98] Furthermore, dynein at the cell cortex is regulated by astral microtubules to control spindle orientation.[99] Recently, epidermal growth factor receptor (EGFR) signaling was suggested to drive premature centrosome separation and promote mitotic progression.[100]

Concluding remarks

During the cell cycle, centrosomes duplicate only once in a highly spatiotemporally regulated manner that is controlled by many proteins described in the present work. Perturbation of these regulatory mechanisms can affect the proper execution of the various processes and result in the formation of abnormal centrosomes.[101,102] Alterations in centrosome number and structure lead to defective mitosis and consequently in chromosome instability, which is a major source of aneuploidy in cancers.[103,104] In the future, further detailed characterization of centrosome regulation during the cell cycle could provide promising targets for cancer therapy.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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