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Cell Cycle Regulation of the Centrosome and Cilium

Tomer Avidor-Reiss[2,1] and **Jayachandran Gopalakrishnan**[3,4]

[2]Department of Biological Sciences, University of Toledo, Toledo, OH 43606, USA

[3]Center for Molecular Medicine, University of Cologne, Germany

[4]Institute of Biochemistry I, University of Cologne, Germany

Abstract

Centrosomes and cilia are conserved microtubule-based organelles whose structure and function depend on cell cycle stages. In dividing cells, centrosomes organize mitotic spindle poles, while in differentiating cells, centrosomes template ciliogenesis. Classically, this functional dichotomy has been attributed to regulation by cell cycle-dependent post-translational modifications, and recently PLK1, Nek2, Aurora A, and tubulin deacetylase were implicated in regulating the transition from cilia to centrosome. However, other recent studies suggest that tubulin dimers, the core structural components of centrosomes and cilia, also have a regulatory role. These regulatory mechanisms can be a target for chemotherapeutic intervention.

Introduction

The full functional identity of centrosomes and cilia was an enigma for most of the 20th century. However, it is becoming evident that the centrosome and cilium are two different forms of the same cellular organelle represented during distinct phases of the cell cycle. Coordinating the various structural and functional statuses of the centrosome and cilium throughout the cell cycle requires fine regulation. A major mechanism mediating this regulation is post-translational modification (reviewed in [1]). Interestingly, recent findings suggest that tubulin dimers, which are known to function as the building block of centrosomal and ciliary microtubules, also play a role in regulating centrosome structure and function [2]. Malformation of centrosomes and cilia is an important factor underlying many cancers, as well as a group of developmental diseases collectively known as ciliopathies [1]. In this regard, targeting the above regulatory mechanisms may be of therapeutic value [3]. Here, we focus on findings from the last two years that expand our understanding of cell cycle regulation of the centrosome and cilium.

[1]Corresponding author: Tomer Avidor-Reiss, Phone: 419-530-1993 Tomer.AvidorReiss@utoledo.edu.

Conflict of interest
The author(s) have no conflict of interest to declare.

The Cell Cycle Regulates Centrosomes and Cilia *via* Post-translational Modifications

At its core, the centrosome contains a pair of structures known as centrioles (Figure 1K–N). Within each pair, one centriole is structurally and functionally matured, while the other is immatured. Centrioles are microtubule-based barrel-shaped structures with typical dimensions of 200 nm in diameter and 500 nm in length. The most distinctive feature of the centriole in electron microscopy is the microtubules that are organized into an array of 9 triplets (the A, B and C microtubules, Figure 1N) along most of their length. The center of early centrioles (procentrioles) has a cartwheel structure that contains a central tubule emanating 9 spokes (Figure 1K–L). Inside the centrosome, centrioles are embedded in a complex network of proteins called pericentriolar material (PCM) that appears amorphous by electron microscopy.

Typically, it takes two cell cycles for a centriole to mature so that it can function in spindle pole organization and in templating the cilium (Figure 1). The cascade of events is as follows: during the first S phase, the centriole duplicates to give rise to a procentriole (Figure 1A). This step is controlled by the cell cycle kinase CDK2 that is in complex with Cyclin E or Cyclin A [4], as well as by Polo-like kinase 4 (Plk4), a key regulator of that appears to function specifically in centriole duplication [5]. Consistent with this idea, Plk4 binds or phosphorylates several centrosomal protein including Asl/Cep152 (Figure 2A), which is thought to participate in nucleating the procentriole [6–8], and the γ-tubulin ring complex (γ-TuRC) component GCP6 [9]. Plk4 also phosphorylates regulators of centriolar proteins including the E3-ubiquitin ligase FBXW5, which targets the essential procentriole cartwheel protein Sas-6 (Figure 2B) for degradation [10].

During the first G2 phase, the procentriole elongates into an immature centriole (Figure 1B). Sas-4/CPAP has been implicated in centriole elongation [11–14] (Figure 2C) and it was recently shown that CPAP degradation and function is controlled by tankyrase 1, a poly(ADP-ribose) polymerase that has a broad range of cellular activities [15].

During the first M phase, the immature centriole disengages from the mature centriole (Figure 1C), a process that involves Separase-dependent cleavage of pericentrin and cohesin rings [16–18]. However, the immature centriole remains linked to the mature centriole via a proteinaceous linker.

Following mitosis during the first G1 phase, the mature centriole templates ciliogenesis and the immature centriole (Figure 1D) remains nearby *via* the proteinaceous linker.

During the second S phase, the daughter centriole can give rise to a new procentriole, thereby becoming an immature mother centriole (Figure 1E).

During the second G2 phase, this immature mother centriole separates from its own mother and starts to recruit PCM (Figure 1F). This PCM is required to nucleate and anchor the astral microtubules that emanate from the centrosome into the cytoplasm. The astral microtubules are important for positioning the centrosome and may also affect the position of other

cellular organelles [19]. The process taking place in G2 whereby the centriole recruits more PCM and increases astral microtubule nucleation capacity is known as centrosome maturation [20]. Aurora A is a cell cycle kinase that is implicated in centrosome maturation and this is regulated by Nucleophosmin/B23, a centrosome activator of Aurora A [21]. Also implicated in centrosome maturation is another central regulator of the cell cycle, Polo-like kinase (Plk1). Plk1 phosphorylates pericentrin [22] and also regulates centrosome separation, a process which takes place in parallel to centrosome maturation through a signalling module composed of Nek9/Nercc1, Nek6 and Nek7 [23]. NIMA-related kinase (Nek2) is another cell cycle-regulated kinase implicated in centrosome separation in G2 [24].

During the second M phase, the new centrosome that emerged from the procentriole formed two cell cycles before is localised at the opposite spindle pole in relation to the old centrosome (Figure 1G). This opposing localisation is important for two distinct functions. One is to assure accurate segregation of the centrioles during cell division such that one, and only one, centrosome will be inherited by each of the daughter cells. The second role is to help orient the mitotic spindle [25].

After cell division, in the second G1 phase, the mother centriole templates the formation of a cilium (Figure 1H). During ciliogenesis, the A and B microtubules of the centriole (Figure 1I–G) elongate and form the axoneme, which is essentially the skeleton of the cilium. Recently, it was found that αTAT1 is required for acetylating ciliary microtubules during cilium assembly and to promotes ciliogenesis [26].

Finally, once the cell commits to another cell division and re-enters the third cell cycle, cilia are typically eliminated in two steps in a process known as cilium resorption: first in S phase and again in G2. It was proposed that initial ciliary resorption is necessary for a cell to enter S phase [27] and that final resorption was required for entry into mitosis [28]. Cilium resorption can trigger Plk1 kinase activity, suggesting that cilium resorption releases a factor that can participate in cell cycle regulation [29]. Nek2 was reported to localize to the distal portion of the mother centriole and to be required for cilium resorption in G2 [30]. In addition, Aurora A activation of the tubulin deacetylase HDAC is also required for cilium resorption [31].

In summary, one of the major mechanisms mediating tight regulation of cell cycle-dependent changes in the centrosome and cilia occurs by a variety of enzymes utilizing various post-translational protein modifications. Considering that these enzymes control distinct aspects of centrosome and cilium assembly and function, they may provide beneficial targets to control centrosome and cilium structure and function in a cell. For example, since centrosomes are deregulated in cancer [32], targeting the enzymes that mediate post-translational modification of centrosomal proteins presents a potential opportunity for cancer treatment [3,33].

Tubulin dimer regulation of centrosome biogenesis

Centrosomes and cilia are composed of microtubules that play both structural and functional roles. Microtubules are polymers of tubulin dimers (a heterodimer of α-tubulin and β-

tubulin) [34]. Here, we will use the term “tubulin dimer” to refer to cytoplasmic tubulin that is not part of microtubules, the term “tubulin polymer” to refer to tubulin assembled in microtubules and the term “tubulin” to refer to tubulin in general. Tubulin is a guanine nucleotide binding protein normally bound to GTP. Tubulin-dimer-GTP can readily polymerize to form microtubules. Tubulin is also a GTPase, hydrolyzing tubulin-GTP into tubulin-GDP. However by itself, the tubulin dimer has a low intrinsic GTPase activity. In microtubules, tubulin-tubulin interactions activate the GTPase activity of tubulin polymers and, as a result, microtubules become enriched over time with tubulin-polymer-GDP, which favours microtubule disassembly. The capacity of tubulin to switch from tubulin polymer-GTP to tubulin polymer-GDP allows microtubules to undergo rapid transition from growth to disassembly, a phenomenon known as dynamic instability, which is critical for microtubule function. In this context, tubulin acts as a molecular switch in which tubulin polymer-GTP is the “on” state supporting microtubule growth and tubulin polymer-GDP is the “off” state enhancing microtubule disassembly.

Tubulin concentration in a cell is thought to remain constant, and in the cytoplasm, tubulin is primarily present as tubulin dimer-GTP rather than tubulin dimer-GDP. The reason for this is that, unlike polymerized tubulin, the tubulin dimer has a high guanine exchange activity and readily exchanges its bound GDP with GTP [35]. Therefore, tubulin dimer-GDP resulting from microtubule depolymerization is rapidly converted to tubulin dimer-GTP. However, mathematical models [36] and cytoskeleton remodelling assays [37] suggest that the tubulin dimer-GDP concentration can increase as a result of microtubule remodelling during the cell cycle. Although the increase in tubulin dimer-GDP concentration is transient, this spike of tubulin dimer-GDP concentration may be a signal that can regulate cellular process such as centrosome and cilia formation.

Tubulin dimers are known to directly interact with only a few distinct types of proteins [38–41]. One of them, the voltage-dependent anion-selective channel (VDAC) on the outer mitochondrial membrane, was studied in detail and was shown to be regulated by tubulin dimers in a series of studies [40,41]. Interestingly, two centrosomal proteins, centrobin and CPAP/Sas-4, directly interact with tubulin dimers. Centrobin is a daughter centriole protein and the centrobin-tubulin interaction is required for centriole elongation and stability [39]. CPAP (aka CenpJ) is the human ortholog of Sas-4 in invertebrates. CPAP/Sas-4 is an essential conserved centrosomal protein and the CPAP/Sas-4-tubulin interaction is implicated in centriole elongation and PCM formation [2,14,42].

The interaction between the tubulin dimer and CPAP has been studied in detail, and these studies suggest that CPAP does not bind to centrosome microtubules *via* the tubulin-binding site. CPAP-tubulin dimer binding site was shown to be essential and sufficient for binding to tubulin dimers [42,43], indicating that CPAP has only one tubulin dimer binding site. Mapping of the tubulin dimer CPAP binding site suggests that CPAP interacts with a β-tubulin surface that becomes embedded within microtubules upon polymerization [44]. This argues that CPAP cannot bind tubulin-polymers and is consistent with the observation that CPAP does not coprecipitate with microtubules [43], providing an explanation to an earlier observations that CPAP/Sas-4 overexpression leads to microtubule disassembly [42,43]. Accordingly, CPAP/Sas-4, which is normally found in minute amounts in the cell, can

sequester tubulin upon overexpression to non-physiological levels, resulting in microtubule destabilization [44]. Therefore, the CPAP/Sas-4 tubulin binding site specifically binds to tubulin dimers but not to tubulin polymers and the CPAP/Sas-4-tubulin interaction does not appear to occur at centrosomal microtubules.

The physiological role of the tubulin dimer interaction with Sas-4 has been studied in detail both genetically and biochemically in *Drosophila* [2]. Genetically engineered flies that express a Sas-4 mutant that cannot interact with tubulin exhibit enlarged centrosomes due to an increase in PCM recruitment. These centrosomes also nucleate abnormally large amounts of microtubules, suggesting that tubulin-regulated Sas-4 PCM recruitment involves an increase in the microtubule nucleation activity of the centrosome (Figure 2D–E). Biochemical experiments found that Sas-4 forms multiple complexes that include a large number of PCM proteins. One complex, termed S-CAP, includes tubulin, Sas-4, Cnn, Asl, D-PLP [45]. A second complex S-γ-TuRC, includes tubulin, Sas-4, and all of the components of the microtubule nucleation complex (γ-TuRC complex, i.e. Grip91, Grip84, Grip163, Grip128, Grip75, Grip91 and Grip84) [2]. The formation of S-CAP and S-γ-TuRC depends on whether Sas-4 is bound to tubulin dimer-GDP or tubulin dimer-GTP. While tubulin dimer-GDP favours the formation of Sas-4 complexes with PCM proteins, tubulin dimer-GMPCPP (a non-hydrolyzable GTP analog) limits the association of PCM with Sas-4 (Figure 3). These findings collectively argue that tubulin nucleotide status controls the interaction of Sas-4 with other PCM proteins and can function as a molecular switch for PCM recruitment to the centrosome. In this context, tubulin dimer-GTP is the “off” state and tubulin dimer-GDP is the “on” state. This is the opposite situation to that occurring in microtubules and holds key implications for the regulation of centrosome biogenesis.

An increase in tubulin dimer-GDP concentration may happen during G2. During this time, microtubule network remodelling [37] and cilium resorption take place [30]. It is therefore tempting to speculate that a transient spike during this time in tubulin dimer-GDP concentration may regulate centrosome activity. It is noteworthy that during G2, centrosomes recruit more PCM and exhibit an increased microtubule nucleation capacity as part of centrosome maturation [20]. This raises the possibility that an increase in tubulin dimer-GDP levels may serve as a signal to control centrosome maturation. There are several pieces of experimental evidence that support this premise. First, treating cells with griseofulvin, a compound that induces hydrolysis of tubulin dimer-GTP into tubulin dimer-GDP, increases PCM size [2,46]. Second, treating cells with taxol, a compound that stabilizes microtubules and reduces tubulin dimer-GDP release into the cytoplasm, reduces PCM size [2]. Therefore, it is possible that tubulin dimer-GDP can regulate PCM assembly and centrosome maturation.

Conclusions

Centrosomes and cilia undergo dramatic structural changes during the cell cycle. These structural changes are required to perform distinct functions according to the cells’ need and coordinating these structural changes requires a large number of regulatory elements. Until recently, studies have focused on post-translational modifications and, in particular, on phosphorylation mediated by mitotic and cell cycle-dependent kinases. Most of these

kinases are implicated in diverse cellular functions and participate in centrosome and cilium biogenesis at a particular cell cycle stage in order to couple centrosome and cilium status to the cell cycle. Therefore, with the exception of PLK4, most of these kinases are not inherent to the centrosome and cilium. This begs for the presence of other intrinsic centrosomal and ciliary mechanisms that can control their structure and function. One such mechanism may involve the function of tubulin, a major centrosomal, ciliary and cytoskeletal building block, as a regulatory subunit of centrosome biogenesis. It is thus possible that a tubulin-driven signalling mechanism can relay information on the state or outcome of cell cycle events such as microtubule remodelling, and provide feedback or homeostatic control on centrosome/cilium structure and function. So, while cell cycle kinases coordinate centrosome biogenesis throughout the cell cycle, tubulin may monitor these events and provide feedback.

Tubulin can complement other post-translational mechanisms in regulating centrosome and cilium biogenesis. First, unlike the proteins that mediate post-translational modifications, tubulin is abundant and readily available in the cell. In some aspects, it resembles other abundant cellular molecules that play regulatory roles such as ATP, which functions as the cell's main energy carrier. Second, an increase in overall levels of tubulin-GDP is also expected to take place during pathological situations when cellular energy supplies are reduced. This increase in tubulin-GDP may provide a way to activate PCM formation when kinases may be less active. Finally, regulation by post-translational modification and by tubulin signalling are likely to work in coordinated way. As an example, tubulin regulation of VDAC channels was reported to be sensitive to the state of VDAC phosphorylation [41], suggesting that both post-translational modification and tubulin activity provide a means for exquisite control.

Precisely how tubulin functions to regulate centrosome and cilia biogenesis and how this regulation is coordinated with other mechanisms such as cell cycle dependent post-translational modifications remains to be investigated. Since tubulin is the target of one of the best class of cancer chemotherapeutic drugs available to date, understanding how tubulin regulation and other cellular mechanisms function together is an important goal. Furthermore, one of the drawbacks of a tubulin-based therapeutic approach is that it results in significant untoward deleterious effect. However, the mechanism of action underlying the anti-cancer activity and the associated side effects of tubulin-targeting drugs is not fully understood. The newly discovered role for tubulin in regulating centrosome biogenesis independent of its well-known role as a building block of microtubules may help in generating more effective tubulin-targeting drugs that have fewer side effects.

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References

1. Nigg EA, Raff JW. Centrioles, centrosomes, and cilia in health and disease. Cell. 2009; 139(4):663–678. [PubMed: 19914163]

2. Gopalakrishnan J, et al. Tubulin nucleotide status controls Sas-4-dependent pericentriolar material recruitment. Nat Cell Biol. 2012 Using a combination of genetics and biochemistry, the authors demonstrate that tubulin regulates the formation of Sas-4-PCM complexes and thereby PCM recruitment to the centrosome. This is the first study that demonstrates that tubulin nucleotide status can serve as a switch in a process other than microtubule formation.
3. Mazzorana M, et al. The centrosome: a target for cancer therapy. Curr Cancer Drug Targets. 2011; 11(5):600–612. [PubMed: 21486219]
4. Meraldi P, et al. Centrosome duplication in mammalian somatic cells requires E2F and Cdk2-cyclin A. Nat Cell Biol. 1999; 1(2):88–93. [PubMed: 10559879]
5. Holland AJ, et al. Polo-like kinase 4 controls centriole duplication but does not directly regulate cytokinesis. Mol Biol Cell. 2012; 23(10):1838–1845. [PubMed: 22456511]
6. Cizmecioglu O, et al. Cep152 acts as a scaffold for recruitment of Plk4 and CPAP to the centrosome. J Cell Biol. 2010; 191(4):731–739. [PubMed: 21059844]
7. Dzhindzhev NS, et al. Asterless is a scaffold for the onset of centriole assembly. Nature. 2010; 467(7316):714–718. [PubMed: 20852615]
8. Hatch EM, et al. Cep152 interacts with Plk4 and is required for centriole duplication. J Cell Biol. 2010
9. Bahtz R, et al. GCP6 is a substrate of Plk4 and required for centriole duplication. J Cell Sci. 2012; 125(Pt 2):486–496. [PubMed: 22302995]
10. Puklowski A, et al. The SCF-FBXW5 E3-ubiquitin ligase is regulated by PLK4 and targets HsSAS-6 to control centrosome duplication. Nat Cell Biol. 2011; 13(8):1004–1009. [PubMed: 21725316] This study is a good example to the intricate cell cycle regulation involve in generating robust cell cycle control and for the involvment of cell-cycle-regulated E3-ubiquitin ligase. The authors demonstrate that Plk4 phosphorylates FBXW5 and suppress its ability to ubiquitylate HsSAS-6. Anaphase-promoting (APC/C) complex suppress FBXW5 levels during M amd G1 alowing FBXW5 to reach peack expression at the G1/S transition
11. Blachon S, et al. A proximal centriole-like structure is present in Drosophila spermatids and can serve as a model to study centriole duplication. Genetics. 2009; 182(1):133–144. [PubMed: 19293139]
12. Kohlmaier G, et al. Overly long centrioles and defective cell division upon excess of the SAS-4-related protein CPAP. Curr Biol. 2009; 19(12):1012–1018. [PubMed: 19481460]
13. Schmidt TI, et al. Control of centriole length by CPAP and CP110. Curr Biol. 2009; 19(12):1005–1011. [PubMed: 19481458]
14. Tang CJ, et al. CPAP is a cell-cycle regulated protein that controls centriole length. Nat Cell Biol. 2009; 11(7):825–831. [PubMed: 19503075]
15. Kim MK, et al. Tankyrase 1 regulates centrosome function by controlling CPAP stability. EMBO Rep. 2012
16. Lee K, Rhee K. Separase-dependent cleavage of pericentrin B is necessary and sufficient for centriole disengagement during mitosis. Cell Cycle. 2012; 11(13)
17. Matsuo K, et al. Kendrin is a novel substrate for separase involved in the licensing of centriole duplication. Curr Biol. 2012; 22(10):915–921. [PubMed: 22542101]
18. Schockel L, et al. Cleavage of cohesin rings coordinates the separation of centrioles and chromatids. Nat Cell Biol. 2012; 13(8):966–972. [PubMed: 21743463]
19. Zhao T, et al. Growing microtubules push the oocyte nucleus to polarize the Drosophila dorsal-ventral axis. Science. 2012; 336(6084):999–1003. [PubMed: 22499806] Using live imaging and laser ablation, the authors demonstrate that microtubule polymerization from centrosomes can push massive cellular organelle such as the nucleus by the force exerted by growing microtubules. This demonstrates that, at least in some cases, centrosome positioning and microtubule polymerization from centrosomes but not pulling force exterted by dynein is the critical for this process.
20. Palazzo RE, et al. Centrosome maturation. Curr Top Dev Biol. 2000; 49:449–470. [PubMed: 11005031]
21. Reboutier D, et al. Nucleophosmin/B23 activates Aurora A at the centrosome through phosphorylation of serine 89. J Cell Biol. 2012; 197(1):19–26. [PubMed: 22451695]

22. Lee K, Rhee K. PLK1 phosphorylation of pericentrin initiates centrosome maturation at the onset of mitosis. J Cell Biol. 2012; 195(7):1093–1101. [PubMed: 22184200]
23. Bertran MT, et al. Nek9 is a Plk1-activated kinase that controls early centrosome separation through Nek6/7 and Eg5. EMBO J. 2012; 30(13):2634–2647. [PubMed: 21642957] This study is a good example to the intricate cell cycle regulation involve in generating robust cell cycle control. The authors propose a two-step activation mechanism were by sequential phosphorylation by CDK1 and Plk1 activate Nek9 which regulate centrosome seperation.
24. Fry AM, et al. C-Nap1, a novel centrosomal coiled-coil protein and candidate substrate of the cell cycle-regulated protein kinase Nek2. J Cell Biol. 1998; 141(7):1563–1574. [PubMed: 9647649]
25. Yuan H, et al. Regulation of cyclin A localization downstream of Par-1 function is critical for the centrosome orientation checkpoint in Drosophila male germline stem cells. Dev Biol. 2012; 361(1):57–67. [PubMed: 22024320]
26. Shida T, et al. The major alpha-tubulin K40 acetyltransferase alphaTAT1 promotes rapid ciliogenesis and efficient mechanosensation. Proc Natl Acad Sci U S A. 2010; 107(50):21517–21522. [PubMed: 21068373]
27. Li A, et al. Ciliary transition zone activation of phosphorylated Tctex-1 controls ciliary resorption, S-phase entry and fate of neural progenitors. Nat Cell Biol. 2011; 13(4):402–411. [PubMed: 21394082]
28. Kim S, et al. Nde1-mediated inhibition of ciliogenesis affects cell cycle re-entry. Nat Cell Biol. 2011; 13(4):351–360. [PubMed: 21394081]
29. Seeger-Nukpezah T, et al. The centrosomal kinase plk1 localizes to the transition zone of primary cilia and induces phosphorylation of nephrocystin-1. PLoS One. 2012; 7(6):e38838. [PubMed: 22701722]
30. Spalluto C, et al. Nek2 localises to the distal portion of the mother centriole/basal body and is required for timely cilium disassembly at the G2/M transition. Eur J Cell Biol. 2012
31. Pugacheva EN, et al. HEF1-dependent Aurora A activation induces disassembly of the primary cilium. Cell. 2007; 129(7):1351–1363. [PubMed: 17604723]
32. Chan JY. A clinical overview of centrosome amplification in human cancers. Int J Biol Sci. 2011; 7(8):1122–1144. [PubMed: 22043171]
33. Valsasina B, et al. NMS-P937, an orally available, specific small-molecule polo-like kinase 1 inhibitor with antitumor activity in solid and hematologic malignancies. Mol Cancer Ther. 2012; 11(4):1006–1016. [PubMed: 22319201]
34. Desai A, Mitchison TJ. Microtubule polymerization dynamics. Annu Rev Cell Dev Biol. 1997; 13:83–117. [PubMed: 9442869]
35. Melki R, et al. Cold depolymerization of microtubules to double rings: geometric stabilization of assemblies. Biochemistry. 1989; 28(23):9143–9152. [PubMed: 2605248]
36. Janulevicius A, et al. Compartment volume influences microtubule dynamic instability: a model study. Biophys J. 2006; 90(3):788–798. [PubMed: 16410484]
37. Zhai Y, et al. Microtubule dynamics at the G2/M transition: abrupt breakdown of cytoplasmic microtubules at nuclear envelope breakdown and implications for spindle morphogenesis. J Cell Biol. 1996; 135(1):201–214. [PubMed: 8858174]
38. Duvernay MT, et al. Alpha2B-adrenergic receptor interaction with tubulin controls its transport from the endoplasmic reticulum to the cell surface. J Biol Chem. 2011; 286(16):14080–14089. [PubMed: 21357695]
39. Gudi R, et al. Centrobin-tubulin interaction is required for centriole elongation and stability. J Cell Biol. 2011; 193(4):711–725. [PubMed: 21576394]
40. Gonzalez-Granillo M, et al. Studies of the role of tubulin beta II isotype in regulation of mitochondrial respiration in intracellular energetic units in cardiac cells. J Mol Cell Cardiol. 2011; 52(2):437–447. [PubMed: 21846472]
41. Sheldon KL, et al. Phosphorylation of voltage-dependent anion channel by serine/threonine kinases governs its interaction with tubulin. PLoS One. 2011; 6(10):e25539. [PubMed: 22022409]
42. Hung LY, et al. Identification of a novel microtubule-destabilizing motif in CPAP that binds to tubulin heterodimers and inhibits microtubule assembly. Mol Biol Cell. 2004; 15(6):2697–2706. [PubMed: 15047868]

43. Hsu WB, et al. Functional characterization of the microtubule-binding and -destabilizing domains of CPAP and d-SAS-4. Exp Cell Res. 2008; 314(14):2591–2602. [PubMed: 18586240]

44. Cormier A, et al. The PN2-3 domain of centrosomal P4.1-associated protein implements a novel mechanism for tubulin sequestration. J Biol Chem. 2009; 284(11):6909–6917. [PubMed: 19131341]

45. Gopalakrishnan J, et al. Sas-4 provides a scaffold for cytoplasmic complexes and tethers them in a centrosome. Nat Commun. 2011; 2:359. [PubMed: 21694707]

46. Rebacz B, et al. Identification of griseofulvin as an inhibitor of centrosomal clustering in a phenotype-based screen. Cancer Res. 2007; 67(13):6342–6350. [PubMed: 17616693]

Highlights

- Centrosomes and cilia are distinct functional states of the same organelle
- Cell cycle-dependent modifications regulate centrosome functional changes
- Tubulin dimer is a molecular switch that also regulates centrosome functional changes

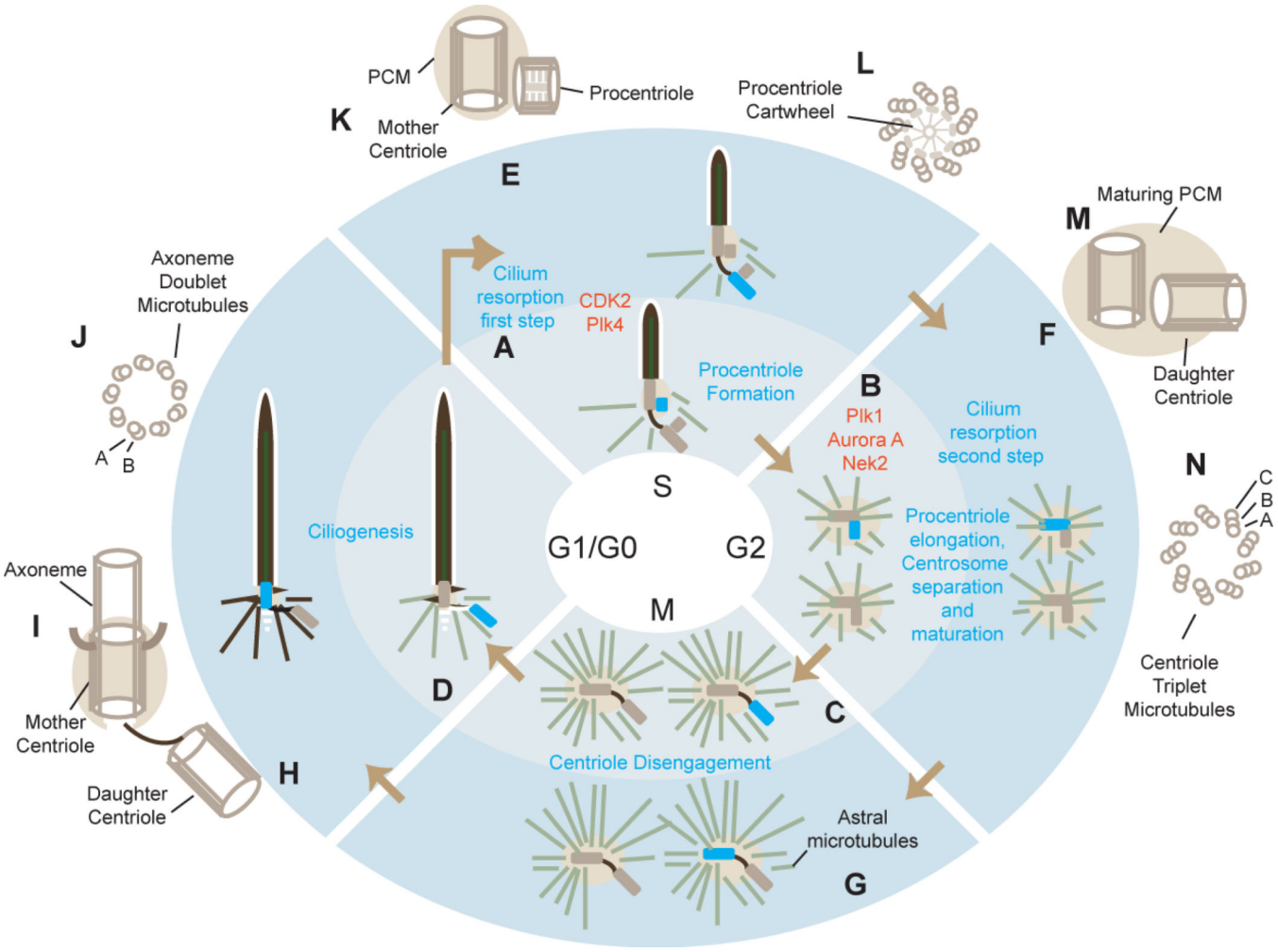

Fig 1. Cell cycle control over centrosome and cilium biogenesis

The cell cycle events taking place from the initial formation of one of the procentrioles (blue square in **A**) through two consecutive cell cycles (first cell cycle in light blue background (**A–D**), second cell cycle in dark blue background (**E–H**)) until it becomes a mature centriole having distal appendages and can form a centrosome, as well as give rise to a cilium (**H**). (**I–N**) Magnified structure of a centrosome and cilium are depicted at the periphery of the figure, as they would appear from a side view (**I, K** and **M**) and cross section (**J, L** and **N**). Major events in centrosome and cilium biogenesis are noted in blue. Cell cycle kinases are indicated in red.

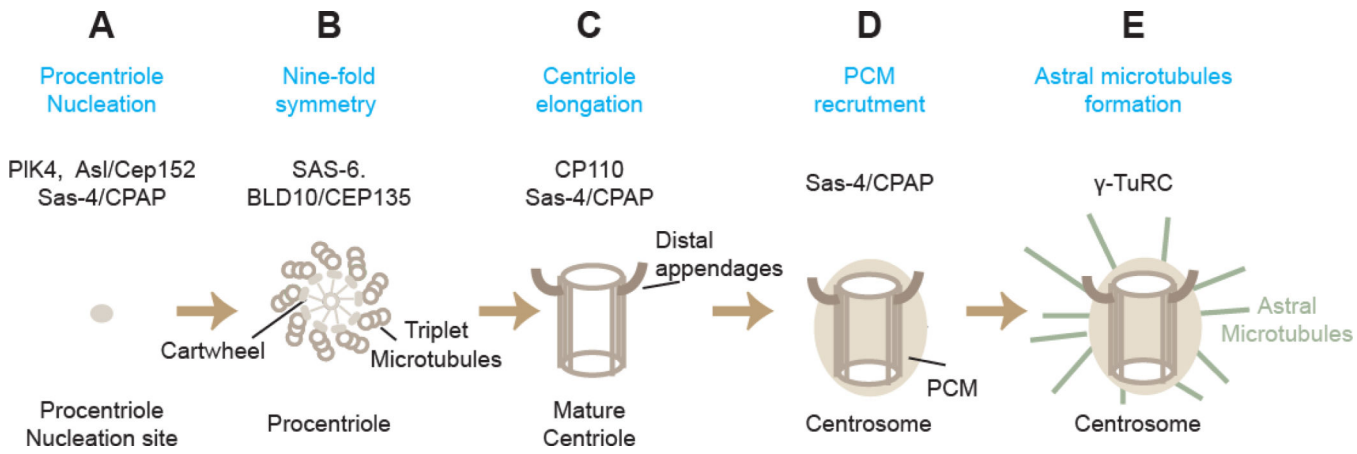

Fig 2. Key players in centrosome biogenesis

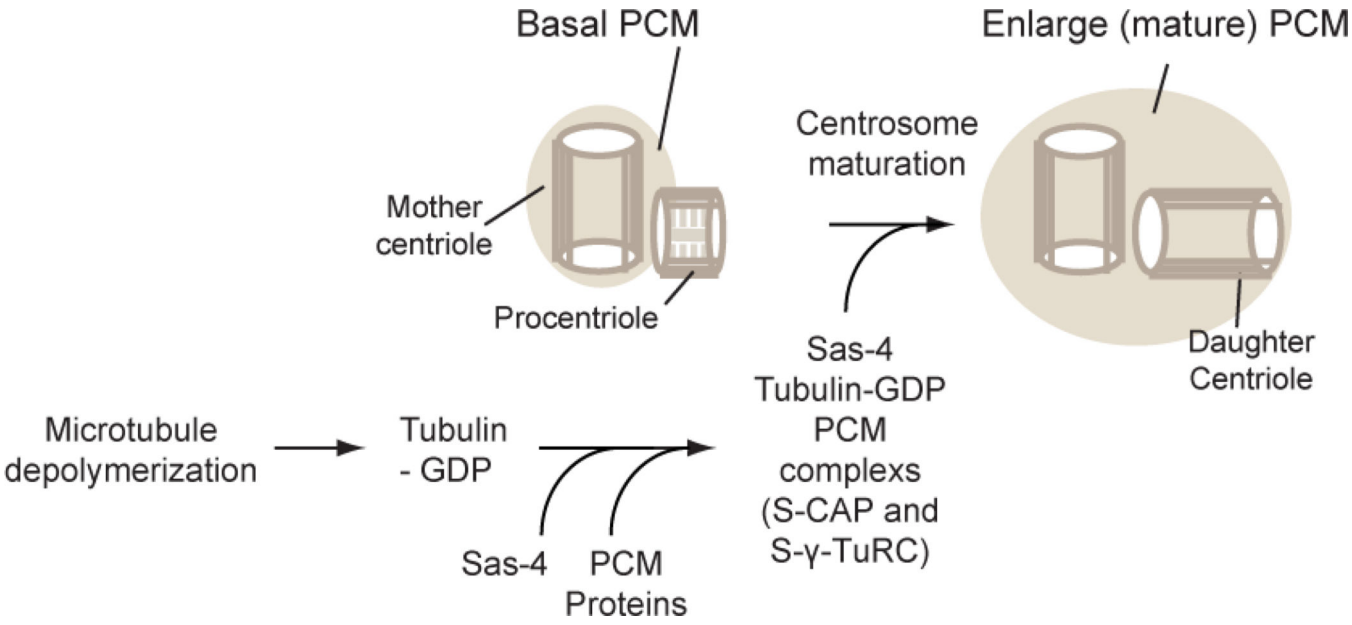

Figure 3. A model for the regulatory control of the tubulin dimer in centrosome biogenesis

Tubulin dimer-GDP produced from depolymerization of microtubules binds to Sas-4 and promotes the formation of PCM complexes. These complexes are recruited to the centrosome, enabling an increase in PCM size and an increase in microtubule nucleation activity.