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Building a centriole

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Centrioles are the key foundation of centrosomes and cilia, yet a molecular understanding of how they form has only recently begun to emerge. Building a fully functional centriole that can form a centrosome and cilium requires two cell cycles.

Centriole building starts with procentriole nucleation, a process that is coordinated by the conserved proteins Plk4/Zyg-1, and Asterless/Cep152. Subsequently, Sas-6, a conserved procentriole protein, self-assembles to provide nine-fold symmetry to the centriole scaffold. The procentriole then continues to elongate into a centriole, a process controlled by Sas-4/CPAP and CP110. Then, centrioles recruit Sas-4-mediated pre-assembled centrosomal complexes from the cytoplasm to form the pericentriolar material (PCM). Finally, CP110 and its interacting proteins are involved in controlling the timing of centriole templating of the cilium.

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Introduction

Centrioles are microtubule-based, conserved eukaryotic cell structures measuring $\sim 200 \times 500$ nm in size that have a distinctive radial nine-fold symmetry. Typically, an animal cell requires two cell cycles to build a fully functional centriole, which is then required to form an independent centrosome and a cilium (Figure 1). In the first cell cycle, the building of a centriole starts at S phase with the formation of a procentriole (Figure 1A and B). At its core, the procentriole harbors a central tubule that radiates nine spokes, which together resemble a cartwheel (Figure 1B). The cartwheel spokes are connected to nine triplet microtubules that form the centriole wall. In G2, M and G1 phases, the centriole elongates to ~ 500 nm and is referred to as an immature centriole. During this time, the immature centriole appears to be non-functional.

As the immature centriole proceeds through the second cell cycle, it starts to acquire characteristics of a mature centriole in a step-by-step manner. In S phase, the immature centriole serves as a platform for the formation of a procentriole (Figure 1F). In G2, the immature centriole (together with the procentriole attached to it) acquires large PCM, starts to nucleate astral microtubules, and in general, begins to function as an independent centrosome (Figure 1G). However, this centrosome is functionally distinct from the second preexisting mature centriole [1*,2]. In G1, the now mature centriole has acquired distal appendages and docks to the plasma membrane, where it templates the formation of the ciliary axoneme to initiate ciliogenesis (Figure 1I). Thus, a centriole requires two cell cycles from its initial formation to become fully mature.

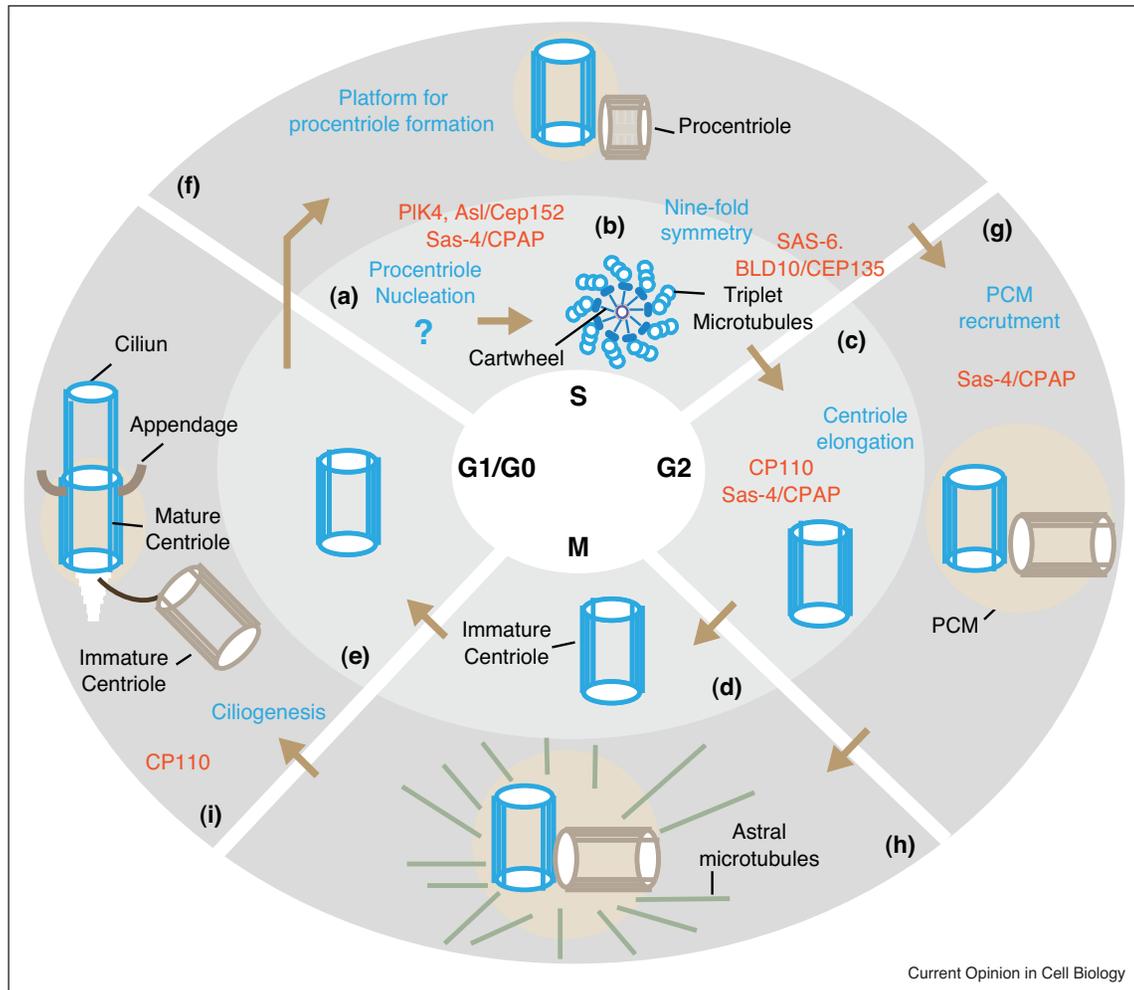
Over the past decade, many of the centriolar proteins involved in building the centriole have been identified and have begun to be characterized. Here, we describe insights into centriole biogenesis gained in the past few years, limiting our discussion to the proteins that function in nucleation of the procentriole, establishing the centriole's nine-fold symmetry, centriole elongation, and the recruitment of PCM.

Procentriole nucleation

A single procentriole forms at a right angle to the proximal segment of the preexisting centriole (Figure 1F). Despite being one of the most conserved aspects of centriole duplication, the mechanisms that govern this restricted pattern remain enigmatic. A major difficulty in addressing this question is that it is hard to monitor the early events that take place in procentriole formation (i.e. procentriole nucleation) in sufficient detail (Figure 1A). Previous studies in various model organisms have suggested that the PCM is essential for procentriole formation [3] and that *Caenorhabditis elegans* Zyg-1 (and its Human analog Plk4) [4,5], *Drosophila* asterless (and its mammalian ortholog Cep152) [6], and Sas-6 [4] are early players essential to this process.

While many cell cycle kinases regulate centriole duplication, Plk4/Zyg-1 is thought to be the key kinase responsible for the initiation of centriole duplication. Consistent with this idea, Plk4 is found in the PCM where the procentriole nucleates [7]; Plk4 binds to or phosphorylates several centriolar proteins including the procentriole nucleation protein Asl/Cep152 [7–9] and GCP6, a component of the γ -TuRC microtubule nucleating complex [10]. Plk4 also phosphorylates regulators of centriolar proteins including the E3-ubiquitin ligase FBXW5,

Figure 1



Building of a centriole. Depiction of the structural and molecular events taking place during the formation of one of the centrioles in a cell (depicted in blue) through two consecutive cell cycles. During the first cell cycle (light gray background, A–E), the basic structure of the centriole is formed. During second cell cycle (darker gray background, F–I), the immature centriole acquires functions in a step-by-step manner until it become fully mature and functional (H). A second centriole formed near the original centriole is depicted in light brown. Major events in the formation of the centriole are noted in blue. Key proteins are indicated in orange. Centrioles are depicted as they would appear from a cross section (B) and a side view (C–I).

which targets the cartwheel protein Sas-6 for degradation [11]. These are some of the events probably orchestrate the initiation of procentriole nucleation.

The PCM protein Asl and its ortholog Cep152 is also found where the procentriole nucleates and is critical early in centriole formation, leading to the idea that Asl/Cep152 nucleates procentriole formation [6]. Recently, a model was proposed where the interaction of Asl/Cep152 with Plk4 and Sas-4/CPAP provides a scaffold for procentriole formation [7,8]. However, a more recent study in *Drosophila* suggests that the interaction of Asl with Sas-4 is important for Asl localization in the PCM, and that this localization is not essential for initiating centriole formation [12]. How exactly the PCM proteins Plk4 and Asl/Cep152 coordinate the nucleation

of a single procentriole near to the preexisting centriole remains unclear. One possibility is that Plk4 activates a yet unidentified complex containing Asl/Cep152, which then triggers procentriole formation.

Centriole nine-fold symmetry

Centrioles display a conserved structural signature of nine-fold radial symmetry (Figure 1B). Since centrioles template ciliogenesis, the symmetry of the centriole is also translated to cilium. Based on earlier electron microscopy studies, it has long been evident that the first structure in the developing centriole that displays nine-fold symmetry is the cartwheel [13] (Figure 1B). Based on this observation, it is apparent that the cartwheel is a structural scaffold in establishing the centriole and, as a result, the nine-fold symmetry of the cilium. Several

candidate proteins including Sas-6, Bld10/Cep135, Poc1, and Sas-5/Ana-2/STIL were previously proposed to be cartwheel proteins, but only Sas-6 [14] and Bld10 [15] have so far been shown to be essential to organize the nine-fold symmetry of the centriole.

Recently, Sas-6 was shown to self-assemble into a central tubule-like structure, and analysis of the Sas-6 crystal structure suggests that Sas-6 polymers display the nine-fold symmetry found in the cartwheel central tubule [16^{••},17^{••},18]. Sas-6 interacts with Sas-5, a protein that is thought to be the ortholog of *Drosophila* Ana2 and mammalian STIL. Indeed Sas-5 [19], Ana-2 [20] and STIL [21,22] were reported to be essential for centriole formation. Strikingly, overexpression of *Drosophila* Sas-6 and Ana-2 resulted in the formation of large aggregates composed of cartwheel-like structures [23], arguing that Sas-5/Ana-2/STIL and Sas-6 are limiting factors in cartwheel formation. Still, it is not clear if Sas-6 and Sas-5/Ana-2/STIL are the only players in this process, as it is likely that other proteins participate in nucleating and capping the cartwheel.

Centriole elongation and size control

Centriole elongation takes place in at least 3 stages along centriole formation. First, the procentriole exists only for a brief period of time during S phase (Figure 1A and B), forming at approximately 200 nm in length. Second, the procentriole elongates through G2 to M phase until it reaches its final size ~500 nm in length (Figure 1C). Finally, the mature centriole further elongates to form the axoneme of the cilium (Figure 1I). The molecular players and mechanisms that determine the size control of a centriole have just recently started to emerge. These include CPAP/Sas-4, Bld10/Cep135, Poc1, CP110, Cep97, and Kinesin-13 homologues Kif24 and Klp10A. These proteins appear to play a role in multiple elongation stages, but this may be because it is difficult to dissect the stages of the elongation process independently.

Sas-4/CPAP has been implicated in centriole elongation by the observation that *Drosophila sas-4* mutants have short centrioles [24], as well as by over expression studies of Sas-4 in cell culture that produced elongated centrioles [25–28]. Interestingly, over expression of a CPAP mutant that cannot bind tubulin does not induce centriole elongation, and it was argued that this suggests that CPAP promotes centriole elongation by stabilizing centriolar microtubules [27]. However, there is evidence that CPAP binds tubulin dimers in a way that interferes with microtubule elongation [29,30], and that its tubulin binding capacity functions to regulate Sas-4/CPAP recruitment to the centrosome [31^{••}]. Regardless, it is probable that CPAP is only involved in determining the size of the procentriole or proximal end of mature centrioles, as Sas-4/CPAP normally localizes only to these locations [5,24].

Indeed, it was recently found that PLK2 phosphorylation is critical for the function of CPAP in procentriole formation and centriole elongation [32].

Like *Drosophila sas-4* mutants, *Drosophila bld10/cep135* and *poc1* mutants have short centrioles [24,33], and Poc1 over expression in cell culture was reported to induce centriole elongation [34]. However, unlike Sas-4, which is restricted to the proximal end of the centriole, Bld10/Cep135 and Poc1 can be found all along the centriole's length [24,33]. Therefore, it is possible that these proteins are involved in determining centriole size by stabilizing the centriole along its length.

CP110 localizes to distal centrioles and its depletion results in centriole elongation and the formation of a cilium, suggesting that CP110 blocks centriole elongation and prevents ciliogenesis [35]. CP110 interacts with multiple proteins such as Cep97, Cep290, as well as the Kinesin-13 homologs Kif24 and Klp10A. All four proteins are localized to the distal centriole, but they have differential roles in centriole formation and ciliogenesis. Cep97 recruits CP110 to centrosomes and, like CP110 depletion, its depletion result in centriole elongation and the formation of an aberrant cilium [35]. In mammalian cells, loss of Kif24 leads to the disappearance of CP110 from mother centrioles, resulting in defective cilium assembly. However, unlike CP110 and Cep97 loss, the absence of Kif24 does not promote the growth of abnormally long centrioles [36^{••}]. Similarly, in *Drosophila*, CP110 appears to cooperate with Klp10A in restricting centriole elongation [37]. CP110 also interacts with Cep290 and Rab8a, which are also essential for ciliogenesis, but their depletion does not result in the aberrant formation of centrioles or cilia [38]. Interestingly, CP110 forms at least two discrete complexes that appear to participate in distinct functions [38]. It is possible that CP110 and its interacting proteins function as a capping complex at the distal end of the centriole to block or allow centriole elongation based on cell cycle cues.

PCM formation

Traditionally, the PCM is thought to be a distinct structure surrounding the centriole that is involved in nucleating and organizing cytoplasmic microtubules (Figure 1G). However, recent studies also suggest an intimate involvement of the PCM in building the centriole [3,39] and common mechanisms for centriole and PCM formation [31^{••}]. In the past, several mechanisms were proposed to mediate PCM formation [40,41]. Recently, it was suggested that the centriolar and PCM protein Sas-4 plays a role in PCM recruitment [12,31^{••}]. Originally, Sas-4 was reported to be essential for both centriole and PCM recruitment in *Caenorhabditis elegans* [42,43]. However, upon reduction of Sas-4 levels to varying degrees, a correlation has been observed between centriole defects and the amount of PCM recruitment,

leading to the idea that PCM recruitment defects are a consequence of structurally compromised centrioles [42]. This idea was reinforced by the observation that in *Caenorhabditis elegans*, Sas-4 is a stable component of the centriole that is incorporated only during initial centriole formation [43].

However, studies in human cells and *Drosophila* show that Sas-4 and CPAP (one of the two human orthologs of Sas-4) have distinct characteristics, suggesting that they may have specific roles in PCM function. For example, Sas-4 and CPAP are not only found in the centriole's proximal region but can also be found in the PCM [12]. CPAP is dynamically exchanged throughout the cell cycle between the centrosome and cytosol [44], and centrosomal levels of Sas-4 *in vivo* change along the cell cycle [12]. CPAP levels are cell cycle-dependent and are at their highest in G2 when PCM recruitment takes place [25,27]. Finally, Sas-4 forms complexes with PCM proteins such as γ -tubulin [45], Asl/Cep152 [7,8], CNN/Cep215, and *Drosophila* Pericentrin-like-protein [12,46].

Direct evidence for the role of Sas-4 in PCM formation has come from studies of *sas-4* point mutations in *Drosophila*. In these studies, Sas-4 mutants are expressed in the background of a *sas-4* null mutant to avoid complications raised by the presence of wild type protein. This approach also allows the expression of Sas-4 via its own promoter, avoiding artifacts that result from Sas-4 overexpression. It was found that eliminating the conserved PN2-3 segment of Sas-4 leads to a reduction in PCM recruitment without blocking centriole duplication [12]. Furthermore, mutating the Sas-4-tubulin binding site resulted in an increase in PCM recruitment without effecting centriole number [31^{••}].

Additional evidence for the role of Sas-4 in PCM formation has come from biochemical studies of the interaction between Sas-4, tubulin dimers, PCM proteins, and whole centrosomes. It was found that Sas-4 scaffolds complexes of PCM proteins and can tether them to purified centrosomes that have been stripped of PCM [12]. This function is regulated by a guanine nucleotide that binds to the tubulin dimer attached to Sas-4 [31^{••}]. Tubulin-GDP favors binding to Sas-4 and promotes PCM complex formation while binding of tubulin to a GTP analog blocks this process. Similarly, the binding of tubulin-GDP to Sas-4 promotes Sas-4-PCM complex tethering to the centrosome while the tubulin-GTP analog blocks this tethering activity. These studies have led to a model in which tubulin dimers regulate Sas-4-mediated PCM recruitment to the centrosome [31^{••}].

Summary

Classically, the centrioles and their surrounding PCM have been thought to be structurally and functionally distinct entities. However, recent studies aiming to understand

how the centriole is built point to a more holistic point of view where centriole and PCM formation are interdependent. In addition, our initial simplistic understandings of centriole and centrosome building as linear processes, where centriole formation precedes PCM formation, may not necessarily be the case. Finally, a common way of thinking is that centriole proteins mediate centriole formation once they are recruited to the centriole where they play structural and regulatory functions. However, studies that are even more recent point to an alternative and equally important function for centriolar proteins in the PCM and the cytosol. A good example of this holistic model can be found in considering the important function of Sas-4, a protein that was initially thought to only be important for centriole formation [42,43] and has now been found to also have a function in the cytosol and PCM [12,31^{••}].

The complexity in how centriole proteins function, together with the small size of the centriole, the low abundance of centriolar proteins, and the speed in which procentriole formation takes place, are ongoing challenges in understanding how the centriole and centrosome are built. However, recent developments that employ a combination of technologies such as subdiffraction light microscopy, less invasive genetic approaches, and the development of biochemical approaches towards reconstituting centriole formation provide an exciting avenue by which the long lasting question of how the centriole is built can be addressed.

Conflict of interest

The authors have no conflict of interest to declare.

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