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Review

The centrosome duplication cycle in health and disease

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ABSTRACT

Centrioles function in the assembly of centrosomes and cilia. Structural and numerical centrosome aberrations have long been implicated in cancer, and more recent genetic evidence directly links centrosomal proteins to the etiology of ciliopathies, dwarfism and microcephaly. To better understand these disease connections, it will be important to elucidate the biogenesis of centrioles as well as the controls that govern centriole duplication during the cell cycle. Moreover, it remains to be fully understood how these organelles organize a variety of dynamic microtubule-based structures in response to different physiological conditions. In proliferating cells, centrosomes are crucial for the assembly of microtubule arrays, including mitotic spindles, whereas in quiescent cells centrioles function as basal bodies in the formation of ciliary axonemes. In this short review, we briefly introduce the key gene products required for centriole duplication. Then we discuss recent findings on the centriole duplication factor STIL that point to centrosome amplification as a potential root cause for primary microcephaly in humans. We also present recent data on the role of a disease-related centriole-associated protein complex, Cep164-TTBK2, in ciliogenesis.

1. Introduction

Centrosomes are the major microtubule organizing centers of animal cells [1–4]. Each centrosome usually comprises two centrioles embedded in a pericentriolar protein matrix (PCM). Centrioles are barrel-shaped structures that, in human cells, are made up of triplet microtubules. The older of the two centrioles, often referred to as the 'mature' centriole, carries distal and subdistal appendages, and the two centrioles can be distinguished by staining for marker proteins [5–8]. In most species, centriole biogenesis involves the early formation of a so-called cartwheel at the base of the nascent centriole [4]. One major evolutionarily conserved component of the cartwheel is the coiled-coil protein SAS-6 [9–11]. As demonstrated by beautiful structural studies, SAS-6 imparts the typical nine-fold symmetry to the centriole [12–16]. Importantly, centrioles function not only as important building blocks for centrosome assembly [17], but also as crucial organelles in ciliogenesis. In fact, in most quiescent cells the mature centriole gets anchored underneath the plasma membrane, where it triggers the formation of a single, axoneme-containing cilium [18]. This so-called primary cilium is non-motile but functions as an antenna-like receiver for chemical and mechanical signals [19]. The PCM was long considered an amorphous structure, but recent super-resolution microscopy has revealed a considerable degree of organization amongst various coiled-coil proteins [20–23]. One major function of the PCM is to recruit γ-tubulin ring complexes that are in turn required for microtubule nucleation [24]. In addition, it is widely held that centrosomal PCM recruits various signaling components, thereby acting as a solid-state platform to enhance and integrate intracellular signal transduction [25–27].

Early studies in the nematode *Caenorhabditis elegans* had identified five genes as being critical for centriole biogenesis: *ZYG-1, SPD-2, SAS-4, SAS-5, SAS-6*. Furthermore, the corresponding proteins were shown to act sequentially, with Spd-2 being important for the recruitment of the Zyg-1 kinase, followed by the association of SAS-5/SAS-6 and the SAS-4-mediated assembly of microtubules [28]. Although it was initially difficult to identify homologs of these proteins in non-nematode species, subsequent studies have demonstrated the existence of structural or functional counterparts also in other organisms, both invertebrates and vertebrates (Table 1). In particular, a distant member of the Polo kinase family, Plk4 (Polo-like kinase 4), was discovered as a key regulator of centriole biogenesis in both human cells and *Drosophila* [29–31]. Depletion of this kinase from proliferating cells causes loss of centrioles, and, conversely, overexpression of Plk4 triggers the near-simultaneous formation of multiple daughter centrioles. In most cells analyzed to date, Plk4 is a very low abundance protein, due to its propensity to dimerize and trans-autophosphorylate, which then triggers the recruitment of the ubiquitin ligase β-TrCP, followed by proteasome-mediated degradation [32–36]. In addition to the evolutionarily conserved centriole duplication factors first

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identified in *C. elegans*, additional gene products were found to be important for centriole biogenesis in *Drosophila* [37,38] and/or human cells [31,39]. Thus, complementing the evolutionarily conserved core mechanism for centriole duplication, a number of species-specific extensions and variations have been observed. Conversely, some of the core factors originally identified in *C. elegans* are not essential in all species. For example, no Spd-2 homolog is present in the planarian *Schmidtea mediterranea* and the parasite flatworm *Schistosoma mansoni*, even though these species form centrioles [40]. Thus, Spd-2 may generally be more important for PCM assembly than centriole formation *per se*. In support of this view, the *Drosophila* homolog of Spd-2 is clearly important for PCM recruitment but dispensable for centriole duplication [41,42]. Also, whilst Spd-2 recruits the Zyg-1 kinase in *C. elegans*, a structurally distinct protein, Asterless, is critical for Plk4 recruitment in *Drosophila* [43]. In human cells, the recruitment of Plk4 to centrioles is accomplished through joint efforts of the Spd-2 and Asterless homologs, the proteins Cep192 and Cep152, respectively [44,45]. This readily explains why both proteins are required, albeit to different degrees, for the maintenance of correct centriole numbers in human cells. As our understanding of the molecular details of centriole biogenesis progresses, additional species- and cell type-specific differences will undoubtedly be uncovered.

Our current understanding of the mechanisms underlying centriole biogenesis in proliferating cells, as well as in multiciliated epithelial cells, has been described in excellent recent reviews [4,46]. Likewise, authoritative reviews covering the importance of centrioles for ciliogenesis and the impact of ciliary dysfunction on human health are available [2,18,19,47,48]. In the following, we will briefly discuss the implications of centrosome aberrations for cancer and then focus on two recent studies from our laboratory that relate to microcephaly and ciliopathies/spinocerebellar ataxia, respectively.

2. Centrosome aberrations in cancer

Several decades prior to the discovery of oncogenes and tumor suppressor genes, Theodor Boveri (1862–1915) proposed that tumors develop as a consequence of chromosomal imbalances, and, furthermore, suggested that centrosome aberrations constitute one prominent root-cause of such imbalances [49]. While the fundamental importance of mutations and genetic imbalances for tumorigenesis is well established, the impact of centrosome aberrations on tumor development continues to be a subject of debate. On the one hand, many human tumors carry extensive centrosome aberrations, and there is a strong correlation between the extent of these aberrations and the clinical aggressiveness of tumors [50–52]. On the other hand, direct genetic evidence to support the involvement of any particular centrosomal gene product in carcinogenesis remains scarce [53]. Most tumors carry both numerical and structural centrosome aberrations and it is difficult, therefore, to disentangle the physiological consequences of these aberrations. However, from a conceptual perspective it is interesting to consider the two types of aberrations separately. Numerical aberrations, most commonly excessive numbers of centrioles, have been studied extensively, both with regard to their origin and their consequences. Prominent causes for 'supernumerary' centrioles are overduplication or division failure. Overduplication may reflect loss of either cell cycle control or copy number control [54], whereas division failure results in a centriole amplification that is accompanied by an increase in ploidy [55]. In short-term cell culture experiments, the two mechanisms can readily be distinguished by staining of extra centrioles with antibodies against centriolar appendage proteins [56]. The consequences of centriole amplification have also been examined in considerable mechanistic detail. As already noticed by Boveri, excessive numbers of centrioles frequently results in the formation of multipolar spindles [49]. However, live cell imaging has revealed that multipolar spindles do not inevitably lead to multipolar divisions, and when they do, the resulting progeny is rarely (if ever) viable [57–59]. Instead, evidence has been reported for occasional inactivation of supernumerary centrosomes [58,60,61]. In addition, many cells use centrosome-independent spindle assembly mechanisms to cluster extra centrosomes, so that supernumerary centrosomes coalesce to allow the formation of bipolar spindles [60,62–64]. These clustering mechanisms are important not only to allow the survival of cells with multiple centrosomes, but they also constitute a common cause of chromosome segregation errors [57,59]. Thus, it remains attractive to postulate that numerical centriole aberrations constitute an important source of chromosomal instability in tumor cells.

Much less attention has so far been focused on structural centrosome aberrations. This is perhaps unfortunate, as, *a priori*, structural centrosome aberrations may well have a profound impact on cytoskeletal organization, and hence on cell shape, polarity and motility. Structural centrosome aberrations commonly reflect deregulated expression and/or posttranslational modification (notably phosphorylation) of centrosomal proteins [52,65]. Excess centrosomal protein often associates primarily with the resident centrosome; in addition, formation of centrosome-related bodies (CRBs) – extra-centrosomal assemblies devoid of centrioles – is commonly observed [66,67]. Depending on the functional properties of the centrosomal proteins that are deregulated in any particular tumor cell, notably their ability to interact with γ-tubulin ring complexes, intracellular microtubule nucleation is expected to be either enhanced or suppressed, with potentially profound consequences for cell shape, polarity and motility [66]. In turn, these parameters have the potential to affect the clinical behavior of tumor cells, including their propensity to metastasize.

Another area that undoubtedly warrants additional exploration concerns the relationship between ciliogenesis and cancer. Aberrations in centriole numbers and/or centrosome structure are expected to influence the number, timing of formation and disassembly, disposition and function of cilia [68,69]. Thus centriolar

Table 1
Major centriole duplication factors.

Caenorhabditis elegans	*Drosophila melanogaster*	*Homo sapiens*
(A) Core components		
Spd-2	DSpd-2*	Cep192+
Zyg-1	Plk4 (Sak)	Plk4 (Sak)
SAS-5	Ana-2	STIL
SAS-6	DSAS-6	HsSAS-6
SAS-4	DSAS-4	CPAP
(B) Additional components		
	DBld10*	Cep135
	DCP110*	CP110
	Centrobin*	Centrobin
	Asterless	Cep152
	Poc1	hPoc1
		hPoc5
		Spice
		Cep120
		Cep63
		Cep97
		Cep76
		Centrins+
	Ana1	

This table lists major proteins implicated in centriole duplication in the indicated species, but we emphasize that the list is not meant to be comprehensive. Also, we apologize for incomplete referencing, caused by editorial restrictions on citations. Proteins marked by * do not necessarily play essential duplication roles in all species; for example, DSpd-2, DCP110, DBld10 and Centrobin are not required for duplication in *Drosophila* [8,41,111–113]. In other cases – proteins marked by + – controversial data have been reported [31,114–117].

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