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Anatomy, Biogenesis, and Role in Cell Biology of Centrioles

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Abstract

Centrioles are essential cellular organelles that play a key role in cell division, cytoskeletal organization, and microtubule dynamics. Their unique structure and ability to self-replicate make centrioles indispensable for the regulation of cellular processes. This article focuses on the anatomy of centrioles, their biogenesis, and their role in cell biology.

The first part of the study describes the structural features of centrioles, including the ninefold symmetry that forms the foundation of their morphology. Special attention is given to centriole biogenesis, covering processes such as the initiation of assembly, the establishment of ninefold symmetry, microtubule assembly, and elongation. Mechanisms of temporal regulation, length control, and the formation of the distal end are also discussed.

Additionally, the article examines centriole maturation processes and their functional significance in the context of the cell cycle, cell polarity, and intracellular transport. The presented data are based on a review of contemporary studies, including structural models and biochemical mechanisms.

This work highlights the importance of centrioles for understanding fundamental cellular biology processes and provides a foundation for further research into their roles in health and disease.

Keywords: centrioles, biogenesis, microtubules, cell cycle, cell polarity, maturation

Introduction

Centrioles are fundamental organelles that play a critical role in maintaining cellular polarity and regulating cellular signaling. Their structural and functional importance has been recognized for several decades; however, more in-depth studies in recent years have revealed that centrioles also hold significant importance in the differentiation process and in the progression of cell progeny toward the

Hayflick limit. Disruptions in their function can lead to a wide range of diseases, including cancerous tumors, and can also accelerate tissue aging.

Centrioles play an indispensable role in the differentiation process of cells. Embryos that fail to sustain centriole replication cease development at a very early stage (Stevens, 2007). These organelles are also involved in the formation of cilia, which, in turn, are responsible for perceiving external signals such as molecules that regulate cellular polarity and differentiation. Consequently, any alterations in the structure of centrioles can impact the cell's ability to sense external signals, leading to disruptions in the normal process of differentiation.

Cilia, which are organized by centrioles, are pivotal in cellular signaling. One of their key functions is regulating a range of molecules that affect cellular differentiation and tissue development (Schatten et al., 2011). For instance, cilia are involved in regulating signaling pathways such as Wnt and Hedgehog, which are crucial for cell differentiation in various tissues of the body. This discovery is supported by numerous scientific works, including studies such as those by (Pedersen et al., 2012) and others, which underscore the relationship between the function of centrioles and cellular differentiation processes.

Centrioles also play a critically important role in what is known as replicative cellular aging. During this process, there is selective accumulation of older (and, according to the second law of thermodynamics, more defective) centrioles (Hayflick, 2021), which impair their function during mitosis and other cellular processes. When older centrioles/centrosomes cannot efficiently participate in cell division, it leads to cellular malfunctions, reduced proliferative capacity, and accelerated tissue aging (Schatten, H., & Sun, Q. Y., 2009). Recent studies show that organismal aging is linked to the selective accumulation of defective centrioles and also to the selective segregation of chromosomes in stem cells, which can reduce their ability to differentiate and repair damaged tissues (Charville, G. W., & Rando, T. A., 2011).

It is known that replicative cellular aging is accompanied by the inheritance of new centrioles during asymmetric divisions, while the maintenance of replicative age is linked to the inheritance of old centrioles (Reina, J., & Gonzalez, C., 2014). Old centrioles can cause disorganization of the mitotic spindle and other problems in the cell cycle. This is confirmed by research showing that a decrease in the regeneration rate is associated with a decline in stem cell division rate, meaning the accumulation of old (more defective) centrioles leads to disruptions in normal cell division and accelerates the aging process (Lavasani et al., 2012). Such defects in centrioles can have a significant impact on normal cell function, as also demonstrated in studies investigating the effects of centriole dysfunction on stem cells (Wu et al., 2020).

Stem cells possess the unique ability to undergo asymmetric divisions, leading to the differentiation of one daughter cell and the self-renewal of the stem cell pool by the second daughter cell, which makes them crucial objects for research in tissue regeneration and aging. However, the efficacy of stem cells also depends on the condition of their centrioles. Disruptions in centriole function can result in the loss of stem cells' ability to undergo normal

differentiation and regeneration. This discovery is supported by several studies (Cheng et al., 2008) that emphasize the importance of maintaining normal centriole function for stem cell operation.

Despite the presence of centrioles at the poles of the mitotic spindle, centrioles are often not essential for mitosis, even in species that typically possess them (Debec et al., 2010). Cell cycle progression and cytokinesis can be defective in the absence of centrioles (Mikule et al., 2007), though this may be related to indirect effects. For example, the G1 arrest in mammalian cells after centriole removal is the result of increased sensitivity to stress, rather than an absolute need for centrioles during cell cycle progression (Uetake et al., 2007).

Although centrioles are not required for spindle assembly, they are crucial for spindle positioning. When centrioles are experimentally removed, spindles drift within the cell (Hinchcliffe et al., 2001). In vertebrates, centriole positioning appears to respond to signals from planar cell polarity (Montcouquiol M. & Kelley MW., 2003), which is consistent with the localization of some planar cell polarity proteins in centrioles (Park et al., 2006). The proper positioning of the spindle by centrioles is believed to be essential for correct tissue development, as defects in spindle orientation caused by mutations in genes related to centrioles can lead to nephronophthisis, a cystic kidney disease associated with abnormally wide ducts (Simons M, & Walz G., 2006).

An interesting possibility is that the pathway for centriolar positioning may be specific to the mother centriole, which is the oldest of the two centrioles in the G1 centrosome and the only fully mature centriole (i.e., capable of acting as a basal body) in a typical vertebrate cell. This is suggested by the analysis of dividing stem cells in the male germline of Drosophila, where the mitotic spindle is always oriented so that the old centriole is anchored on the side of the cell adjacent to the stem cell niche (Yamashita et al., 2007). A similar shift in the positioning of the mother centriole is observed in radial glial progenitor cells in mice (Wang et al., 2009). Notably, after depletion of ninein, a protein necessary for the stable attachment of microtubules to mother centrioles, this asymmetry in the segregation of mother centrioles is lost, ultimately leading to premature exhaustion of the stem cell pool (Mogensen et al., 2000). In Chlamydomonas mutants, where the connection between the mother and daughter centrioles is disrupted, the mother centrioles move to the correct position, but the daughter centrioles do not, suggesting that the mother centriole uniquely responds to the positioning pathway (Feldman et al., 2007).

One of the key aspects attracting the attention of researchers is the selective inheritance of old centrioles in stem cells during asymmetric divisions. This leads to the deterioration of cell division quality and a reduction in the ability of stem cells to maintain normal tissue regeneration. Such disruptions may be associated with chronic inflammation and decreased stem cell activity, resulting in age-related diseases and a general decline in organismal health. The phenomenon of inheriting new centrioles by the differentiating daughter cell, which is progressing toward the Hayflick limit, remains an unexplained phenomenon.

Studying the molecular mechanisms by which centrioles regulate cell differentiation and replicative aging is key to understanding the aging processes of the organism and developing new therapeutic strategies. Disruptions in centriole function can lead to the development of a range of diseases, including cancer, and can also accelerate the aging process of the organism. For example, centriole defects are linked to tumor development as they affect the cell cycle and can lead to uncontrolled cell division (Qi, F., & Zhou, J., 2021).

Moreover, centrioles can be targeted for therapy in diseases related to dysfunction. For instance, in cases of cancer or other diseases involving the impairment of centriole function, drugs could be developed that restore their function, thereby slowing disease progression and promoting the restoration of normal cell division. It is likely that centrioles will also be a primary target in the therapeutic approach to aging-related diseases.

Centrioles/centrosomes play a pivotal role in cellular differentiation and organismal aging—essentially in the vitality of stem cells. Their function has a profound impact on tissue regeneration and the maintenance of cellular homeostasis. Disruptions in centriole function can lead to various diseases, including cancer, and accelerate the aging process of the organism. Therefore, further research into the role of centrioles in these processes may lead to new therapeutic strategies for treating age-related diseases, cancer, tissue and organ regeneration, and organism rejuvenation.

Anatomy of Centrioles

The centriole represents a magnificent molecular structure, several gigadaltons in size, and is one of the largest organelles in eukaryotic cells, with its atomic structure still remaining elusive (Paintrand et al., 1992). However, numerous studies employing electron microscopy, cryotomography, and super-resolution techniques have allowed for the creation of a comprehensive understanding of its architecture, including its distinct subregions. These investigations expand our knowledge, providing additional insights into cellular and structural biology.

Centrioles are among the most distinctive and remarkable cellular organelles due to their beautiful, tenfold symmetrical arrangement of microtubules. Although significant progress has been made in enhancing our understanding of centriole architecture, technical limitations continue to constrain the ability to observe the structural details that characterize it. Moreover, as our knowledge of centriole structure advances, it becomes increasingly apparent that there is no single, uniform structure; rather, each species exhibits unique differences. One of the most striking distinctions is that microscopy reveals variations between canonical centrioles, which unite several species, such as humans, Chlamydomonas, Paramecium, Naegleria, Trichonympha, Teranympha, and the centrioles of Ecdysozoa, including nematodes and arthropods. The latter possess centrioles that are approximately 100 nm in length, composed of single or paired microtubules, whereas canonical centrioles measure around 450 nm in length and are composed of triplet microtubules. With the improvement in resolution of imaging methods, architectural similarities between

the so-called canonical centriole have been challenged, revealing anatomical differences between species that were previously invisible (Klena et al., 2020).

A canonical centriole is characterized by a ninefold symmetric organization of microtubules composed of triplets. This formation resembles a polarized cylinder or barrel-shaped structure, approximately 450 nm in length and 250 nm in external diameter, containing various substructures along its axis from the proximal to distal ends. These substructures define three primary regions of the centriole: the proximal, central, and distal regions. The proximal region contains the A-C linkage, which accounts for about 40% of the centriole, the cartwheel structure—important for centriole assembly—as well as additional elements such as the head and base of the triplets. The central core is defined by an internal scaffold that lines the centriole cavity and maintains connections between adjacent microtubules (Le Guennec et al., 2020). At the distal end, two groups of appendages emerge from the outer side of the microtubule wall, forming a radial ninefold arrangement through fibrous connections with each microtubule triplet, which participates in fusing with the plasma membrane (Bowler et al., 2019). Another group of appendages, referred to as subdistal appendages, forms conical structures that do not always follow the ninefold symmetry and are located around the centriole.

The microtubules of triplets consist of a complete A-microtubule, on which incomplete B- and C-microtubules are formed from the walls of the A-microtubule and B-microtubule, respectively. It is worth noting that in the human centrosome, triplet microtubules become doublets (only A- and B-microtubules) approximately halfway up the centriole, but the boundaries are rather variable. Furthermore, triplet/doublet microtubules are not perfectly straight, with their position varying from the proximal to the distal regions. From the proximal side, the triplet microtubules form an angle of approximately 120° to the center of the centriole, which decreases to 100° at one-third of the centriole's height, and they exhibit a counterclockwise orientation, which is one of the chiral characteristics of the centriole (Uzbekov, R., & Prigent, C., 2007). Additionally, in the percentage of Chlamydomonas centrioles, a diaphragm-like movement of the triplet microtubules is observed at the proximal end, possibly enabling the centriole to alter its configuration during the assembly of various structural elements.

The proximal region of the centriole is composed of several substructures. One of the earliest likely identified structures was the cartwheel (Guichard et al., 2018), which possesses the characteristic ninefold organization within the cavity of the proximal region. On average, the length of the cartwheel is around 100 nm, consisting of an internal tube with a diameter of about 20 nm, known as the central hub, from which nine spokes radiate outward to the microtubule wall. Studies in the green alga Chlamydomonas have demonstrated that the main component of the cartwheel is the protein SAS-6 (van Breugel et al., 2011). SAS-6 proteins have a globular N-terminal domain, followed by a helical region and an unstructured C-terminal segment. Biochemical and crystallographic studies proposed a model in which nine homodimers of SAS-6 proteins form a ring via their N-terminal domains (Kitagawa et

al., 2011), and the arrangement of the rings leads to the formation of the cartwheel (Guichard et al., 2017). Cryo-electron tomography studies on the exceptionally long cartwheel of Trichonympha confirmed that the central hub consists of rings but also revealed densities in the middle of the central hub, termed the internal densities of the cartwheel (CID), whose molecular identity remains unknown. Studies with higher resolution in an evolutionarily diverse group of species have shown that the central hub exhibits periodicity of about 4 nm and confirmed the ubiquitous presence of CID, which also exists in a fibrous form (fCID) in Teranympha. Interestingly, although the overall organization of the central hub appears similar across species, the arrangement of the spokes differs somewhat.

Averaging the tomograms in Paramecium and Chlamydomonas demonstrated that the three pairs of cartwheel rings contain six outgoing spokes, likely consisting of SAS-6 helices, which gradually merge into a single bundle separated by 25 nm, forming one structural unit of the cartwheel. In contrast, a similar analysis in Trichonympha and Teranympha showed that the spokes consist of two pairs of cartwheel rings containing four outgoing spokes, which merge into a single bundle separated by 17 nm. Notably, along the spokes in Chlamydomonas, two densities were identified, called D1 and D2. The D2 density, located approximately 47 nm from the central hub, connects the end of the spokes to a structure called the pinhead. The D2 density represents a rod that connects the ends of the cartwheel spokes along the axis, and this connection is also present below the wall of the microtubules.

The pinhead extends from the proximal end of the microtubule wall and terminates at or within a few nanometers of the end of the cartwheel. The pinhead, presumably composed of two microtubule-associated proteins, Cep135 (Kraatz et al., 2016) and CPAP (Sharma et al., 2016), is connected to the A-microtubule of each microtubule triplet. The pinhead contacts another proximal structure—the base of the triplet. The base of the triplet is about 35 nm in length and runs parallel to the microtubules of the triplets until it reaches the A-C linkage. The A-C linkage, composed of proteins whose exact identity is not yet known, connects the A-microtubule of one microtubule triplet to the C-tubule of another and spans 270 nm of the centriole in mammalian cells.

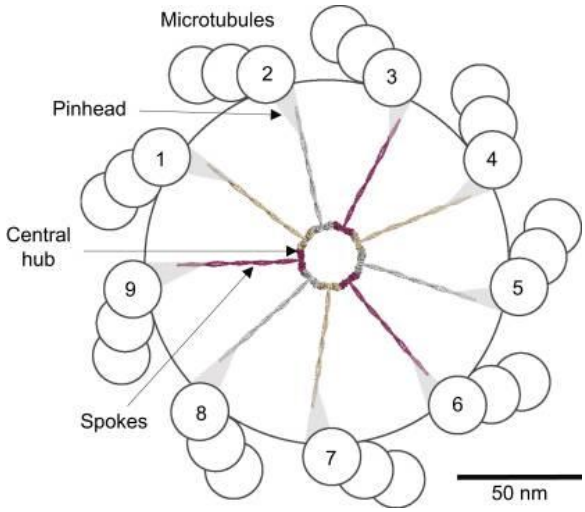
The central core, located immediately behind the proximal region and extending to the distal end of the triplet microtubules, includes the internal scaffold. This structure was initially described as a "ring of connections," "peripheral fibers," "legs of A-tubules," and later as "Y-shaped" or "L-shaped," but it was not conclusively confirmed whether these elements belong to a single structure. These descriptions suggested a similar arrangement along the length of the centriole, covering about two-thirds of its distal region.

Cryo-electron tomography has provided the opportunity to study this structure in great detail. In cells of Chlamydomonas and Paramecium, the reconstruction of the central region revealed a spiral internal scaffold covering the wall of the microtubules in the central area. Interestingly, like the A-C linkage, the structure of the internal scaffold varies between species, likely due to molecular

differences. However, the overall spiral structure linking the A-B microtubules through a rod remains conserved across species.

Comparing early observations with older technologies to cryo-electron tomography results suggests that the internal scaffold represents a highly conserved structure related to the internal connection of A-B microtubules.

Figure 1. Structural Model of the Cartwheel (Kitagawa et al., 2011)



Cryo-electron tomography has provided a detailed opportunity to explore the structure of the cartwheel. In the cells of Chlamydomonas and Paramecium, the reconstruction of the central region revealed a helical internal scaffold surrounding the wall of microtubules at the core. Interestingly, similar to the A-C link, the structure of the internal scaffold exhibits variability between species, likely due to molecular differences.

However, the overall helical configuration that connects the A-B microtubules via the central rod remains conserved across species. Comparing the initial observations made with older techniques to the results obtained through cryo-electron tomography, it can be inferred that the internal scaffold is a highly conserved structure involved in the internal connection of the A-B microtubules.

Using ultra-structural expansion microscopy (U-ExM), it has been shown that five proteins—FAM161A, POC1B, POC5, Centrin-2, and WDR90—localize in a manner consistent with the positioning of the internal scaffold in human centrioles (Steib et al., 2020). In addition to its central localization, Centrin-2 exhibits a unique “bottle-neck” signal at the distal end of the centriole, reminiscent of previously described immunolocalization in Chlamydomonas cells (Geimer, S., & Melkonian, M., 2005).

Given that the internal scaffold is a massive and intricate structure, it is likely that additional proteins, beyond those already described, are involved in the central core. Furthermore, fibers can be observed in the central lumen of centrioles in both Chlamydomonas and mammals, which may transiently interact with the internal scaffold.

Thus, the centriole represents a large supramolecular structure, divided into three primary regions: proximal, core, and distal, each containing specific structural components. The complex is composed of more than 100 distinct proteins (Bauer et al., 2016), many of which are present in multiple copies, with α-β tubulins being the most abundant. The estimated mass of the centriole is approximately 1600 MDa, making it roughly 10 times larger than nuclear pores (Lin, D. H., & Hoelz, A., 2019) and 400 times larger than eukaryotic ribosomes (Ben-Shem et al., 2010). Due to

its molecular mass and size, cryo-electron tomography remains the primary technique for studying the architecture of the centriole, with a resolution of 15−30 Å. However, this method does not permit atomic-level resolution. To achieve such a resolution, it will be necessary to either isolate substructures of the centriole or reconstruct them in vitro to use cryo-electron microscopy and single-particle analysis. This approach has already yielded impressive results in studying ciliary microtubules, where internal microtubule-associated proteins (MIPs) were localized and identified (Ma et al., 2019). These proteins, which are also present in centriole triplets, likely stabilize the microtubule blades and provide spatial orientation between protofilaments.

Centriolar Biogenesis

Initiation of Assembly

The initiation of centriole duplication is tightly regulated to ensure proper control of centriole numbers (Bettencourt-Dias M., & Glover DM., 2007). In mammalian cells, one procentriolar structure begins to form perpendicularly to the wall of each parental centriole around the G1/S transition. Once the assembly of two new procentrioles has been initiated, further duplication is suppressed until the cell progresses through mitosis (Wong C., & Stearns T., 2003). The release of the close association between procentrioles and parental centrioles, termed separation, occurs in late mitosis in animal cells. This separation involves protease separase and Polo-like kinase 1 (Plk1) and is a prerequisite for the subsequent round of centriole duplication (Tsou et al., 2009). When centrioles are absent, new centrioles can form de novo, suggesting that the role of existing centrioles is not to template procentrioles as previously thought, but rather to shift the spatial location where procentrioles self-organize (Peel et al., 2007). When too many centrioles are present, cells can suppress the synthesis of new centrioles—a mechanism that allows for the correction of centriole number errors (Marshall, 2007).

A key regulator of centriole assembly is a kinase known as Polo-like kinase 4 (Plk4) or SAK in Drosophila. Inhibition of Plk4 prevents centriole duplication in both human cells and Drosophila (Habedanck et al., 2005). In contrast, overexpression of Plk4 and SAK can lead to the assembly of additional centrioles (Bettencourt-Dias et al., 2005). Interestingly, orthologs of Plk4 are not found outside of the Fungi/Metazoa group, indicating that centriole duplication is initiated through different mechanisms in other eukaryotes, possibly involving other Polo-like kinases (Carvalho-Santos et al., 2010).

Furthermore, the Plk4 ortholog is absent in Caenorhabditis elegans, where centriole duplication is initiated by the non-orthologous kinase ZYG-1 (O'Connell et al., 2001). ZYG-1 controls the recruitment of the structural component SAS-6, which serves as a substrate for ZYG-1 (Kitagawa et al., 2009). The recruitment of ZYG-1 itself requires SPD-2, a component of the PCM necessary for centriole duplication in C. elegans embryos (Kemp et al., 2004). Interestingly, SPD-2 family members are found only in the genomes of Unikonts, a branch of the eukaryotic tree that includes Fungi/Metazoa, as well as Amoebozoa, such as the model organism Dictyostelium discoideum (Schulz et al., 2009). Studies of

SPD-2 orthologs in humans and flies suggest that the primary function of SPD-2 and related proteins is in recruiting the PCM around centrioles (Zhu et al., 2008). The human SPD-2 ortholog, Cep192, is essential for centriole duplication, while its Drosophila ortholog appears not to be required for this process (Dix CI, & Raff JW., 2007).

However, Cep192 may influence centriole duplication indirectly by recruiting PCM and microtubule-nucleating factors, as PCM is known to play a role in centriole duplication (Loncarek et al., 2008). In contrast, Drosophila Asterless (Asl) and related proteins are components of the PCM that are specifically required for centriole assembly (Blachon et al., 2008).

In Drosophila, Asl localizes near the wall of the centriole in proliferating cells and in testes, and it is required for centriole duplication in both contexts (Varmark et al., 2007). Cep152, the vertebrate ortholog of Asl, is a component of the PCM in proliferating human cells. Interestingly, Cep152 in zebrafish has also been shown to be necessary for the assembly of basal bodies in multiciliated cells. In these cells, hundreds of basal bodies are assembled simultaneously around structures of unknown composition called deuterosomes as the cells undergo differentiation. A defect found in zebrafish with a Cep152 deficiency supports the idea that the initiation of basal body assembly in multiciliated cells is at least partially based on the same mechanisms as centriole duplication in proliferating cells.

Establishment of Ninefold Symmetry

The initiation of centriole assembly and the establishment of ninefold symmetry require a structure known as the cartwheel. The cartwheel is located at the proximal end of basal bodies across a wide range of species. In vertebrate centrosomes, the cartwheel structure is present at the base of procentrioles but is no longer observed in daughter and mother centrioles (Guichard et al., 2010). The cartwheel structure is best described in unicellular organisms. It consists of a central hub, from which nine evenly spaced spokes radiate, each ending in a knob-like structure to which triplet microtubules attach.

In Chlamydomonas, the cartwheel assembles before microtubules are added to the tips of each spoke (Cavalier-Smith, 1974). Two components of the cartwheel structure have been described in this species. CrSAS-6/Bld12p, a homolog of C. elegans SAS-6, has been proposed as part of the internal spokes or hub of the cartwheel (Nakazawa et al., 2007). Bld10p, also a member of a conserved protein family, has been shown to form the outer spoke and the cartwheel-spoke tip structure (Hiraki et al., 2007). Recent studies of mutants with defects in these genes have provided important insights into how the cartwheel assembles and establishes the radial symmetry of centrioles.

When Chlamydomonas BLD12 is deleted, most cells lack the proper centriolar structure, but about 20% of cells form defective centrioles, which sometimes contain an abnormal number of triplets—7, 8, or 10—or lack triplets entirely. Strikingly, mutant centrioles in bld12 cells lack the

cartwheel-spoke (Nakazawa et al., 2007). Similarly, depletion of SAS-6 by RNA interference (RNAi) in Paramecium leads to the formation of centrioles with an altered number of triplets, which retain the cartwheel spokes but lack the central hub (Jerka-Dziadosz et al., 2010).

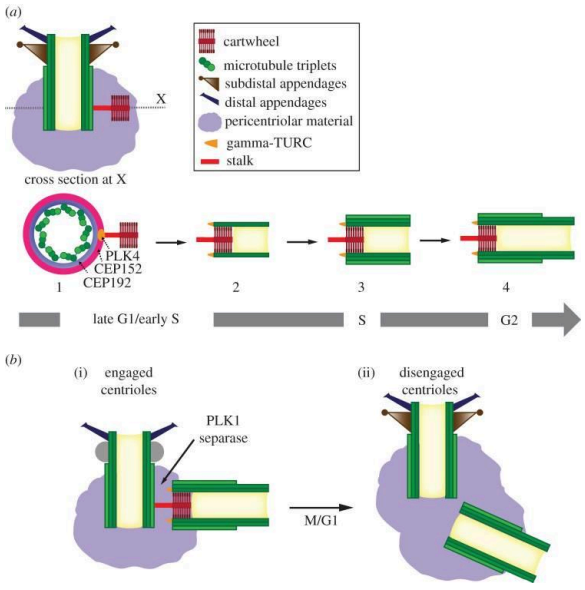
It has also been found that the null mutant SAS-6 in Drosophila exhibits a significant reduction in the number of centrioles and forms centrioles with structural defects, such as missing triplets (Rodrigues-Martins et al., 2007). As in Chlamydomonas, the orthologs of SAS-6 in Paramecium and Drosophila localize to the central hub of the cartwheel (Gopalakrishnan et al., 2010).

The collective findings substantiate the hypothesis that the SAS-6 protein family plays an essential role in assembling the central hub, with the hub itself being crucial for establishing the ninefold symmetry of centrioles.

The assembly of centrioles initiates towards the end of the G1 phase or at the beginning of the S phase with the formation of the cartwheel structure. This process is reliant on the HsSAS-6 protein for the central hub and Cep135 (the ortholog of Bld10p) for the spokes and/or cartwheel-spoke tip. CPAP (the ortholog of SAS-4) triggers the γ-tubulin-dependent initiation of the A-tubules and their attachment to the cartwheel-spoke tip, likely participating in recruiting the γ-tubulin ring complex (γ-TuRC) at the proximal end of the cartwheel.

Each A-tubule originates from γ-TuRC and grows unidirectionally from the proximal to the distal end. The A-tubule remains capped by γ-TuRC throughout the assembly process but is lost from both daughter and mother centrioles. At the distal end of the procentrioles, a cap-like structure forms, containing CP110 and Cep97. This cap is crucial for regulating the growth of the microtubules of the procentrioles and likely also plays a role in stabilizing the nascent procentriole. The B- and C-tubules are formed through a mechanism independent of γ-TuRC and grow bidirectionally until they reach the length of the A-tubule. The microtubule triplets are stabilized by ε- and δ-tubulin, marking the commencement of centriole elongation. During the S phase, the procentrioles elongate to approximately 70% of their final length. This process is dependent on hPOC5 and may also involve hPOC1.

Figure 2. Structure of the centriole and its biogenesis (Fırat-Karalar et al., 2014)



The elongation of the procentrioles continues after the transition to the G2 phase. At this stage, centriole length is regulated by two mechanisms: (1) the balance between the activity of CPAP, which

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promotes the incorporation of α/β-tubulin at the distal end, and the cap structure containing CP110 and Cep97; and (2) a mechanism involving Ofd1.

Following mitosis, procentrioles mature into daughter centrioles. At this stage, inclined discs, surrounded by electron-dense material, are observed at the distal end of the centriole. Markers such as centrin and hPOC5 accumulate in the distal lumen as the cell cycle progresses, which likely reflects the gradual maturation of the centriole. HsSAS-6 is no longer associated with the proximal portion of the daughter centrioles, which may correlate with the disassembly of the central hub of the cartwheel. In contrast, the spokes may be partially preserved, as Cep135 remains associated with both the mother and daughter centrioles.

After the second mitosis, centriole maturation is completed when distal and subdistal appendages are assembled. The formation of both appendage types depends on ODF2, a maturation-specific marker recruited to the distal end of the daughter centrioles during the previous G2 phase. The assembly of distal appendages also depends on Ofd1 and possibly the Cep164 component of the distal appendage.

HsSAS-6, the human homologue of SAS-6, is also required for the early stages of centriole assembly, but unlike its homologs in other species, which remain associated with mature centrioles, it is no longer found bound to daughter and mother centrioles (Kleylein-Sohn et al., 2007). The loss of HsSAS-6 from procentrioles correlates with its proteasomal degradation at the end of mitosis and likely also with the disassembly of the cartwheel structure, which occurs when procentrioles mature into daughter centrioles.

Interestingly, SAS-6 staining persists at the proximal end of the basal bodies in ciliated rat tracheal cells, suggesting that the cartwheel may not disassemble in this case. Interestingly, SAS-6 is also localized at the proximal region of the axoneme in these cilia, which suggests a potential role in the assembly or functioning of the cilia (Vladar, E. K., & Stearns, T., 2007).

In C. elegans, where SAS-6 was first identified, short centrioles are formed consisting of nine singlet, rather than triplet, microtubules, and no recognizable cartwheel structure is observed. Instead, the singlet microtubules assemble around a structure that appears as a hollow cylinder under electron microscopy. The assembly of this structure, known as the central tube, requires SAS-6. Although they differ at the ultrastructural level, the central tube and cartwheel, therefore, share at least one common component and are likely equally essential for establishing the ninefold symmetry of centrioles.

For the incorporation of SAS-6 into procentrioles in C. elegans, the protein SAS-5 is required, which physically interacts with SAS-6 and, like SAS-6, is essential for centriole duplication in this species (Delattre et al., 2004). Recently, the protein Ana2 was identified as a likely ortholog of SAS-5 in Drosophila (Stevens et al., 2010). While Ana2 is poorly conserved at the amino acid level, it interacts with DSAS-6 and, like its counterpart in C. elegans, is necessary for centriole duplication (Dobbelaere et al., 2008). Interestingly, the human ortholog of Ana2, known as STIL or SIL, has been shown to be required for proper mitotic

spindle assembly and is associated with microcephaly, which is reminiscent of the centriole duplication factor CPAP, the human ortholog of SAS-4 in C. elegans (Kumar et al., 2009). Analysis of the dynamic properties of SAS-5 in C. elegans, however, has indicated that SAS-5 may be necessary for recruiting SAS-6 to the sites of procentriole assembly, rather than acting as a structural component of the centrioles themselves.

In addition to the proteins associated with SAS-6, the assembly of the cartwheel also depends on the conserved Bld10p/Cep135 protein family. Bld10p was initially identified as the product of a gene mutated in a Chlamydomonas strain that completely lacks basal bodies, and it has been shown to be a component of the spokes of the cartwheel. When the Chlamydomonas bld10 mutant is complemented with a truncated version of Bld10p, centrioles with eight triplets are often observed. These centrioles assemble around the cartwheel with shorter spokes, leading to the formation of centrioles with a smaller diameter than can accommodate only eight triplets. The cartwheel still forms nine spokes, one of which is not associated with a triplet. Thus, if the central hub plays a decisive role in achieving the correct ultrastructure by establishing radial symmetry in the centrioles, then the radial spokes, whose length depends on Bld10p, perform this function, determining the diameter of the centrioles.

Cep135, the human ortholog of Bld10p, is also localized to the cartwheel and is necessary for centriole assembly (Oht et al., 2002). In contrast, the function of Bld10/Cep135 appears to be nonessential for the initiation of centriole assembly in Drosophila, as centrioles are generally duplicated in mutant flies that lack the Bld10/Cep135 homolog (Blachon et al., 2009). Depletion of Drosophila Bld10 by RNA interference in S2 cells results in partial inhibition of centriole duplication, suggesting that Bld10 may be required under certain conditions.

Ultrastructural analysis shows that the axonemes of sperm in bld10 mutant flies contain nine outer doublet microtubules, indicating that the centrioles from which they are assembled possess the correct ninefold symmetry. However, the sperm centrioles in these mutants are shorter than those in wild-type flies, and most flagella lack the central pair of microtubules, leading to male sterility (Mottier-Pavie, V., & Megraw, T. L., 2009). It is unknown whether the cartwheels assembled in the bld10 mutant are normal.

The stages preceding the formation of the cartwheel remain poorly studied. In Chlamydomonas and Paramecium, the cartwheel assembles on an amorphous, disk-like structure. Besides serving as the site for the assembly of the cartwheel, this amorphous disk may play a role in establishing the ninefold symmetry by controlling the diameter of the centrioles and, thereby, the number of microtubule triplets they can accommodate. In the Chlamydomonas bld12 mutant, 70% of basal bodies that retain the ring-like assembly of triplet microtubules demonstrate ninefold symmetry, despite the absence of the central hub of the cartwheel.

This suggests the presence of additional mechanisms influencing the radial symmetry of centrioles. In Paramecium, depletion of Bld10 by RNA interference

leads to the formation of centrioles that lack the spokes of the cartwheel but retain the central hub, suggesting that the hub is connected to the microtubule cylinder by a different structure, likely the amorphous disk. Similar disk-like structures have not been described in animal cells: instead, the procentrioles are seemingly connected to the walls of the parent centrioles via a connective stem.

Assembly of Microtubules

The assembly process of microtubules in the triplet structure of centrioles appears to occur in a stepwise manner. Initially, the singlet microtubules, or A-tubules, are attached to the spokes of the cartwheel-like structure, followed by the formation of doublets and triplets, which correspond to the incomplete B- and C-tubules, respectively. It is widely accepted that the attachment of singlet microtubules requires the action of a conserved protein family known as SAS-4, which is defined by the C. elegans SAS-4 gene and plays a crucial role in centriole duplication across a variety of organisms (Basto et al., 2006). A likely homolog of SAS-4 in human cells is called CPAP. Although CPAP shows significant amino acid divergence from C. elegans SAS-4, it concentrates in the proximal lumen of centrioles, where the cartwheel structure forms, and is essential for centriole duplication.

This observation confirms that CPAP is a true homolog of SAS-4 in C. elegans (Kohlmaier et al., 2009). In C. elegans embryos, the central tube forms during the S phase and elongates during prophase, while microtubules begin to assemble around it during prometaphase. In embryos lacking SAS-4, the central tube forms and elongates, but the microtubules are unable to attach. The centriole-localized SAS-4 increases in concentration as the S phase progresses, suggesting that SAS-4 interacts with the central tube, and its amount increases as the tube elongates. Interestingly, centriole-localized SAS-4 remains in dynamic exchange with the cytoplasmic pool until prophase/prometaphase, where it becomes stably associated with the centrioles (Dammermann et al., 2008).

This implies that centriole-localized SAS-4 may be stabilized through the assembly of centriole microtubules. This model is further supported by the observation that stabilization of centriole-localized SAS-4 requires γ-tubulin, which is believed to form the core of centriole microtubules, as well as β-tubulin. Additionally, γ-tubulin is necessary for the accumulation of SAS-4 in the pericentriolar matrix, suggesting a potential interaction between these two proteins. In human cells, it has been demonstrated that CPAP co-immunoprecipitates with γ-tubulin (Hung et al., 2000). The role of γ-tubulin in centriole assembly seems to be conserved, as γ-tubulin is required for centriole duplication in a wide range of eukaryotes (Haren et al., 2006). The function of γ-tubulin appears critical for controlling centriole assembly, as introducing specific mutations in γ-tubulin is sufficient to trigger the assembly of additional centrioles in Tetrahymena (Shang et al., 2005).

Recent advances in cryo-electron microscopy have provided important new insights into the mechanism of microtubule assembly in centrioles within human centrosomes. In nascent procentrioles, the proximal or minus-end of the A-tubules is

covered by a conical structure resembling the γ-tubulin ring complex (γ-TuRC), a structure known to form the microtubule nucleation core in animal cells. This observation suggests that each A-tubule is formed by a γ-TuRC core, and then it grows unidirectionally from the proximal to the distal end.

Confirming this hypothesis, the distal or plus-end of the A-tubules in assembling procentrioles displays outward-curved extensions typical of growing microtubule ends. In contrast, the incomplete B- and C-tubules never close at their proximal ends, implying that their assembly is initiated by a different mechanism. The B- and C-tubules seem to begin assembly at various positions along the A- or B-tubules, respectively, and undergo bidirectional growth, as evidenced by the presence of curved extensions at both proximal and distal ends of the B- and C-tubules before they reach their final length. The proximal ends of B- and C-tubules become blunt when they reach the proximal end of the A-tubules, suggesting that a stabilization mechanism occurs at this point.

Studies on Chlamydomonas and Paramecium have revealed the role of the δ- and ε-tubulin families in the formation or stabilization of B- and C-tubules (Dupuis-Williams et al., 2002). In the Chlamydomonas bld2-1 mutant, which expresses a truncated form of ε-tubulin, doublet and triplet microtubules are absent. In Chlamydomonas and Paramecium cells defective in δ-tubulin, the C-tubule is often missing, and most centrioles consist of only doublet microtubules. The requirement for δ-tubulin in the formation of C-tubules may be bypassed by suppressor mutations in α-tubulin, suggesting that δ-tubulin may be necessary for stabilizing the triplet rather than for the assembly of C-tubules (Fromherz et al., 2004).

Additionally, the genes encoding ε- and δ-tubulins are absent from the Drosophila genome, despite the fact that this species forms centrioles containing triplet microtubules (Callaini et al., 1997). To date, the precise mechanism underlying the formation of incomplete B- and C-tubules remains unclear.

Elongation of Centrioles

Temporal Regulation

At the stage where the assembly of B- and C-tubules begins, the procentrioles are short, with their length slightly exceeding that of the cartwheel structure (approximately 70–100 nm). During subsequent stages of procentriole assembly, the centrioles undergo elongation, eventually reaching their full length (400–500 nm in most species).

The length of the centriole appears to be under active control, not only due to the limited length change observed in any given cell type but also because the length undergoes dynamic changes at specific stages of the assembly process. For example, in Chlamydomonas, procentrioles assemble during mitosis and elongate during the subsequent G2 phase. In proliferating mammalian cells, procentrioles that assemble during the G1/S transition or early S-phase begin elongating during the S-phase, with elongation continuing into G2 and mitosis (Chrétien et al., 1997). Centriole elongation appears to be associated with cell cycle progression. In mammalian cells

arrested in the S-phase by DNA replication inhibitors, procentrioles elongate to approximately 70% of their full length, which corresponds to the length of procentrioles in late S-phase of untreated cells, but do not elongate further. This suggests that the completion of centriole elongation requires progression into G2 (Azimzadeh et al., 2009). Moreover, studies of the conserved centriole component hPOC5 suggest that centriole elongation and cell cycle progression are also linked earlier in S-phase. In human cells depleted of hPOC5, centriole elongation is suppressed, and procentrioles remain roughly the same length as those in early S-phase. Furthermore, cell cycle progression is impaired, with cells accumulating in the S-phase. It is not clear whether these two events are linked or if hPOC5 independently regulates centriole elongation and cell cycle progression.

The elongation of centrioles may also be restricted in certain cell types or specific stages of development, as observed in Drosophila and Apicomplexans (Morrissette et al., 2002). In these species, centriole elongation primarily occurs before the formation of cilia and flagella. In the uncoordinated Drosophila mutant (unc), centrioles do not elongate in ciliated sensory neurons and sperm cells, leading to the inhibition of ciliogenesis and, consequently, sensory dysfunction and male sterility. Interestingly, the product of the unc gene, which specifically localizes to basal bodies in these two cell types, has no orthologs outside of Dipteran insects (Baker et al., 2004), suggesting that centriole elongation in these organisms may depend on somewhat distinct molecular mechanisms.

Centriole Length Control

How do the triplet microtubules elongate, and what molecular mechanisms regulate their final size? In animal cells, the incorporation of tubulin dimers into centriolar microtubules likely occurs under the distal cap, which contains the protein CP110. CP110 is highly conserved across animals and is essential for centriole duplication (Chen et al., 2002). In addition to its role in centriole duplication, CP110, along with another centriolar protein known as Cep97, also participates in controlling the formation of primary cilia in mammalian cells.

Depletion of these proteins in the ciliated cell line RPE1 increases the fraction of cells that form a primary cilium. Conversely, overexpression of CP110 prevents primary cilium assembly under conditions that typically induce ciliogenesis (Spektor et al., 2007). Interestingly, in non-ciliated cell lines such as U2OS or HeLa, inhibition of either CP110 or Cep97 results in the formation of elongated structures initially believed to be primary cilia. However, recent findings have revealed that these structures actually correspond to abnormally elongated centrioles (Schmidt et al., 2009). Three recent reports have shown that similar structures form upon overexpression of CPAP, the human homolog of SAS-4 (Tang et al., 2009).

These centriole-like structures, which can grow several micrometers in length, result from excessive elongation of the centriole microtubules, originating both from the parental centrioles and from procentrioles. Ultrastructural analysis demonstrated that, despite their abnormal size, the elongated centrioles induced by CPAP overexpression

or CP110 depletion often resemble authentic centrioles. This observation is further supported by immunofluorescence data showing that markers for specific substructures of the centriole are properly localized in the elongated centrioles. Taken together, these findings led the authors of these studies to propose a model in which both CPAP and CP110 are necessary for centriole length control. CPAP likely promotes elongation, possibly by facilitating the incorporation of tubulin dimers at the plus end of the centriole microtubules, while the CP110 cap activity would limit microtubule growth.

In accordance with this hypothesis, members of the CPAP/SAS-4 family contain a domain that can bind tubulin dimers and induce microtubule depolymerization, a process that is essential for CPAP to aid in centriole elongation (Cormier et al., 2009). Notably, elevated CPAP expression induces high rates of centriole elongation during the G2 phase and mitosis, but not in cells arrested in S-phase. This may reflect differences in the mechanisms underlying centriole elongation in S-phase versus G2 or M-phase.

Another centriolar component, Ofd1, plays a role in regulating centriole length in mammals (Singla et al., 2010). Ofd1 is a conserved centriolar protein that is known to mutate in various types of ciliopathies (Coene et al., 2009). Studies of knockout mice lacking the Ofd1 gene show that Ofd1 is essential for the formation of primary cilia in the embryonic node and kidneys (Ferrante et al., 2006). This phenotype is recapitulated in the embryonic stem cell line of mice deficient in Ofd1.

Moreover, approximately one-third of these cells exhibit elongated centrioles, similar to those observed after depletion of either CP110 or Cep97 or after CPAP overexpression. In most cases, only the mother centriole elongates in Ofd1-deficient cells, although in control cells, Ofd1 localizes at the distal ends of both the mother and daughter centrioles, as well as procentrioles. Interestingly, the localization of CP110 and Cep97 at the distal ends of centrioles does not depend on the depletion of Ofd1, suggesting that these proteins act through a separate pathway for controlling centriole length. However, abnormal elongation of the mother centriole occurs during the G2 phase, but not in S-phase, in Ofd1-deficient cells, similar to the context of CP110 depletion and CPAP overexpression.

Finally, centriole elongation may require another conserved protein family known as POC1 proteins. When human POC1 is overexpressed in U2OS cells arrested in S-phase, a stage at which centriole elongation is typically initiated, POC1-containing filaments are observed. These filaments resemble those induced by CPAP overexpression. These filaments contain centrin and γ-tubulin, suggesting that they may also correspond to abnormally elongated centrioles, although further ultrastructural analyses are needed to determine how closely they resemble true centrioles.

The role of POC1 proteins in centriole elongation is also supported by the study of two mutant lines deficient in the Drosophila POC1 homolog. In these mutants, spermatid centrioles are shorter than those in wild-type animals, suggesting a partial disruption of centriole elongation. In contrast, centriole length does not change

upon POC1 depletion in Tetrahymena (Pearson et al., 2009). In Tetrahymena strains with a POC1 deletion, basal bodies show breaks in the microtubule blades, and these defects are exacerbated when mutant cells are grown at higher temperatures, leading to the loss of most basal bodies. Additionally, basal bodies in poc1 Δ cells are more sensitive to nocodazole, suggesting that Tetrahymena POC1 may play a role in stabilizing centrioles rather than directly controlling their length.

Formation of the Distal End

In addition to the elongation of the triplet microtubules, centriole elongation involves the assembly of intraluminal structures at the distal end of centrioles. Little is known about the function and molecular composition of these structures, which exhibit remarkable ultrastructural diversity among species. In mammalian cells, the distal lumen of centrioles is filled with a periodic stack of rings (Ibrahim et al., 2009). In Paramecium, the lumen contains a spiral structure, while in Tetrahymena, another ciliate, a cylindrical electron-dense structure is observed. The lumen of the basal bodies in Chlamydomonas appears to be filled with fibers that connect the microtubule triplets to each other (Geimer & Melkonian, 2004).

Despite this variability in architecture, intraluminal structures in different eukaryotes seem to share common properties. Specifically, the distal lumen of centrioles in mammalian cells, ciliates, and Chlamydomonas contains centrin proteins (Paoletti et al., 1996). Centrin proteins are calcium-binding proteins related to calmodulin, and they are found associated with centrioles in most species and present in the genomes of all species that assemble motile cilia (Salisbury et al., 2002). However, their precise role remains unclear, possibly because they bind to several different partners within the centrioles. For instance, human centrin proteins directly bind to hPOC5 and the related centriolar component hSFI1 and co-immunoprecipitate with CP110 (Kilmartin, 2003).

Maturation

A centriole is considered mature when it is capable of nucleating a cilium or flagellum. Vertebrate centrosomes contain only one mature centriole, which carries two sets of ninefold symmetric appendages. Only the mother centriole can anchor to the plasma membrane and initiate primary cilium formation. In mice with defects in the central protein ODF2, these appendages fail to assemble, mother centrioles cannot anchor to the plasma membrane, and ciliogenesis is suppressed (Ishikawa et al., 2005). The most distal set of appendages likely participates in anchoring the centrioles. Similar structures, often referred to as transitional fibers, adorn the distal end of mature centrioles in most eukaryotic species that assemble cilia. In human cells, a protein named Cep164 has been identified, which specifically localizes to the distal appendages. Although it is unclear whether Cep164 is required for the assembly of distal appendages, ciliogenesis is suppressed in RPE1 cells lacking Cep164 (Graser et al., 2007). Cep164 is found in the genomes of most ciliating species, suggesting that distal appendages and transitional fibers are likely connected at the molecular level. Recently, it has been shown that the assembly of distal appendages depends on Ofd1, as Ofd1-deficient cells lack distal appendages

and do not show Cep164 staining. Notably, by studying the effects of five disease-associated mutations in Ofd1 in Ofd1-deficient cells, Singla and colleagues identified mutations that affect centriole length but not distal appendage assembly, suggesting that these two processes are independently regulated by Ofd1.

In addition to distal appendages, the mother centriole in vertebrate cells is adorned with ninefold symmetric subdistal appendages. These subdistal appendages are thought to play a role in stabilizing microtubules (Piel et al., 2000), and, like distal appendages, their assembly requires the protein ODF2.

The maturation of centrioles is intricately linked with the progression of the cell cycle. In vertebrate cells, the full maturation of centrioles requires one and a half cell cycles. Centrioles formed during the previous cell cycle remain immature until mitosis, at which point two sets of appendages assemble at their distal ends (Vorobjev, I. A., & Chentsov YuS, 1982).

In cells that are arrested in the S-phase for prolonged periods, the daughter centrioles fail to acquire appendages, suggesting that passage through the G2 phase or mitosis is essential for the maturation of centrioles (Guarguaglini et al., 2005). The maturation of centrioles in vertebrate cells may be regulated in such a way that each cell contains only one mature centriole at any given time, a condition that appears to be crucial for proper differentiation, tissue development, and organ formation in multicellular organisms. In contrast, unicellular organisms, such as Chlamydomonas, possess two mature centrioles, each bearing appendages. Interestingly, studies of cells deficient in δ-tubulin suggest that the two mature centrioles are not strictly equivalent. In these cells, centriole maturation occurs more slowly, and many cells only possess a single flagellum, which originates from the older centriole (Dutcher, S. K., & Trabuco, E. C., 1998).

Some algae species exhibit a series of functional transitions in their centrioles, passing through as many as three distinct states, so that daughter, mother, and grandmother centrioles give rise to flagella with different structures and motility (Melkonian et al., 1991). These studies indicate that centrioles can have at least three generations, though the mechanisms by which this occurs remain entirely unknown.

In vertebrate cells, several proteins, including centrin and hPOC5, appear to associate with daughter centrioles in increasing amounts as the cell cycle progresses. Additionally, centriole pools of centrin and hPOC5 are highly phosphorylated (Paoletti et al., 2003). These changes in the composition of centrioles may be part of the maturation process.

Role of Centrioles in Cellular Biology

Typically, centrioles exist in pairs: one older centriole is referred to as the "mother," and the other, which is newer, is called the "daughter." These centrioles are orthogonally oriented, meaning they are positioned at a 90-degree angle to each other, which allows them to effectively participate in the process of mitosis. The mother centriole plays a pivotal role in

organizing the mitotic spindle and the formation of basal bodies (Debec et al., 2010), while the daughter centriole is involved in the process of cell division as well as in the organization of cilia and flagella (Breslow et al., 2019), which are crucial for cellular signaling and polarity.

Centrioles are indispensable for organizing the mitotic spindle, a structure responsible for ensuring the even distribution of chromosomes between daughter cells. During cell division, centrioles replicate, and one centriole from the pair moves to the opposite pole of the cell. This movement facilitates the formation of the mitotic spindle, which directs the chromosomes during cell division. Disruptions in centriole function can lead to improper chromosome segregation, which is often linked to the development of cancer and other pathologies (Piemonte et al., 2021).

Centrioles also play an essential role in maintaining cellular polarity. This is especially critical for cells that need to maintain strict orientation within tissues, such as epithelial cells. For instance, centrioles participate in the formation of basal bodies, which are structural components of cilia and flagella. Cilia are responsible for sensing external signals and maintaining cell polarity. Disruptions in these processes can result in defects in cellular organization and the development of various diseases, such as cystic fibrosis and other conditions associated with defective cilia function (e.g., ciliopathy syndromes) (Ware et al., 2011).

Furthermore, centrioles influence the process of cellular differentiation. This is because they are involved in organizing cellular structures necessary for the proper differentiation of cells. For example, during stem cell differentiation, centrioles play an important role in establishing cellular polarity and interacting with neighboring cells. Moreover, centrioles affect signaling pathways such as Wnt and Hedgehog, which regulate differentiation and tissue development. This discovery highlights the importance of normal centriole function in maintaining healthy tissue and proper cellular differentiation.

One of the most intriguing and relevant areas of contemporary research is the role of centrioles in limiting differentiation potential and the aging process of organisms. It is well-known that maternal (older) centrioles accumulate selectively in stem cells, gradually impairing their ability to divide normally and slowing the division rate (Yang et al., 2018). This results in a slowdown of cell replication and a decline in the regenerative capabilities of tissues.

Cancer is one of the most evident examples of diseases related to dysfunctional centrioles. Under normal conditions, centrioles ensure proper cell division; however, defects in them or the accumulation of older centrioles can lead to problems with chromosome segregation, which promotes tumor development. Recent research has shown that centriole defects are a major cause of chromosomal instability, which can result in uncontrolled cell division—a hallmark of cancerous tumors (Marteil et al., 2018).

In addition, altered centriole function can affect cellular migration, which is crucial for tumor metastasis. Some studies suggest that defective centrioles may facilitate the migration of tumor cells and the formation of metastases (Weier et al., 2022), making

centrioles important targets for the development of new cancer treatments.

In summary, centrioles play a critical role in cellular biology by performing vital functions in cell division, maintaining cellular polarity, cellular differentiation, and aging. Disruptions in their function can lead to a variety of diseases, including cancer, and accelerate the aging process. Understanding the molecular mechanisms by which centrioles regulate these processes will open up new opportunities for developing therapeutic strategies aimed at treating age-related diseases, cancer, and other disorders related to disrupted cellular homeostasis.

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