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ARTICLES

# What is the Function of Centrioles?

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**Abstract** The function of centrioles has been controversial and remains incompletely resolved. This is because centrioles, in and of themselves, do not directly perform any physiological activity. Instead, their role is only to act as a jig or breadboard onto which other functional structures can be built. Centrioles are primarily involved in forming two structures—centrosomes and cilia. Centrioles bias the position of spindle pole formation, but because spindle poles can self-organize, the function of the centriole in mitosis is not obligatory. Consequently, lack of centrioles does not generally prevent mitosis, although recent experiments suggest acentriolar spindles have reduced fidelity of chromosome segregation. In contrast, centrioles are absolutely required for the assembly of cilia, including primary cilia that act as cellular antennae. Consistent with this requirement, it is now becoming clear that many ciliary diseases, including nephronophthisis, Bardet-Biedl syndrome, Meckel Syndrome, and Oral-Facial-Digital syndrome, are caused by defects in centriole-associated proteins. J. Cell. Biochem. 100: 916–922, 2007. © 2006 Wiley-Liss, Inc.

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Back in the early days of cytology, invention of chemical stains allowed microscopists to recognize the organelles within a cell as physical entities, but gave little clue as to their function. Among these many newly discovered structures, the centriole stood out because its position suggested a function. While the function of the nucleus or mitochondria was completely mysterious, the centriole, because of its location at the poles of the spindle, was immediately implicated in the process of cell division. The presumed role of centrioles in mitosis attracted the attention of the leading cell biologists of the day, and for a time it seemed the centriole would be the first organelle whose function would be clearly determined. It is therefore ironic that, a century later, our understanding of centriole function has lagged far behind all other organelles. This was largely the result of a mistaken expectation. It was assumed that if centrioles are important, then a cell without centrioles should not be able to divide. When it turned out that cells without centrioles can still divide, the sense of excitement that had surrounded the centriole vanished overnight, to be replaced by apathy. With the initial obvious function of centrioles in mitosis apparently ruled out, less-obvious functions were proposed for centrioles, including suggestions that the centriole acts as a gyroscope [Bornens, 1979], an infrared photodetector [Albrecht-Buehler, 1994], or a computing device [Hameroff, 1987]. But were the early ideas about centrioles in mitosis wrong after all?

## CENTRIOLE FUNCTION IN MITOSIS

The mitotic centrosome, which is found at the poles of the mitotic spindle, consists of a pair of centrioles embedded in a fibrous matrix of pericentriolar material (PCM). It is the PCM, and not the centrioles themselves, which nucleates microtubule formation. Because centrioles are found within the core of the centrosome, it seems reasonable that the mitotic role of centrioles might involve some aspect of centrosome assembly. However, a role for centrioles in centrosome assembly, and hence a role for centrioles in cell division, was apparently ruled out by many demonstrations that mitosis can occur in animal cells lacking centrioles [Dietz, 1966; Berns and Richardson, 1977; Debec et al., 1982; Abumuslimov et al., 1994; Khodjakov et al., 2000]. These data were interpreted as evidence that a centrosome can form without a centriole. The logic of this argument runs as

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follows: spindle assembly requires centrosomes, but spindles can form without centrioles, *ergo* centrioles are not needed to make a centrosome, *Q.E.D*. This argument invokes the premise that centrosomes are necessary for making a bipolar spindle. This assumption may seem obvious, but it is wrong.

It turns out that bipolar spindles have a remarkable ability to robustly self-organize, and this phenomenon provides the real explanation for centriole-less mitosis. Animal cells without centrioles can form bipolar spindles but these spindle lack centrosomes, as judged by a failure of pericentriolar material to organize into discrete microtubule organizing centers [Matthies et al., 1996; Bobinnec et al., 1998]. Thus, it appears that centrioles are in fact necessary for centrosome formation, but this role was missed because centrosomes themselves are dispensable for mitosis. It is now clear that centriole-less cells form spindles via an alternative pathway that does not rely on centrosomes but rather relies on motor-driven self-organization of chromosome-nucleated microtubules [Matthies et al., 1996; de Saint Phalle and Sullivan, 1998]. Because centrosomes are required to nucleate astral microtubules at the poles, acentriolar spindles should be anastral, and this is universally the case [Wilson, 1928]. Thus, the proposition that cells lacking centrioles cannot make centrosomes is supported by the fact that acentriolar cells grow their spindle microtubules starting at the chromosomes rather than at the poles, and also by the lack of microtubule-nucleating activity at the acentriolar spindle poles.

Although cells with acentriolar spindles carry out normal-looking mitosis [Khodjakov et al., 2000], such imaging studies cannot rule out more subtle effects on mitotic fidelity, because they can only analyze small numbers of cells. Rare defects in chromosome segregation would generally be missed. A genetic approach has thus been developed to test centriole function in mitosis. Quantitative measurement of genomic instability in a *Chlamydomonas* mutant in which centrioles are dissociated from spindle poles [Zamora and Marshall, 2005] revealed a 100-fold increase in chromosome loss rates. Although this is a large increase over the normal rate of chromosome loss, the resulting loss rate is still quite low since the normal loss rate is low. Consequently, abnormal chromosome segregation is still a rare event, which explains why it is not apparent in live-cell imaging studies of small numbers of cells.

Current evidence thus indicates that centrioles, while not essential for making a spindle per se, may somehow contribute to the fidelity or robustness of chromosome segregation. What might a centriole contribute to this process? Bornens and co-workers [Abal et al., 2005] have proposed a fascinating explanation. They show that centrosomes from which centrioles are ablated by antibody injection become fragmented due to mitotic forces. Based on these results, it is suggested that the centriole provides a strong solid core around which the softer, more amorphous pericentriolar material can be structured. In this model, the centriole performs a role analogous to that played by the steel "rebar" found within reinforced concrete. When mitosis takes place, the microtubules anchored in the PCM exert forces on the chromosomes and on other microtubules, and Newton's third law of motion guarantees that equivalent forces will be exerted onto the attachment point of these microtubules in the PCM. Imaging studies have shown the PCM is composed of a filamentous network [Dictenberg et al., 1998] and the work of Abal et al. suggests that without a reinforcing centriole to hold it together, this filamentous PCM might unravel and fragment.

The experiments just mentioned were done by removing centrioles from centrosomes that had already assembled. In a cell lacking centrioles from the outset, it is likely (as discussed above) that a centrosome would never form in the first place. Consequently, factors that would normally dock on the centrosome might be disorganized in such cells during mitosis. This would include factors like NuMA with demonstrable roles in spindle pole focusing and organization. The acentriolar, acentrosomal spindle poles that would thus form may thus be less effective at forming or maintaining bipolar attachments. It is thus unclear whether the chromosome loss defects seen in mutant cells with acentriolar spindles [Zamora and Marshall, 2005] are primarily due to loss of mechanical integrity during segregation, or to structural defects in the spindle pole.

Before leaving the question of centriole function in mitosis, we should briefly consider the persistent confusion concerning mitosis in higher plants. All plants lack centrioles during normal vegetative cell division. Lower plants such as ferns and cycads do form centrioles

during spermatogenesis, but this is clearly done in order to support ciliogenesis (see below) on the motile sperm, and is unlikely to indicate a role in cell division. The fact that plants routinely perform mitosis without centrioles is sometimes taken to suggest that centrioles have no mitotic function in animal cells. This is a fallacy. Plants form mitotic spindles via a pathway that is highly divergent from animals. In plant mitosis, spindle microtubules are first nucleated from the surface of the nuclear envelope, and are then self-organized into a bipolar spindle with relatively broad poles. This pathway does not require a centrosome, and in fact plants do not contain centrosomes as we know them. The lack of centrosomes in plants, and their adaptation to a perpetually acentrosomal mode of spindle formation, provides the explanation for the lack of centrioles in plants: centrioles are needed to make centrosomes, but plants do not have centrosomes, hence plants do not need centrioles. Thus, the lack of centrioles in higher plants tells us absolutely nothing about centriole function in animal cells. If anything, the coincident lack of both centrioles and centrosomes in plants actually serves as evidence in favor of a role for centrioles in centrosome formation in animal cells.

Evidently, the initial cytological suggestion that centrioles function in mitosis is probably correct after all, but not in the way the early workers thought. Centrioles do not directly drive the assembly of the spindle, rather they recruit a centrosome which sculpts the inherently self-assembling spindle into a more precise form, and they then act as structural reinforcements to allow the spindle pole to resist the forces it meets during mitosis. Such functions in mitotic fidelity may help explain the near-universality of supernumerary centrioles in solid tumor cells [Brinkley and Goepfert, 1998; Doxsey, 2002]. Most tumor cells have abnormal numbers of centrioles, but if this simply resulted in cell death, the tumor would not progress. If, on the other hand, centriole defects result in decreased fidelity of chromosome segregation, then this could contribute to genomic instability during tumor progression.

## CENTRIOLE FUNCTION IN CYTOKINESIS

A role for centrioles in modifying spindle structure, particularly in facilitating astral microtubule formation, would also have an impact on cytokinesis. Cleavage furrow position is dictated by the spindle [Kawamura, 1960; Rappaport and Rappaport, 1974], and spindle microtubules, including both astral and midbody microtubules, have been implicated in furrow placement, ingression, and abscission [Ehler and Dutcher, 1998; Murata-Hori and Wang, 2002; Canman et al., 2003]. Centrioles may thus play an indirect role in cytokinesis via their role in spindle organization. In animal cells, when centrioles (along with the centrosomes) are ablated by laser microbeams, the acentriolar bipolar spindle drifts within the cell, inducing transient ectopic cleavage furrows [Khodjakov and Rieder, 2001].

Centrioles may also play a direct role in cytokinesis beyond the indirect influence they exert via spindle structure. Abscission (the final dissociation of the two daughter cells after furrow ingression) appears to coincide with, and may be triggered by, the close approach of the mother centriole to the cytoplasmic bridge between daughter cells [Piel et al., 2001]. Moreover, proteins associated with centrioles and centrosomes are required for proper membrane trafficking and actin organization during cytokinesis [Stevenson et al., 2001; Gromley et al., 2003]. These studies suggest signals from the centriole drive discrete steps of cytokinesis and predict that defects in centriole structure or copy-number might lead to defects in cytokinesis, particularly in the final stages of abscission.

Centrioles may also regulate cell-cycle progression. Cells from which centrioles were removed either by microsurgery or laser ablation progressed through mitosis, but then arrested in $G_1$ of the following cell cycle and never progressed to S-phase [Hinchcliffe et al., 2001; Khodjakov and Rieder, 2001]. This result suggests a signaling role for centrioles, consistent with the anchoring of many signaling molecules to these structures [Takada et al., 2003]. Perhaps centrioles act as scaffolds on which signaling molecules may be concentrated and coordinated.

## CENTRIOLE FUNCTION IN CILIOGENESIS

When cells enter $G_1$ following cell division, centrioles migrate to the cell surface and direct the formation of cilia. Centrioles acting in this capacity are called "basal bodies" because they are located at the base of the cilium. Cilia and

flagella are membrane-enclosed arrays of nine microtubule doublets which extend from the cell surface and play both motile and sensory roles. The nine doublet microtubules of the cilium appear to grow from the A and B tubules of the centriole triplet microtubules. It is probable that the ciliary microtubules are nucleated directly by the centriolar microtubules. Consistent with this idea, isolated centrioles have been shown to be capable of nucleating microtubules from the plus-ends of their triplet microtubules in vitro [Snell et al., 1974]. The ninefold symmetric pattern of microtubules in the centriole is thus thought to act as a template for the ninefold symmetry of the cilium. However, cases have been reported in which the cilium contains more microtubule doublets than the centriole contains triplets [Raff et al., 2000], suggesting that the extraneous doublets either formed without centriolar templating, or were released after templating to allow additional doublets to be templated.

In addition to acting as a template for microtubules, centrioles also play a key role in membrane docking during ciliogenesis. Cilia are anchored onto the cell cortex via the centriole, which contacts the plasma membrane through ultrastructural features called transitional fibers. These fibers project outwards from the centriole and contact the cell surface much like the landing pads of the Apollo lunar excursion module. Although the molecular basis of this centriole-membrane interaction is not known, one tantalizing hint comes from reports that a protein component of the transitional fibers, p210, shares homology with a class of clathrin adaptor proteins [Lechtreck et al., 1999]. How do these membrane-interacting landing pads locate the plasma membrane? Careful electron microscopy studies [Sorokin, 1968] have shown that the membrane–centriole interaction may be established prior to migration of centrioles to the cell surface. At an early stage of ciliogenesis, centrioles can be seen to dock with vesicles deep within the cytoplasm. It therefore seems likely that the ultimate centrosome association with the plasma membrane arises when these centriole-associated vesicles fuse with the plasma membrane, making centriole surface docking, in effect, a specialized type of exocytosis. It is interesting to consider whether the centriole-directed membrane trafficking functions that occur during ciliogenesis involve the same molecular mechanisms as those that occur during the terminal stages of cytokinesis.

A third key role of centrioles during ciliogenesis appears to be as a gathering point or train-station for ciliary assembly factors en route to the cilium. Elongation of a growing cilium occurs from its distal end, and transport of proteins out to the growth region requires a kinesin-mediated motility within the cilium known as intraflagellar transport (IFT). Proteins involved in IFT accumulate around the centriole [Deane et al., 2001], implying the centriole contains recognition sites to recruit these assembly factors. This function may thus resemble the vesicle docking function.

The strict requirement for centrioles in building cilia makes the centriole a key player in human diseases involving ciliary dysfunction. Because cilia are found in most cells of the body and play a range of roles in physiology and development, patients with defective cilia suffer from multiple symptoms including polycystic kidneys, retinal degeneration, and hydrocephalus. When the centriole proteome was determined [Keller et al., 2005], it was found to contain the products of many cilia disease genes, including the genes altered in Oral-Facial-Digital syndrome [Ferrante et al., 2006], Meckel syndrome [Kyttälä et al., 2006], nephronophthisis [Mollet et al., 2005], and cone-rod dystrophy [Kobayashi et al., 2000]. This short list may be the tip of the iceberg—we do not yet know how many other centriole proteomic components may turn out to encode ciliary disease genes. The presence of multiple ciliary disease proteins in the centriole is consistent with the centriole playing a key role in organizing ciliogenesis, and suggests that an understanding of ciliary disease cannot be attained without a complete understanding of centriole function during ciliogenesis.

Evolutionarily, the role of centrioles in ciliogenesis may predate any mitotic functions. Phyla which lack cilia, such as higher plants and fungi, invariably lack centrioles. Lower plants such as ferns, mosses, Ginkgo, and cycads, which make ciliated sperm cells but otherwise lack cilia in their tissues, lack centrioles through most of their life cycle but suddenly make them de novo when sperm are constructed. There is thus a strict one-to-one relation between phyla that have centrioles and phyla that have cilia. A likely scenario is therefore that eukaryotes first evolved centrioles in

order to make cilia, and then associated them with the spindle poles in order to segregate the centrioles or control ciliary copy number, and then during metazoan evolution the centriole gradually became a more integral part of the centrosome. This represents an example of the evolutionary phenomenon of "exaptation," in which a structure that evolves for one purpose takes on a secondary use for the organism.

## CENTRIOLE FUNCTION IN CENTRIOLE ASSEMBLY

New centrioles always form adjacent to, and at right angles with, pre-existing centrioles. It remains unclear how pre-existing centrioles contribute to the formation of new centrioles. The daughter centriole does not incorporate a significant portion of the mother centriole [Kochanski and Borisy, 1990]. Why new centrioles only form next to old ones has been a long-running question. The most obvious model is that centrioles contain an essential template structure needed to produce a new centriole, so that new centrioles simply cannot form except when nucleated by a pre-existing centriole. This idea was supported by reports that animal cells from which centrioles were removed were unable to form new ones de novo [Sluder et al., 1989; Maniotis and Schliwa, 1991]. More recent experiments [Marshall et al., 2001; Khodjakov et al., 2002] have shown that centrioles can form de novo even in ordinary cells, but such de novo assembly is somehow blocked when pre-existing centrioles are present. This suggests that pre-existing centrioles somehow act as an upstream biasing input to an inherently self-organizing process of centriole assembly. This is conceptually similar to the biasing role that centrioles play in centrosome assembly.

One model for centriole duplication proposes that gamma tubulin forms a ring of nucleation sites on the wall of the mother centriole, from which the microtubules of the daughter are nucleated [Fuller et al., 1995]. An alternative model is that a disc-shaped portion of the mother centriole detaches from the proximal end, like a slice of salami being sliced off in a deli slicer, and then the microtubule segments contained in this slice act as templates for the microtubules of the daughter [Gould, 1975]. This model makes an interesting prediction that mutant centrioles with defective microtubule patterning would produce daughters with a similar defect, even if the wild-type gene product was restored to the cytoplasm. However, this propagation of altered structure during centriole duplication has never been tested.

## CENTRIOLE AS A UNIVERSAL CONSTRUCTOR

Centriole function has been surprisingly hard to come to terms with. I claim that the best paradigm for understanding centrioles may not come from biology, but from abstract computer science. In the 1940s, the mathematician John von Neumann developed a theory for self-reproducing machines. In the von Neumann scheme, a self-reproducing machine has three parts: a one-dimensional "tape" carrying instructions, a computer called the "memory control" that reads the symbols on the tape and switches between a potentially large number of possible "states," and a third part called the "constructing unit" which, in response to instructions from the memory control, is able to join new machine pieces in order to build a variety of new machines, as specified by instructions stored in the tape. von Neumann showed that this system could reproduce itself, and it therefore serves as an early model for artificial life. In terms of modern molecular biology, the "tape" corresponds to the genome and the "memory control" unit corresponds to gene regulation and signal transduction networks. Both of these components are currently the focus of intense study by biochemists and cell biologists. In contrast, relatively little is known about what, in a living cell, would correspond to the "constructing unit." I propose that the primary function of the centriole is to act as a constructing unit, that allows other cellular structures, including astral spindle poles, cilia, and daughter centrioles, to be constructed in a position dictated by the centriole.

The term "constructor" implies that the constructing object can be detached from the constructed object, with the latter taking on its own independent existence that no longer requires the constructor. This is clearly the case with ciliogenesis. Once a cilium has formed, at least in some species, the centriole can detach from the base of the cilium, and move elsewhere in the cell, while the cilium remains intact and motile [Hoops and Witman, 1985]. Centrioles are also able to dissociate from spindle poles once they are initiated, at least in some species

[Lechtreck and Grunow, 1999]. This ability is not universal—it seems that in vertebrate cells, dissociation of centrioles leads to rapid fragmentation and scattering of centrosomes. This may reflect a difference in the underlying dynamics of the final construct—if centrosomes in a given species are stable, they may not need the continued presence of the centriole to remain intact, while if they are more dynamic in other species, they may require continual construction in order to remain intact. Such centrosomes would resemble an old and crumbling house that requires constant carpentry and repair to prevent collapse. They therefore require centrioles to act continuously as recruiting foci, without which they rapidly lose coherence. This argument highlights a point that should be obvious—in order to understand centriole construction activity in a given context, we need to understand the details, especially dynamics, of the structure that the centriole constructs.

Why employ one organelle to construct another? One possible evolutionary advantage would be to separate the positional cue that determines WHERE a structure should be formed, from the assembly instructions that determine HOW a structure should be formed. The centriole can be repositioned in response to cell polarity cues [Montcouquiol et al., 2003], and also can be actively repositioned via direct interactions with microtubules [Mogensen et al., 2000] as well as an array of associated contractile and non-contractile fibers [Geimer and Melkonian, 2004]. By using a single, orientable, mechanically stable object as a constructor for other objects like cilia or spindle poles, the cell gains greater flexibility in changing the location of these structures. From this point of view, understanding the pathways that determine centriole position may be key for understanding the mechanism by which cellular architecture develops.

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