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Mechanics of Centriole Microtubules

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Abstract

This is a review paper describing recent findings about the physical properties of centriolar microtubules. Microtubules are the principal structures making up the centrioles. The centrioles in turn are the principal agents in cell duplication and division (mitosis). The microtubules are seen to be long hollow cylinders: approximately 400 nm in length, with a 24 nm outside diameter, and a 5 nm wall thickness. Within the centrioles, the microtubules are arranged into nine parallel sets of triplets—thus numbering 27 parallel cylinders per centriole. Each normal eukaryotic (human and animal) cell, not in mitosis, has two perpendicular centrioles connected at their proximal (base) ends. During mitosis, these two become four, resulting in a total of 108 centriolar microtubules. The structure of the microtubules themselves is found to consist of 13 parallel filaments making up the cylinder walls. The filaments are composed of approximately 40 and β-tubulin connected end-to-end with their proximal (base) ends anchored in γ-tubulin. The longitudinal vibrations of the filaments are believed to create an electro-magnetic field within the cell which plays an important role in mitosis.

Keywords

Microtubules, Centrioles, Tubulin, Cell Magnetism

1. Introduction

Adjacent to the nucleus in all human and animal (eukaryotic) cells is a cloud of electron dense proteins known as the "centrosome" [1]-[13]. Within the centrosome, and as a part of the centrosome, is a pair of centrioles—hollow cylinders, perpendicular to each other, and connected at their base (proximal) ends. The perpendicularity is due to one of the centrioles (the "daughter") developing and growing on the side, at the base of the other centriole (the "mother"). The daughter is only about 80% as long as the mother [1] [14]-[17]. But with the daughter adjoining the mother at its base, the pair forms a perpendicular structure with nearly equal legs.

Figure 1 presents drawings of the nucleus, centrosome, and centrioles.

Each centriole cylinder consists of nine sets of triplets of microtubules, spaced evenly around the circumference,

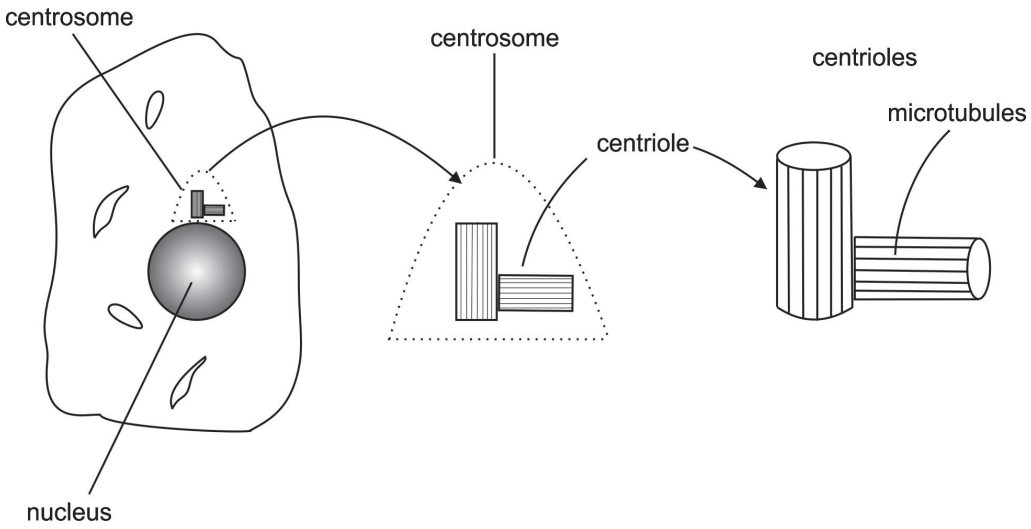

Figure 1. Drawings of the nucleus, the centrosome, and the centrioles.

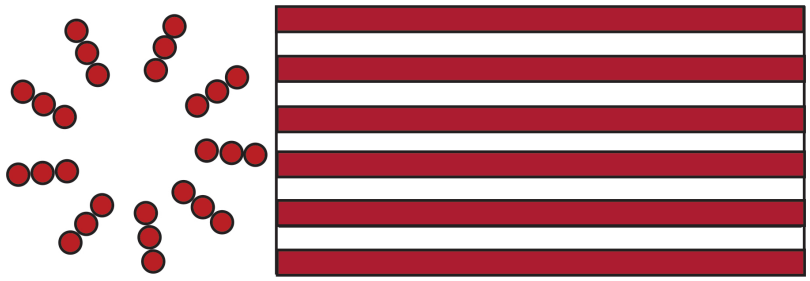

Figure 2. A centriole composed of microtubules (MTs).

and extending along the length of the centriole cylinder (see **Figure 2**). These microtubules (27 in total) form the subject matter of this paper. For efficiency in reading and writings, "microtubules" is abbreviated as "MT".

Each MT is itself a hollow cylinder having the same length as the centriole but with only a small fraction of the centriole diameter. The sets of triplets of MTs have the appearance of "blades" around the centriole circumference, and the entire collection of MTs may be compared to heating pipes of a boiler. But unlike a boiler, and unlike other biological organs, the centriole set of MTs has no membrane cover.

The centrioles via their MTs are the principal agents of cell duplication and separation (mitosis): at the beginning of mitosis, the centrioles duplicate each other and at the same time the DNA of the nucleus is copied. The centriole pair becomes two pair, and then they separate with the newly formed pair migrating to the opposite side of the nucleus and establishing a new centrosome at that opposite site.

Once the nucleus has diametrically opposed centrosomes, the MTs of the embedded centrioles elongate and spread out about the nucleus and form the "mitotic spindle". At the same time, the nuclear membrane, midway between the opposing centrioles, begins to soften and shrink away. The ends of the elongated microtubules then seek to connect to anchors, known as "kinetochores" [1] [2] [18], within the dividing nucleus. Finally the kinatochore-connected MTs begin to shorten, pulling the nucleus apart.

Each half of the divided nucleus together with its centrosome then separate, divide the remainder of the cell interior (the "cytoplasm") and thereby form two new cells.

While much remains to be discovered about each of these processes, as noted earlier, the focus herein is the mechanics of the MTs as structural elements of the centrioles.

The balance of the paper is divided into seven sections with the following section providing an overall description of the MT geometry. The next two sections describe the development of MTs and their resulting physical properties. The subsequent section (Section 5) then presents what appears to be currently known about MT dynamics. This is followed by a section indicating how MT development and behavior can go awry leading to

cell death and disease—including cancer. The final section provides a brief discussion and concluding remarks.

2. Microtubule (MT) Geometry

The centriole cylinders are approximately 400 to 500 nm long and their diameters are approximately 200 nm [1] [2]. With the microtubules forming the length of the centrioles, the MTs are thus also 400 to 500 nm long, but their diameters are much smaller: The outside diameter is approximately 24 nm and the inside diameter is approximately 15 nm—thus creating a wall thickness of approximately 5 nm. (The use of the adverb "approximately" is due to the minute sizes of the structures. That is, precise measurements are elusive.)

The walls of the MT are composed of 13 filaments running lengthwise along the microtubule. These filaments in turn are composed of approximately 40 tubulin dimers connected end-to-end as in **Figure 3**.

The dimers are composed of alpha and beta-tubulin proteins with the alpha-tubulin toward the proximal end of the microtubule filament, and with a negative charge. Conversely the beta-tubulin is toward the distal end of the MT filament and with a positive charge.

Figure 4 shows a drawing of an alpha/beta-tubulin dimer.

With the α and β-tubulin being coiled proteins approximately 5 nm in thickness (the thickness of the microtubule wall), the dimer length is approximately 10 nm.

With the MT filament being approximately 400 to 500 nm long, there are approximately 40 to 50 dimers in a filament.

There are differing views on the longitudinal arrangement and positioning of adjacent filaments [19]-[22]: Some investigators suggest that the longitudinal position of the filaments is such that each alpha-tubulin is adjacent above and below, and to each side, by a beta-tubulin, and vice-versa. This arrangement presents a 45 degree spiral pattern on the wall of the microtubule as in **Figure 5**.

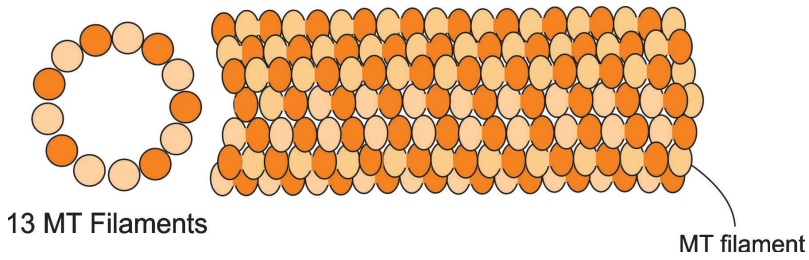

Figure 3. Microtubule (MT) model.

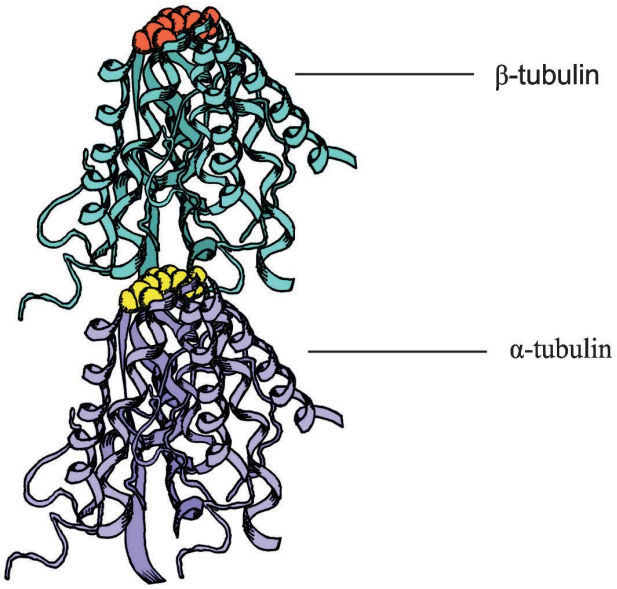

Figure 4. α/β dimer.

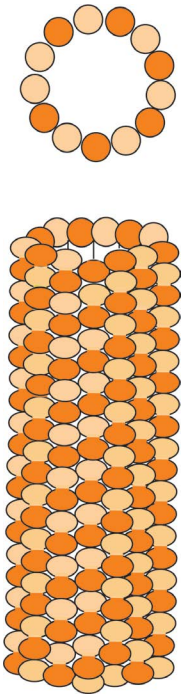

Figure 5. A spiral arrangement of α and β-tubulin.

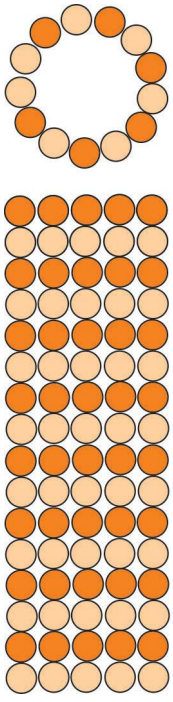

Figure 6. Rings of α and β-tubulin.

Others have suggested a similar arrangement but with spiraling at a lesser angle. In the extreme case, with no spiral angle there are simply alternate rings of α and β-tubulin, as in **Figure 6**.

A difficulty with the spiral arrangements where each α-tubulin is adjacent on both sides with a β-tubulin (and vice-versa) is that with 13 filaments, the pattern becomes disrupted as it completes the MT circumference. That is, with an odd number of filaments (13), if say the α-tubulin is assigned an odd number (and the β-tubulin an

even number) about the circumference, then the α-tubulin numbers: 1 and 13 come together so that two α-tubulin are adjacent (see **Figure 7**).

A difficulty with the ring arrangement of **Figure 6** is that it is inconsistent with the dimer formation and the construction of the microtubule wall via γ-tubulin, as discussed in the following section.

Another, and apparently more plausible, view of the filament pattern is that with the filaments consisting of α/β-tubulin dimers, connected end-to-end, each filament can move longitudinally and independently of adjacent filaments. Also, the external surfaces of the filaments are smooth enabling the relative movement [23].

Finally, the MTs making up the blades of the centrioles have differing lengths. The longest, labelled "A", is closest to the axis; the shortest; labelled "C" is nearest to the outside wall; and then the middle one, known as "B", has intermediate length (see **Figure 8**).

3. Microtubule (MT) Development

In the cell duplication cycle, before the separation begins, the DNA and the centrioles duplicate during a period known as the "S-phase" (this is during an intermediate phase of the cell cycle) [1] [2] [17] [24]. The stimuli for both the DNA separation and the cell duplication occur at the same time.

Much remains to be discovered. But in general terms, the centriole duplication occurs as follows: A collection of proteins within the centrosome act in a serial manner to form new microtubules. As a result of this process, the centrosome minus the centriole pair is known as the "microtubule organizing center" (MTOC). The proteins

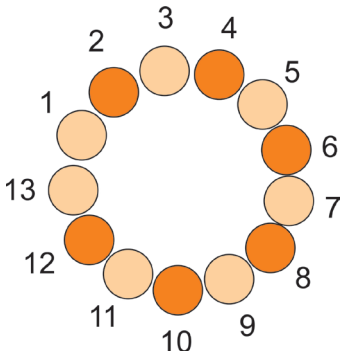

Figure 7. End view of microtubule showing disrupted spiral pattern.

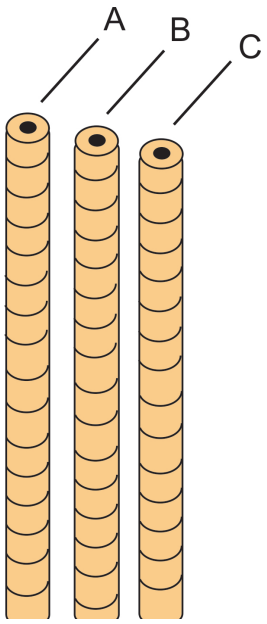

Figure 8. Varying MT filament lengths.

immediately surrounding the centrioles are known as "pericentriolar material".

Of the more than 300 proteins in the MTOC only a few appear to play prominent roles in assembling the new centrioles with the new microtubules. These are: Plk1 and Plk4 (polo-like kinases one and four). Plk4 is also known as "SAK"; Asl (asterless); SAS4; SAS6; ZYG-1; STIL (SIL); p53; separase; Cdk2; cyclin E; and α, β, and γ-tubulin [24].

The duplication of the centrioles, and thus also the creation of new MTs, begins with asterless making a small deposit on an outer MT near the base (the proximal end) of a centriole blade (on a "C-microtubule"). The asterless deposit then recruits Plk4 to form a patch atop and across the deposit. Next, this Plk4 patch, with the aid of SIL, recruits SAS6 in turn atop and across the Plk4 patch.

While this description of the development of the protein structure may not be precise, what is known is that identical base structures are built at the proximal ends of both the mother and daughter centrioles.

After this protein base structure is established, the SAS6 expands symmetrically growing nine outward spokes tangent to the centriole surface. While these spokes are growing they recruit γ-tubulin along their lengths. Finally, the γ-tubulin deposits form the basis for the development of three new MTs along each of the nine spokes.

The complexity of this structure requires regulation to keep it from going awry. This regulation, and to some extent the protein recruitment, is aided by still other proteins: SAS4; Bld10/Cep135; ZYG-1; p53; and probably others as well.

The γ-tubulin deposits on the SAS6 spokes are believed to be suppliers of the α/β-tubulin dimers from the MTOC for construction of the MT [25]-[27]. Although, as before, the details are still somewhat sketchy, the γ-tubulin deposit appears to take the shape of a ring with overlapping ends—having the appearance of a lock-washer [19]. There are 13 ports along this ring through which the α/β dimers are inserted from the MTOC to form the microtubule filaments. This process is known as the "protofilament method" [19] [22] [28] [29].

The γ-tubulin ring is known as the "γ-tubulin ring complex" (γ-TuRC) and/or as "gammasome" [20] [21]. The 13 ports are composed of another tubulin known as the "γ-tubulin small complex" (γ-TuSC). The γ-TuSC is like cylindrical channels perpendicular to the γ-TuRC.

In another process of microtubule nucleation, known as the "template method," the α/β tubulin dimers are inserted through the γ-Tu-SC pores, but then pushed along the γ-TuRC forming a spiral pattern for the microtubule.

There are unresolved issues with each of these methods: 1) In the protofilament method, if each protofilament is independent of its neighbor, an intact microtubule filament 400 nm long would be like a cantilever beam with an 80 to 1 aspect ratio. 2) In the template method, the spiraling of the α/β-tubulin dimers does not conform to the 13 filament structure of the microtubule without a seam of duplicate tubulin, and thus disrupting the symmetry. Also, the spiraling does not allow for independent longitudinal movement of the filaments—a phenomenow believed to be necessary for the microtubule dynamics and the creation of electro-magnetic fields.

Finally, there are two other tubulins contributing to the development of the microtubules: δ and ε-tubulin. δ-tubulin is instrumental in the development of the three microtubule blades in each of the nine blades of the centriole [30] [31], while ε-tubulin is instrumental in the development and maintenance of the paricentriolar material [23].

4. Physical Properties of Microtubules (MTs)

In spite of measurement difficulties, there is still considerable data about the structural and electrical properties of the alpha/beta-tubulin dimers and the complete microtubule structure.

As noted earlier an MT has the shape of a hollow cylinder, approximately 400 nm long, with inside and outside diameters of 15 and 25 nm respectively. The wall thickness is thus approximately 5 nm—the approximate thickness of an α/β-tubulin dimer.

The outside wall of an MT cylinder is smooth—presumably to facilitate MT filament movement within the centrosome. The inside wall, however, does not possess the same degree of smoothness [23].

From a structural perspective MTs are relatively stiff in tension and compression but weak in shear (torsion) [32]. The elastic modulus E is estimated to be approximately 10^9 Pa (N/m^2) [33]. From the known geometric dimensions the second moment of area I of the cross-section is calculated to be: 1.67×10^{-32} m^4 [34]. Then the flexural rigidity EI becomes approximately: 1.7×10^{-23} Nm^2 [35].

Equation (1) summarizes these results:

$$E \cong 10^9 \text{ Pa}, \quad I \cong 1.7\times10^{-32} \text{ m}^4, \quad EI \cong 1.7\times10^{-23} \text{ Nm}^2. \tag{1}$$

For structural analysis, there are two other parameters which may be of interest: 1) Poisson's ratio v; and 2) the shear modulus G. Poisson's ratio is the ratio of transverse (lateral) strain to longitudinal strains, and is also known as the "transverse-contraction ratio". For stiff materials v is approximately: 0.3. The shear modulus, also known as the "modulus of rigidity", may then be evaluated using the expression [34]:

$$G = E/2(1+\nu). \tag{2}$$

Then G becomes:

$$G \cong 3.85\times10^8 \text{ Pa}. \tag{3}$$

Experiments also reveal electrical properties of the MTs: The MTOC is thought to be composed of electron-dense material [4] [36]-[38]. Therefore the MT base is given a negative charge. Consequently, the α/β dimer has a negative charge at the base (or proximal) end of the α-tubulin and a positive charge at the distal end of the β-tubulin [39] [40].

It is believed that the electro-magnetic properties of a cell occur due to independent longitudinal vibrations of the MT filaments, thus oscillating the positive and negative charges of the α/β tubulin dimers [23] [41]-[44].

For a single dimer, the dipole moment is of the order of 10^{-26} Cm (Coulomb meters) [43]-[46].

Finally, the masses of the α-tubulin and the β-tubulin proteins are essentially the same at approximately 4.56×10^{-23} kg, so that the dimer mass is approximately 9.13×10^{-23} kg.

5. Microtubule (MT) Dynamics

MTs are the most dynamic of all the cell organelles. They have continuous movement—analogous to respiration and blood flow. MT dynamics occur by the supply of the α/β dimers being recruited from the MTOC and then inserted at the base of the MT by the γ-TuRC. Each dimer insertion by the γ-TuRC tends to lengthen the MT. But then, at the distal end, the dimers break away and go into the cytoplasm. This breakup tends to shorten the MT.

The continual lengthening and shortening of the MTs is known as "dynamic instability", and it is characterized in four phases: 1) growth, 2) shrinkage, 3) catastrophe, and 4) rescue [47]-[50].

Growth is simply MT elongation and *shrinkage* is MT shortening. Catastrophe is the transition from growth to shrinkage; and correspondingly *rescue* is the transition from shrinkage to growth.

Growth and shrinkage may occur alone or simultaneously. Catastrophe occurs when the growth either stops or the growth rate is less than the shrinkage rate. Similarly, rescue occurs when the shrinkage either stops or the shrinkage rate is less than the growth rate.

Superpose upon the ongoing lengthening and shortening of the MTs as a whole, the individual filaments oscillate longitudinally. Due to the small tubulin mass the oscillation frequency is high: Estimates range from 10^7 to 10^{10} Hz [51]-[53].

The 13 filaments making up the MT wall are believed to keep interactive vibration modes between the filaments to a minimum: 13 is a prime number immediately following 12. With 12 being the product of 4 and 3, if there were only 12 filaments, there would tend to be close coupling of the vibrations across the diameter and at 50˚, 60˚, and 90˚.

Finally it is believed that the γ-tubulin in some way controls the MT dynamics in general and the vibration in particular. The mechanism of this control, however, is unknown.

6. Microtubules (MTs) Going Awry

In view of all that is involved in MT geometries and their development, microtubule properties, and microtubule function, it is easy to envision something (or many things) going awry. When this happens, the centriole is negatively affected, leading possibly to cell death, or worse, to ongoing disease such as tumorigenesis or cancer.

Among the most common defects is a disruption in centriole geometry due to an overgrowth of MTs. Perhaps the most dangerous is the case of "flowering" [6] [54] where there is an excess in the number of centrioles. **Figure 9** shows a conceptual imaging of flowering where a mother centriole may have two or more daughters simultaneously. When this happens the cell has extra or supernumerary centrioles.

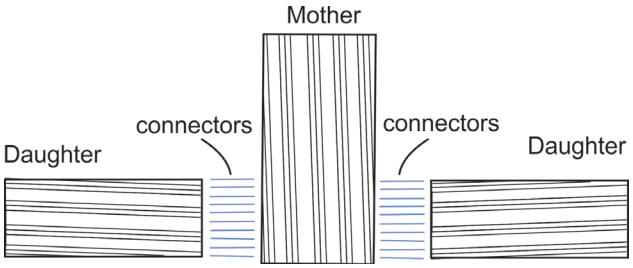

Figure 9. A mother centriole with two daughters ("flowering").

Virtually all cancer cells contain supernumerary centrioles [3] [10] [38] [55]-[86]. These extra centrioles tend to cluster together—presumably due to electromagnetic attraction. In an earlier paper [6], it is suggested that these centriole clusters create an enhanced electromagnetic field and that this enhanced field can then serve as a biomarker for cancer cell identification and therapy.

Much additional work is needed to validate these assertions and to explore their application.

7. Conclusions

This brief review, like many reviews, raises questions with virtually all of the assertions. Admittedly, many of the assertions are based upon limited experimental data. The experimental limitations are primarily due to the minute size of the microtubules, and even more so for the smaller tubulin dimers. Improvements in experimental techniques, however, are likely to clarify many of the unresolved issues.

If, however, the findings and assertions presented herein are generally correct and indicative of microtubule physics, these findings and assertions could be useful in pointing the way to additional research.

Perhaps the most interesting finding is the apparent development of electromagnetic fields via MT oscillations. This needs to be explored in greater detail. If this further exploration leads to finding an enhanced field about centriole clusters in cancer cells, the enhanced electromagnetic field could serve as a biomarker for cancer cells, leading in terms to better imaging and therapies.

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