

A Review of Centriole Activity, and Wrongful Activity, during Cell Division

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Abstract

This is a review paper on centriole behavior and their role in enabling cell division and duplication. The paper is based primarily on articles published in this, the 21st century. Following a description of centriole geometry, the paper discusses centriole duplication and the ensuing events leading to cell division. From a structural perspective each centriole is seen to be a cylindrical composition of nine blades, each having three microtubules which are themselves hollow cylinders approximately 400 nm long, with inner and outer diameters of 15 and 25 nm. The paper then discusses the nucleation of these microtubules. The paper concludes with a description of centriole malfunction and overduplication (supernumerary centrioles), leading to clusters of centrioles—a hallmark of cancer cells. These centriole clusters thus form “biomarkers” for tumor imaging and treatment.

Keywords

Centrioles, Cancer, Mitosis, Microtubules

1. Introduction

This paper presents a selective review of some recently published research findings about centrioles, their duplication, and then their role in cell duplication. The paper also focuses on centriole defects and the potential development of tumors.

The research cited is primarily that published in this, the 21st century. As with most reviews there are undoubtedly important writings that are overlooked, or inadvertently omitted. I sincerely regret any such omissions. Also, some of the material presented herein is rudimentary, establishing a basis for describing the new findings.

The balance of the paper is divided into eight sections with the first of these being a general description of centrioles themselves. The next section briefly describes how centrioles are duplicated. The third section describes

the role of centrioles in cell division (mitosis).

The next two sections provide a closer look at centriole geometry and how it is developed. Sections 6 and 7 then discuss erratic centriole development leading to tumorigenesis and malignant cells.

Finally, the last section provides a summary of what are believed to be the most important findings for going forward, and some concluding remarks.

The paper has 172 references which can also serve as a bibliography for research on open questions identified in the paper.

2. Centrioles

Centrioles are small organelles lying adjacent to the nucleus in human and animal (eukaryotic) cells [1]-[11]. From a small distance away centrioles appear to be a pair of short hollow cylinders perpendicular to each other. Their length is approximately $0.4\ \mu\text{m}$ (400 nm) and their diameter approximately $0.2\ \mu\text{m}$ (200 nm).

But up close, centrioles are seen to be a set of 9 open (uncovered) inclined blades arranged around the circumference. Each of these blades in turn is composed of three hollow cylinders known as “microtubules”, whose outside diameter is approximately 25 nm and inside diameter approximately 15 nm.

Figures 1-3 provide drawings of a cell, of centrioles and of microtubules [1] [11].

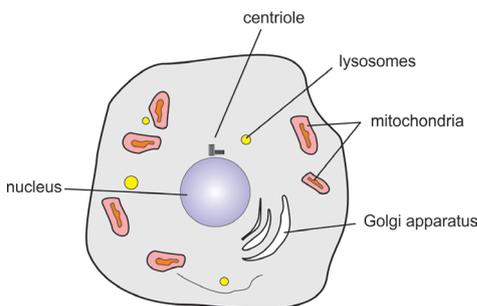


Figure 1. Cell interior showing centriole near the nucleus.

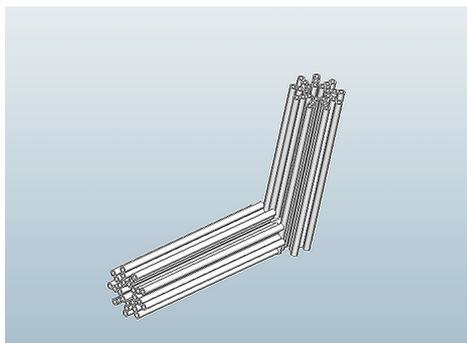


Figure 2. Centriole pair.



Figure 3. A microtubule.

As seen in **Figure 2**, the two centrioles are not identical: instead one, known as the “mother”, is slightly longer than the other (the “daughter”). Also, the daughter has its base attached to the side at the base of the mother. The ends, at the connection of the centrioles are known as the “proximal” ends, with the other ends thus being “distal”.

The proximal ends are believed to be immersed in a cloud of “electron dense” matter [7] [8] [12]-[16]. Therefore, from an electrical perspective, the proximal ends have a *negative* charge, and the distal ends then have a *positive* charge.

The nine sets of microtubule blades are the “building blocks” and principal structure of the centrioles. **Figure 3** provides a more detailed drawing of the individual microtubules. They are composed of 13 lateral filaments made up of tubulin dimers (alpha and beta tubulin attached to each other as batteries in series). The dimers are approximately 8 nm long and 5 nm thick. Observe that the filaments of dimers being odd (13) in number prevents them from being packed tight around the circumference since with tight packing the symmetry around the circumference would be disrupted.

Centrioles were originally discovered with the advent of microscopy in the beginning of the 20th century (circa 1904) [2] [17]-[26]. For many years the purpose of centrioles and their function were unknown. Shortly after the mid-twentieth century, with the development of electron microscopy, the behavior of centrioles was studied and expounded by Paul Schafer [18] [19] [21]. But unfortunately this work was largely ignored since researchers began to focus upon then findings of Watson and Krick about DNA [27]. Also, others regarded centrioles as being relatively unimportant since they do not occur in plant cells or in bacteria.

Near the beginning of the 21st century, however, it became generally accepted that centrioles were the principal organelles driving cell division and duplication (mitosis) in eukaryotic cells (human and animal cells) despite being absent in prokaryotic cells (bacteria) and in plants.

But what is now stimulating interest in researchers is that excessive centrioles and centrioles with distorted geometries are now being seen as the initiators of tumors [17] [28]-[60].

3. Centriole Duplication

When the centrioles begin to duplicate, the mother and daughter separate slightly and then each centriole begins to form a new centriole at its base: the mother with a new daughter and the daughter with a new daughter of its own (a “granddaughter”). As the pair of centrioles are developing daughters, and continue to separate from each other, the original pair becomes two pair. In this way the centrioles duplicate each other [1] [4] [8] [28] [35] [55] [57] [61]-[90].

As the centriole duplication is happening, the DNA of the nucleus is also being duplicated and separated. That is, the current research shows that centriole duplication and DNA separation are, in some way, entangled. [15] [22] [91]-[97].

4. Mitosis (Cell Duplication and Division)

Following centriole duplication and separation into two pair, the younger pair moves around the nucleus to the opposite side. While this is occurring, the nuclear membrane begins to soften. The centrioles at the opposite sides of the nucleus then begin to pull the nucleus apart.

As the nucleus is being elongated the microtubules of the centrioles extend and align themselves along the long axis of the nucleus, forming the “mitotic spindle” [61] [83] [98]-[102], as represented in **Figure 4**. The nucleus then shrinks in the middle and eventually separates into two parts. During their separation, each part takes approximately half of the remainder of the cell (the cytoplasm) with it. The result of this process, known as “cytokinesis”, is then two twin-like cells.

The mitotic process is frequently described in terms of an initiating phase, known as “interphase” followed by four development phases. It is during this interphase that the centrioles duplicate and the DNA divides: Just before the duplication and division there is a relatively inactive period, or gap, called “G1”. Following G1 is the “S-phase”, where the centrioles duplicate and the DNA divide. The interphase then becomes complete with a second gap period called “G2”.

In the first of the four development phases, known as “Phase I” or “Prophase”, the chromosomes condense, drawing close together, and the nuclear membrane begins to dissolve and weaken. At the same time the mitotic spindle forms with the now separated centriole pairs of the spindle ends. In Phase II, called “Metaphase”, the



Figure 4. Microtubule spindle.

chromosome strings move toward and align themselves with the axis of the mitotic spindle. In Phase III, called “Anaphase”, the chromosome strings divide and move toward opposite ends of the elongating spindle. Finally, in Phase IV, known as “Telophase”, new nuclear membranes form about the separated chromosome strings, the mitotic spindle breaks apart and the cell separation begins completion with half the cytoplasm going with each new nucleus [1] [9]-[11].

The centriole pairs at either end of the mitotic spindle appear to be driving influences during this entire cell division process. Moreover these influences appear to be occurring due to forces exerted at a distance via the centrioles electromagnetic fields [4] [5] [63] [91] [99] [103]-[105].

5. Centriole Geometry and the Centrosome

Unlike all other organelles, or for that matter, any organ of the body, the centrioles have precise “straight-line” geometry and symmetry; and the centriole cylinders are exactly perpendicular to each other.

Also, unlike other organelles and organs, centrioles have no membrane cover. They are primarily a structural organization of microtubule blades—nine sets of triplets arranged uniformly about the centriole axis.

The centrioles are immersed in a cloud of proteins—perhaps as many as 300 or more [8] [63] [93] [106]-[108]. These proteins are coiled, twisted bands, with an approximate overall spherical shape. Taken together this protein “cloud” is known as the microtubule organizing center (MTOC), since it provides the protein for microtubule growth and structure. The MTOC is also known as “pericentriolar material”. The centriole pair together with the surrounding MTOC is known as the “centrosome”.

The centrosome is approximately 1 μm in diameter and the centrioles are at the core of the centrosome. As noted earlier the proteins of the centrosome at the base intersection of the centrioles are believed to be “electron dense” and therefore the centriole base is assigned negative polarity.

6. Centriole Development during Interphase

While details of centriole development are still being discovered, it appears that only a few of the many proteins in the centrosome are primarily involved. The remainder probably plays supportive roles.

The primary proteins are: Plk1 (polo-like kinase one), Plk4 [also known as (aka) “SAK”], asterless (AsP), SAS4, SAS6, ZYG-1, STIL (aka “SIL”), p53, separase, Cdk2, Cyclin E, and α , β , and γ -tubulin [4]-[7] [24] [47] [52] [61] [63] [65] [66] [68] [74] [77]-[80] [82]-[86] [88] [91] [95] [97]-[99] [109]-[134].

What appears to occur is that just prior to the creation of a new centriole (“daughter” centriole) near the base of an existing centriole (“mother” centriole), AsP attaches itself to one of the nine outside microtubule blades [79] [80] [88] [131] [135], The AsP then recruits Plk4 to deposit itself atop the AsP, and then expand to being a base for ensuing structure. While this is happening SIL recruits SAS6 to the Plk4 base. The SAS6 then begins to expand symmetrically, tangent to the mother’s outside microtubule surface. In this expansion the SAS6 forms nine spokes which become the platform for the daughter centriole. The platform then recruits γ -tubulin to its center, and the γ -tubulin in turn recruits α and β -tubulin for the structural elements of the microtubules. The α and β -tubulin link together forming a dimer and the dimers connected end-to-end form a longitudinal filament of a microtubule (see **Figure 5**).

SAS4 and yet another protein, Bld10/CEP135, appear to aid in recruiting the tubulin to the centriole base. The process is controlled and regulated by SAS4 itself, together with ZYG-1, and p53 [7] [15] [35] [46] [52] [57] [63] [69] [72] [74] [98] [116]-[118] [123] [125] [129] [130] [132] [133] [136]-[153].



Figure 5. A microtubule dimer (α —red, β —black).

Once the daughter centriole size grows to approximately 80% of that of the mother centriole, they form a new mother-daughter centriole pair. This pair is a duplicate of an adjacent similarly forming centriole pair.

Proteins Plk1, separase, cdk2, and cyclin E then promote the separation of the two centriole pairs. Plk1 is also active in dividing the surrounding centrosome protein between the original mother-new daughter pair and the original daughter-new “granddaughter”.

As the centriole pairs are separating the new daughter centrioles become mature [100].

CPAP and SAS4 are similar as ZYG-1 and Plk4. But of all the proteins it appears that Plk4 is the most involved in new centriole initiation and growth, in that Plk4 is the primary base for the new centriole.

7. Wrongful Centriole Development

While the foregoing description of centriole development is neither comprehensive nor necessarily accurate in all detail, it is clear that centriole development is quite complex. Due to this complexity there are many ways the process can go awry—even though a number of proteins are thought to be regulatory. For example, if there is an imbalance in the ratio of the proteins, the daughter centriole may be defective. Here are some examples of such defects.

- 1) The centriole geometry can get distorted. The axes of a pair can deviate from perpendicularity.
- 2) Multiple daughter centrioles may develop.
- 3) The daughter centriole may reach full length before pair separation.
- 4) Separation of the pairs and their disengagement may be delayed.

When there is a wrongful, or erroneous, suppletion of centrioles either via geometrical defects and/or multiple duplication, the cells can become damaged and even malignant. The DNA can be damaged leading to aneuploidy (an abnormal number of chromosomes). That is, the DNA replication is altered leading to chromosome instability (CIN).

In what may be the same phenomena, it is known that centrosome defects (for example, an enlarged centrosome) leads to CIN. An enlarged centrosome is known to promote the development of multiple daughter centrioles [34] [60] [85] [88] [93] [95] [116] [140] [141] [154]-[163].

Doxey says: “Indeed, it would seem that the answer to some of the big questions of tumorigenesis are hiding in small places like the centrosomes” [47].

Finally, regarding the proteins underlying these wrongful activities, it seems that a dearth of p53 allows for deregulation of the centriole duplication and development process, allowing it to go awry. Also an overexpres-

sion of Plk4 and SAS6 can lead to centrosome amplification. Alternatively, too little Plk4 and SAS6 can lead to duplication error. More research is needed to obtain a clearer understanding of these effects.

8. Abnormal Centrioles and Malignant Cells

Centriole and centrosome abnormalities lead to either: 1) self-correction due to regulatory proteins; 2) cell death; or 3) tumor generation (“tumorigenesis”) when there is tumorigenesis, the centrioles tend to have multiple daughters regulating in a proliferation of centrioles [7] [12] [14] [17] [28]-[31] [37] [52]-[54] [58] [59] [61] [62] [70] [72] [75] [109] [112] [113] [115] [116] [118] [127] [158] [161] [162] [164]-[168], or so-called “supernumerary centrioles”.

The precise mechanisms producing supernumerary centrioles is not yet clearly understood—although the over duplication appears to occur in the S-phase. When supernumerary centrioles appear, abnormal mitosis occurs and tumors develop.

In addition, when there are supernumerary centrioles, the cell polarity (cell shape) is disturbed.

Supernumerary centrioles lead to centrosome amplification which is a “hallmark” of cancer cells.

The supernumerary centrioles tend to cluster together leading to centrosome clustering which appear to be essential for the survival of damaged cells.

The characteristics of cells with supernumerary centrioles include:

- 1) An excess of pericentriolar material.
- 2) Disrupted cylindrical structure of the centrioles.
- 3) Centrioles with excessive length.
- 4) Non-perpendicular centrioles.
- 5) Mispositioned centrioles.

It has been suggested that centriole and centrosome clusters in cancer cells might serve as a target or “bio-marker” for imaging and therapeutic agents, such as super-paramagnetic nanoparticles [7] [32] [169] [170]. More research is needed to explore this promising approach.

9. Summary and Conclusions

From the beginning of the 21st century, centriolar studies have and are becoming increasingly important in the minds of cell biologists, physicists, chemists and medical researchers. This is remarkable in that only a couple of decades ago centrioles were largely regarded as relatively unimportant, or even perhaps unessential for cell division.

The studies cited in this review, however, reveal that centrioles appear to be as important as DNA duplication in eukaryotic cell mitosis.

Here are the principal findings:

1) There are two reasons for this increased interest in centriole behavior: a) There is now better imaging technology revealing the importance of centriole activity; and b) Abherent centriole activity is seen to be the basis for tumorigenesis.

2) Centrioles are the only organelle in biological systems with virtually exact geometry: that is, straight-line perpendicular and circular. This near-perfect geometry is due to the parallel arrangement of nine blades of triplet microtubules forming the centriole cylinder, whose axis is perpendicular to its centriole mother’s axis.

3) The duplication and separation of a centriole pair occurs in the S-phase of the eukaryotic cycle, and at the same time as the DNA and chromosome duplication and separation.

4) New centriole development via microtubule growth is stimulated and regulated by a collection of proteins whose complete number and roles are not yet fully known.

5) Of all the proteins involved in microtubule development, Plk4 (polo-like kinase 4) appears to be the most prominent.

6) An excess or dearth of one or more of the major proteins involved in centriole duplication can lead to structural errors resulting in cell death or aggressive cell development and tumorigenesis.

7) Virtually all cancer cells have supernumerary, or multiple, centrioles. These multiple centrioles tend to cluster together [103]-[105] [171] [172].

8) A cluster of centrioles in a cancer cell is likely to produce a greater magnetic field than a single pair of centrioles in a normal cell. Evidence of this increased magnetism of centriole clusters is seen in increased electro-

magnetic activity of breast cancer cells which can even be measured externally [106]-[108] [171] [172].

9) An increased magnetic field about a centriole cluster in a cancer cell is a “biomarker” or target for tumor imaging and therapy.

These findings provide a documented oasis for additional studies—particularly in the area of cellular electromagnetic properties and their potential use for tumor imaging and therapy.

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