BioCore Exploring Scientific Community

International Journal of Biotechnology and Bioengineering

Review Article ISSN 2475-3432

Polo-like Kinase Four (Plk4) and Cancer

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Abstract

The paper states that the insertions of Polo-like Kinase 4 (Plk4) into the centrosome forms the basis for construction of new centrioles during the time when a cell is about to divide (mitosis). If the inserted amount of Plk4 is too little, the cell will die instead of dividing. Alternatively, excessive Plk4 insertion can produce extra centrioles ultimately leading to tumorigenesis and cancer. Therefore, in order for normal cell division and duplication to occur, the amount of Plk4 inserted needs to be carefully controlled.

The paper also provides a review of centriole construction and geometry as a basis for Plk4 study. The paper is therefore self-contained: that is, a general review ending with a focus on Plk4.

Keywords: Plk4, Centriole, Microtubules, Dimer, Chromosome, Tumorigenesis

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Citation: Ronald L. Huston (2020), Polo-like Kinase Four (Plk4) and Cancer. Int J Biotech & Bioeng. 6:2, 53-59

Received: January 23, 2020

Accepted: February 08, 2020

Published: February 29 , 2020

Introduction

It has long been known that cancer cells have an excess number (a "supernumerary" number) of centrioles[1-17]. On the contrary, normal cells have only a pair of centrioles. From afar, a centriole appears to be a short hollow cylinder (approximately 400nm in diameter and 500nm long). Centrioles appear in pairs with perpendicular axes. It is also known however, that it is not the cancer cells (the tumor cells) which initiate the growth of the supernumerary centrioles, but instead it is the supernumerary centrioles which cause the growth of the tumor of cancer cells.

Therefore, a tumor occurs due to an excess of centrioles in a cell instead of the tumor causing the excess of centrioles. In the following paragraphs, we discuss the duplication of cells and specifically the development of cancer cells.

Overall Cell Description[18, 19]

See Figure 1. Two items in the figure: the centriole and the nucleus are important in the sequel of the paper. The remainder of the items (the "cytoplasm") are germane to the kind of cell but not important in our paper.

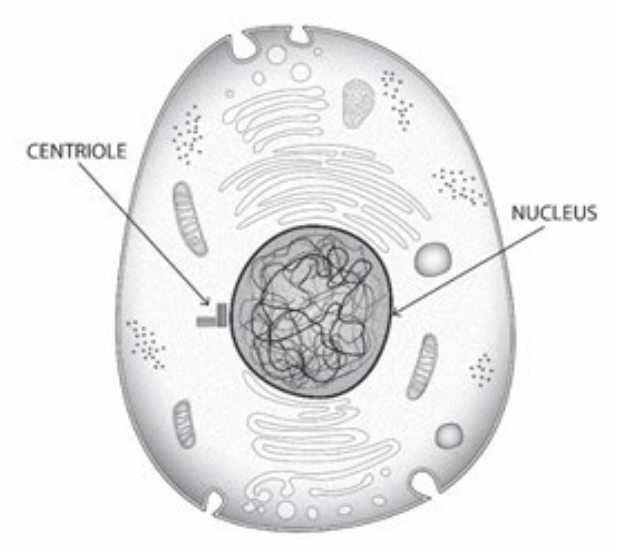

Figure 1: A Cross-Section Representation of a Human Cell

Centrioles[20 – 23]

Observe in Figure 1, the centrioles on the side of the nucleus. The centrioles are integral to cell division and then duplication. Figure 2 provides a sketch of a centriole.

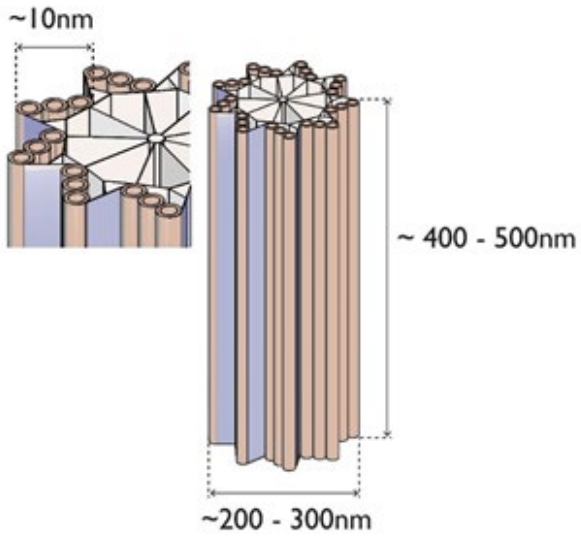

Figure 2: Sketch of a Centriole

From afar, a centriole appears to be a hollow cylinder approximately 200 to 300 micrometers (µm) in diameter, 400 to 500 µm in length, with wall thickness of approximately 10 µm. However, a closer look shows that a centriole is composed of nine blades of microtubule triplets (microtubules are discussed in the next section). The reason for nine blades instead of some other number is not known to this writer. Although the sketch in Figure 2 is that of a single centriole, centrioles always appear in pairs as illustrated in Figure 3.

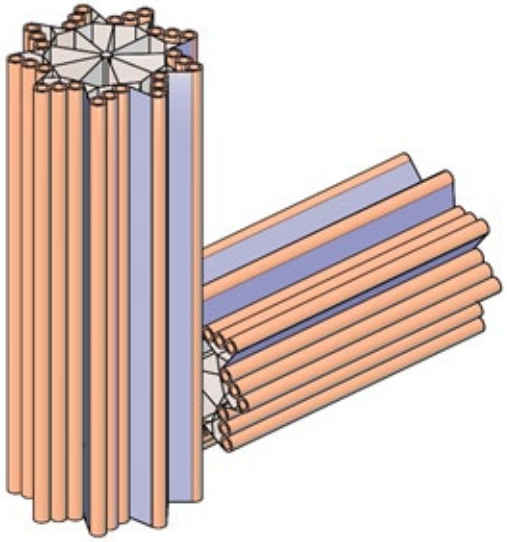

Figure 3: A Centriole Pair

Observe in Figure 3 that the centrioles in the pair have perpendicular axes and that the shorter one is at the base of the longer one. Figure 1 also shows the pair. Observe further in Figure 3, how the microtubule triplets form inclined blades.

The centrioles have the ability to duplicate themselves, the only such organelle with that capability (aside from DNA). This duplication occurs with the attraction of "Plk4" (a protein known as polo-like kinase 4) to the base of one of the centriole's blades. Plk4 is the principal subject of this paper and is described in a subsequent section. Together with the development of microtubules, Plk4 is the base of a new centriole.

Microtubules[24]

Microtubules are long, flexible cord-like structures composed of alternating α and β tubulin. These tubulins are members of a larger tubulin family.

For our modelling purposes, α and β tubulin may be modeled as being approximately cubical. All sides are approximately 5µm, as represented in Figure 4. They are the elements of a microtubule.

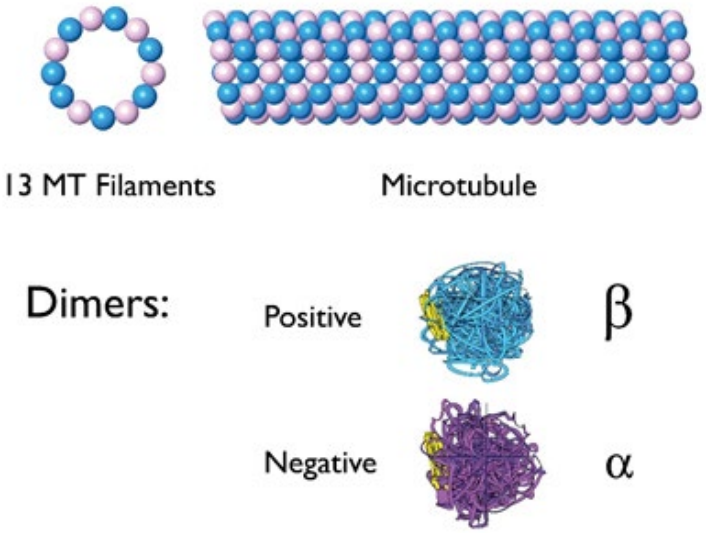

Figure 4: A Representation of α and β Dimers of a Microtubule

As seen in Figure 4, the α and β tubulin are usually connected and known as a "dimer". Dimers, connected end-to-end, form the microtubule.
The α end of the dimer is deemed to have a negative charge. Therefore, the β end has a positive charge. This means that the distal end of the microtubule has an accumulated positive charge.
The proximal end of the microtubule originates at the centrosome, the region containing the centrioles. The centrosome is therefore known as the microtubule organizing center, or "MTOC".

The microtubule is not static relative to its surrounding. Instead, it is continually moving. The dimers at the distal end fall away, thus shortening the overall microtubules length. Therefore, the microtubule is continually getting longer and shorter.
When a microtubule is shortening, this shortening is known as a "catastrophe". When it is getting longer, it is known as a "rescue".
An endwise look at a microtubule shows it to be hollow, with an outside diameter of approximately 25 µm, and an inside diameter of approximately 15 µm, as in Figure 5.

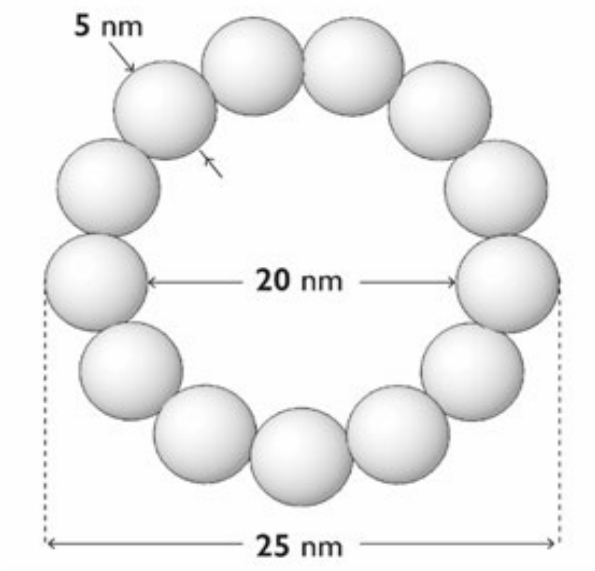

Figure 5: Representation of End-View Dimensions of a Microtubule

Chromosomes[25]

The centrosome, together with the centrioles, is the principal organelle in cell division. Figure 6 provides a sketch of a chromosome.

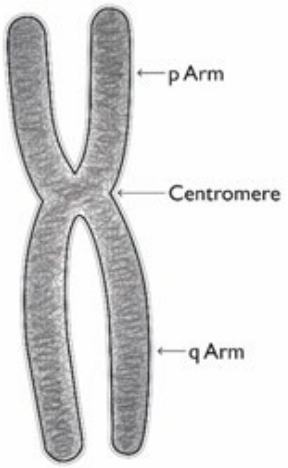

Figure 6: Sketch of a Chromosome

The chromosome is generally symmetric about it long end. It contains the DNA which duplicates itself during cell division (at the same time that the centrioles are duplicating).

During cell division (mitosis), described in the next section, the chromosome emits strands known as "kinetochores", analogies to microtubules, the kinetochores seek to connect with the microtubules to produce forces for cell separation. The separation occurs along the length of the chromosome, so the chromosome behaves like a "zipper", allowing the cells to divide.

Cell Division and Duplication ("Mitosis")[25]

Cell Division followed by cell duplication is one of the most fascinating subjects in all of biology. Referring back to Figure 1, observe again the centrioles, lying adjacent to the nucleus. Recalling that the centrioles have the ability to duplicate themselves, they duplicate when the cell is about to divide itself. Figure 7 illustrates the manner of this centriole duplication and division.

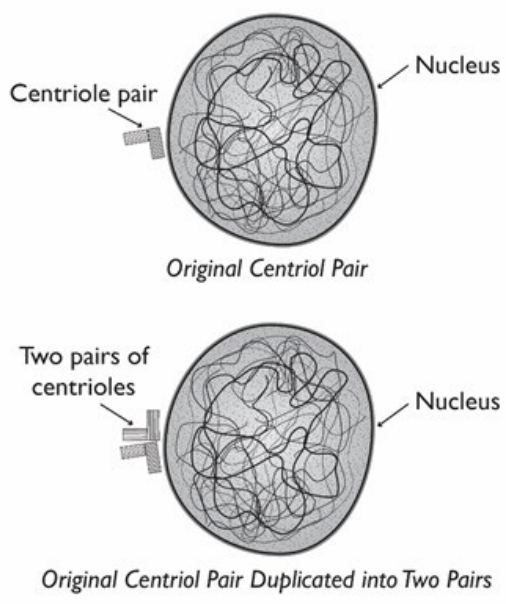

Figure 7: Centriole Pair Duplicated into Two Pairs

Following the duplication, the newer of the two pairs of centrioles migrates about the nucleus to the diametrically opposite side as illustrated in Figure 8.

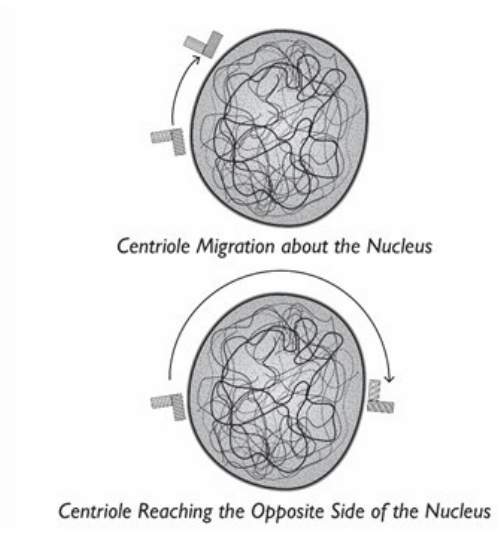

Figure 8: Migration of a Centriole about the Nucleus

Once the centrioles are on diametrically opposite sides of the nucleus, they become surrounded by electron dense proteins forming mounds known as the centrosomes. The centrosomes then emit microtubules spreading out about the nucleus. At the same time, the chromosomes emit kinetochores seeking to connect with the spreading microtubules. Once connection occurs, cell duplication forces arise which eventually pull the nucleus apart. Figure 9 represents the pulling apart of the nucleus.

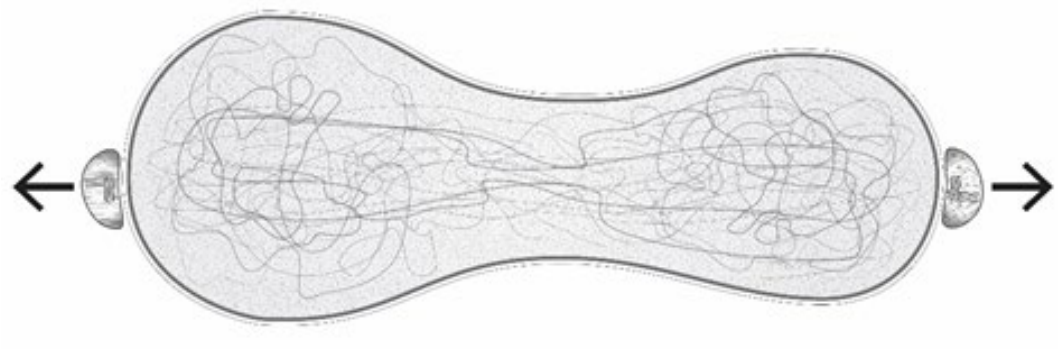

Figure 9: Stretching the Nucleus Toward Separation

General Mechanics of Centriole Duplication (Including Plk4)[20]

Just before a new centriole is created, near the base of an existing centriole, a protein known as "acylation", or (AsP), attaches itself near the base of one of the microtubules of an existing centriole. Plk4 then attaches itself to the AsP. The Plk4, together with γ-tubulin, then recruit α and β-tubulin as structural elements for a new microtubule – and then a new centriole.

Description of Plk4[26, 27]

D. Takao, et al, provide a description of Plk4 (Polo-like kinase 4) in References 26 and 27. They state that Plk4 resembles a pearl necklace that is a set of loosely connected beads. These beads are inserted near the base of an existing centriole for the creation of a new centriole. The exact number of beads is important: If there are too few beads, a centriole base will not occur and a new centriole will not form. If alternatively, there are too many beads, more than one centriole could be created. As noted earlier, extra centrioles produce tumors.

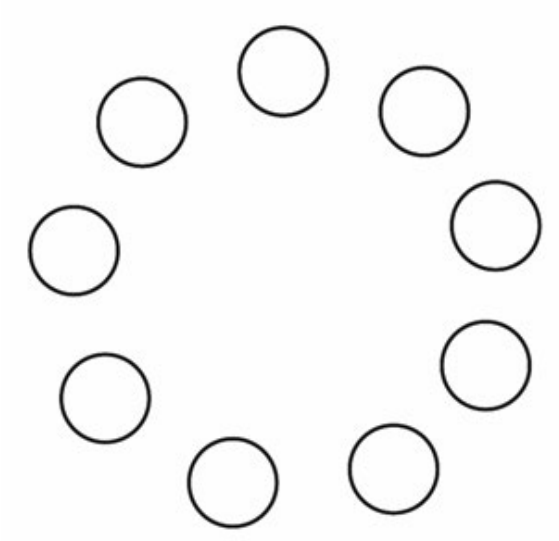

Figure 10: The Base of a Newly Formed Centriole

Discussion

Of all the cellular proteins, Plk4 is the most important in the creation of centrioles. Plk4 has the shape of a bead connected necklace. Its purpose is to deposit beads into the centrosome. These beads then form a ring – the base of a newly formed centriole. Figure 10 provides an illustration. If too few beads are sent, the cell will die. If too many beads are sent, extra centrioles will be created leading to tumorigenesis.

Acknowledgements

Partial funding support for the research has been generously provided by the Schafer for centrioles research, and is sincerely appreciated.

Authors' contributions

All authors have read and approved the final manuscript.

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