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Review

p53, cyclin-dependent kinase and abnormal amplification of centrosomes

Kenji Fukasawa *

Molecular Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA

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ABSTRACT

Centrosomes play a critical role in formation of bipolar mitotic spindles, an essential event for accurate chromosome segregation into daughter cells. Numeral abnormalities of centrosomes (centrosome amplification) occur frequently in cancers, and are considered to be the major cause of chromosome instability, which accelerates acquisition of malignant phenotypes during tumor progression. Loss or mutational inactivation of p53 tumor suppressor protein, one of the most common mutations found in cancers, results in a high frequency of centrosome amplification in part via allowing the activation of the cyclin-dependent kinase (CDK) 2–cyclin E (as well as CDK2–cyclin A) which is a key factor for the initiation of centrosome duplication. In this review, the role of centrosome amplification in tumor progression, and mechanistic view of how centrosomes are amplified in cells through focusing on loss of p53 and aberrant activities of CDK2–cyclins will be discussed.

Contents

1. Basic biology of the centrosome, and its relevance to cancer

The centrosome is a small non-membranous organelle (1–2 μm in diameter) usually found at the periphery of nucleus during interphase, and its primary function is to nucleate and anchor microtubules. The centrosome in animal cells consists of paired centrioles, and surrounding electron dense materials known as pericentriolar material (PCM) (Fig. 1a). The centrioles in the pair are structurally different from each other; one with a set of appendages at the distal ends (mother centriole) and another without them (daughter centriole), and these appendages are believed to play a role in the microtubule anchoring activity [1]. The PCM is composed of a number of different proteins, and the protein composition of the PCM is highly dynamic: some PCM components reside at the centrosome permanently, while some transiently localize to the centrosome during the cell cycle.

In mitosis, two centrosomes form spindle poles, and direct the formation of bipolar mitotic spindles (Fig. 1b). Because formation of proper mitotic spindles is essential for the accurate chromosome segregation into two daughter cells during cytokinesis, two, and only two centrosomes are needed in mitosis. Thus, numeral integrity of centrosomes is carefully controlled, and abrogation of this control results in abnormal amplification of centrosomes (presence of >2 centrosomes). Centrosome amplification leads to aberrant mitotic spindle formation with more than two spindle poles, and subsequent chromosome segregation errors. Cells with amplified centrosomes often form tripolar mitotic spindles, and these cells can undergo cytokinesis (Fig. 2b). Some daughter cells from the tripolar division are viable, yet suffer severe aneuploidy [2]. When the mitotic spindles with more than three poles are formed, cells fail to undergo cytokinesis [2], and become either bi-nucleated or large mono-nucleated

* Tel.: +1 813 745 2824; fax: +1 813 979 7265.
E-mail address: kenji.fukasawa@moffitt.org.

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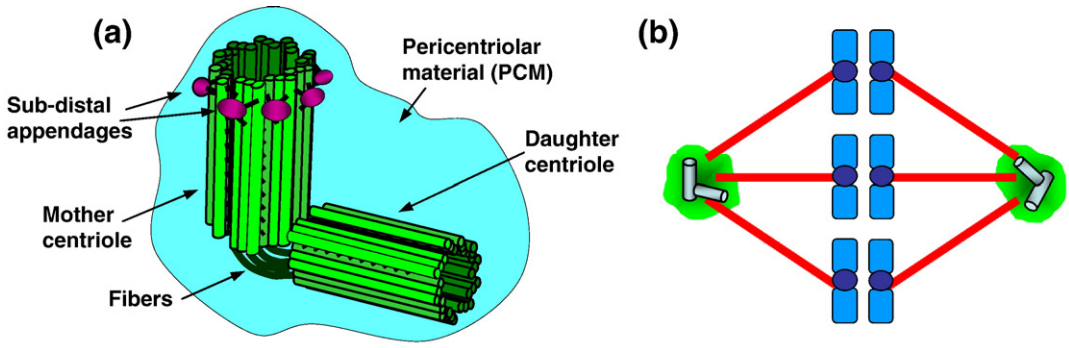

Fig. 1. Structure and function of centrosomes. (a) The basic structure of the centrosome. (b) During mitosis, two centrosomes become the spindle poles, directing the formation of bipolar mitotic spindles.

cells (Fig. 2c). Since failure to undergo cytokinesis triggers the checkpoint response involving the p53 tumor suppressor protein via a mechanism that is poorly understood [3], the cells become arrested in the presence of p53, and eventually undergo cell death. In contrast, in the absence of p53 or the p53-depependent checkpoint function, those bi- or large mono-nucleated cells continue to cycle, and many of them experience repeated cytokinesis block, become very large multi (>2)-nucleated polyploid cells, and eventually undergo cell cycle arrest/cell death [4]. However, some cells resume cytokinesis likely through the formation of pseudo-bipolar spindles (see below). Since the presence of polyploid chromosomes is known to destabilize chromosomes [5], polyploidy resulting from cytokinesis block due to centrosome amplification further promotes the chromosome instability. It is important to note that centrosome amplification does not always result in formation of multi-polar spindles. Amplified centrosomes frequently form "pseudo-bipolar" spindles by positioning on a bipolar axis (Fig. 3a), resulting in mitotic spindles which structurally resemble the "true" bipolar spindles organized by two centrosomes. Although the mechanism underlying this phenomenon known as "centrosome clustering" is not fully understood, the microtubule motor protein dynein has been shown to play an important role [6]. Cells with "pseudo-bipolar" spindles appear to undergo normal cytokinesis without any chromosome segregation errors. However, even these "pseudo-bipolar" spindles often encounter a risk of chromosome segregation errors (Fig. 3b): one

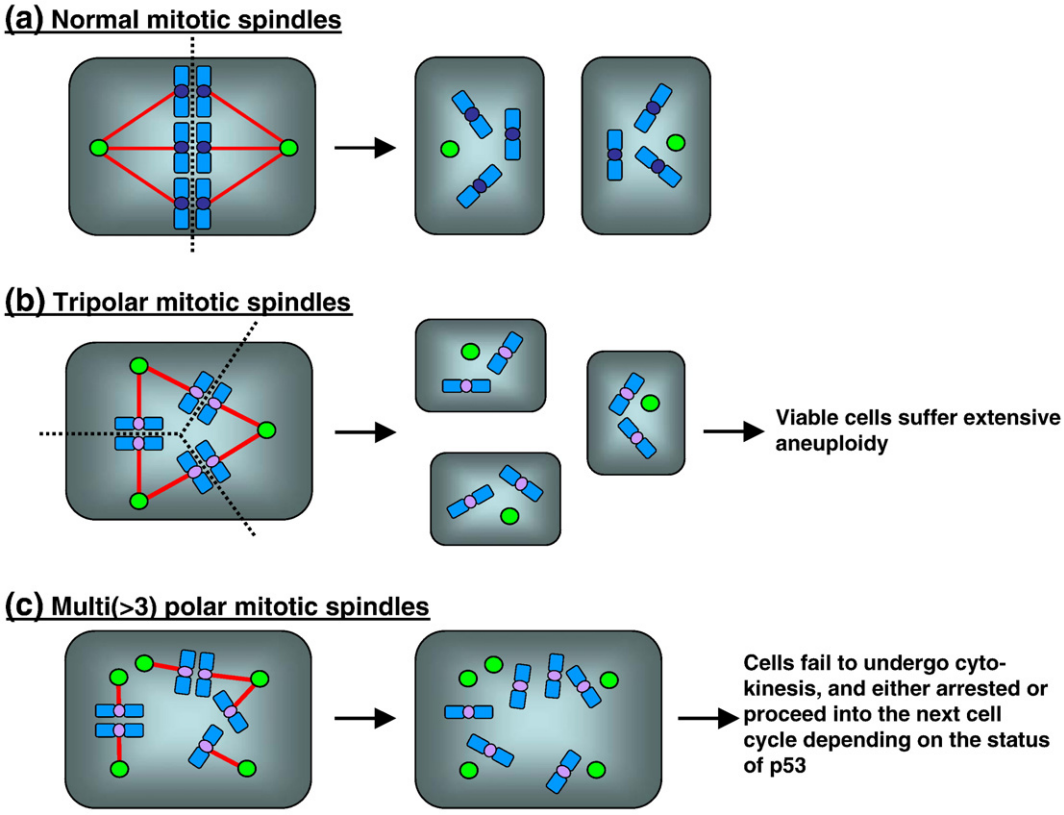

Fig. 2. Mitotic defects associated with numeral abnormalities of centrosomes. In normal mitosis, two centrosomes direct the formation of bipolar mitotic spindles (a). In the presence of amplified centrosomes, cells frequently form multiple (>2) spindle poles. (b) Tripolar spindles can undergo cytokinesis, and some daughter cells are viable, yet suffer severe aneuploidy. (c) Cells with spindles with >3 poles fail to undergo cytokinesis in most cases, becoming either bi-nucleated or large mono-nucleated cells. Because of the p53-dependent checkpoint response to cytokinesis failure, the cells become arrested in the presence of p53, and eventually undergo cell death. In contrast, in the absence of p53, cells continue to cycle, and many of them become very large multi(>2)-nucleated cells and often undergo senescence-like arrest and cell death. However, some cells escape from continuous cytokinesis block, and become polyploid cells.