Mini Review

Atypical mitosis -a catastrophic transformation to cancer?

Abstract

In some abnormal cells, an excessive number of centrosomes can form more than two spindle poles that may orchestrate atypical mitosis, where the chromosome complement is pulled into three or more directions at anaphase, and then one cell divides into three or more daughter cells. In this review, we discuss several examples of atypical mitosis and mechanisms of atypical mitosis in cancer. Molecules involved in atypical mitosis are summarized. For more than one hundred years, since mitosis was found by Walther Flemming in 1870s, people have learned that cells can divide from one into two. However, in recent years, researchers found more and more evidences supporting that there are other kinds of atypical cell divisions, such as one cell divides into three, four or even more daughter cells at a time.[1–9] These atypical divisions are called tripolar and multipolar mitosis. Atypical mitosis has been observed in common cancers, virus-infected cells, the placenta and in the early embryos.[10] Dysfunctional multipolar mitotic figures usually indicate neoplasia in histopathological examination. Although it's a common sense nowadays that cancer is essentially a disease of mitosis, it is still not clear whether atypical mitosis is the cause or a consequence of cancers. However, atypical mitosis often randomly distributes DNA into daughter cells, leading to genomic instability. So it's very necessary to put an emphasis on this promising and underdeveloped topic for cancer research. This review will give an overall summary to the previous studies for atypical mitosis and focus on the link between atypical mitosis and cancer.

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Tripolar mitosis

As shown in Figure 1A, JCV infected astrocyte can form tripolar spindle. Although the author of this figure classified it as a nonneoplastic astrocyte, several studies since 2000 have suggested that JCV is linked to cancer, as JCV has been found in malignant colon tumors. Pictures in Figure 1 indicate static anaphase timepoint during tripolar mitosis of different tissues. Tripolar mitotic spindles can be seen in Figure 1A, B and C. However, it's not enough to prove the tripolar mitosis if we only have static evidence of this process because people may doubt whether cells like Fig.1 can really divide into three daughter cells or not and whether the daughter cells will be viable or not. Our own and other studies further illuminated the tripolar mitosis using living cell micro-imaging (Figure 2). These recording data show direct evidence that cancer cells can undergo tripolar mitosis. Different from Fukasawa's description,[11] no cell death of the daughter cells from these tripolar mitoses was reported.

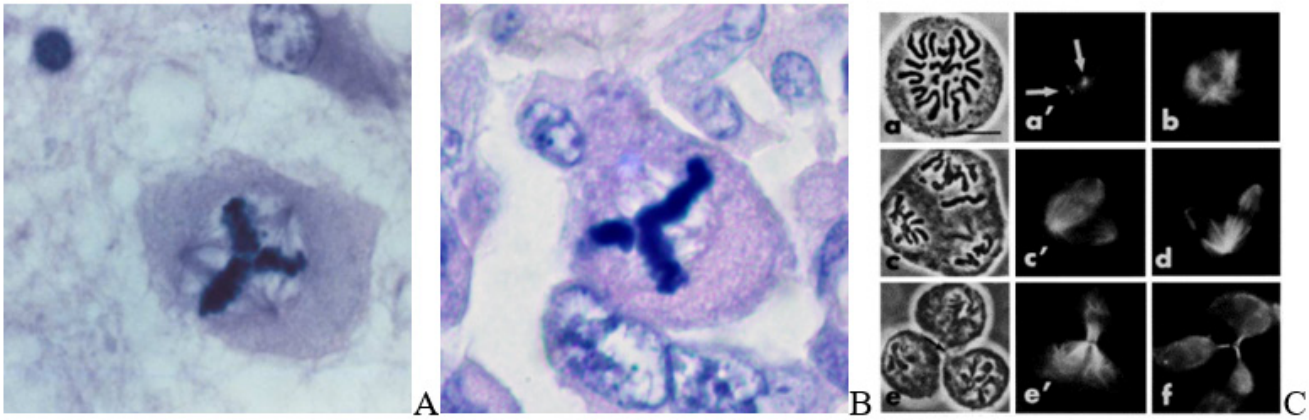

Figure1 Typical tripolar mitotic figures. A) A tripolar dividing astrocyte, presumably infected with John Cunningham virus (JCV), in a patient with progressive multifocal leukoencephalopathy (Hematoxylin and eosin, X1500).[4] B) Tripolar Mitosis from a case of metaplastic (sarcomatoid) carcinoma of the breast (Ed Uthman). C) CHO (Chinese hamster ovary) cells during tripolar division.[3]

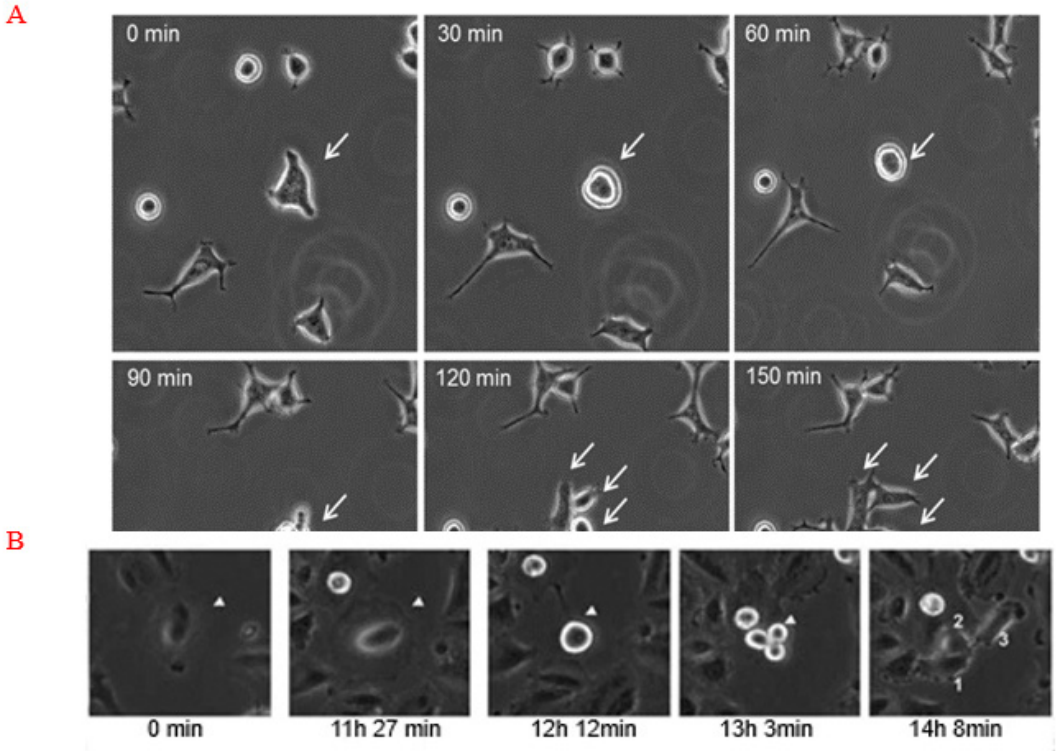

Figure 2 Typical living imaging of tripolar mitosis. A) Tripolar mitosis in cultured Clone A colon carcinoma cell line (our unpublished data). B) Tripolar mitosis of A549 cells (adenocarcinomic human alveolar basal epithelial cells).[6]

Multipolar mitosis

David Gisselsson et al reported multipolar mitosis in WiT49 cells (Figure 3).

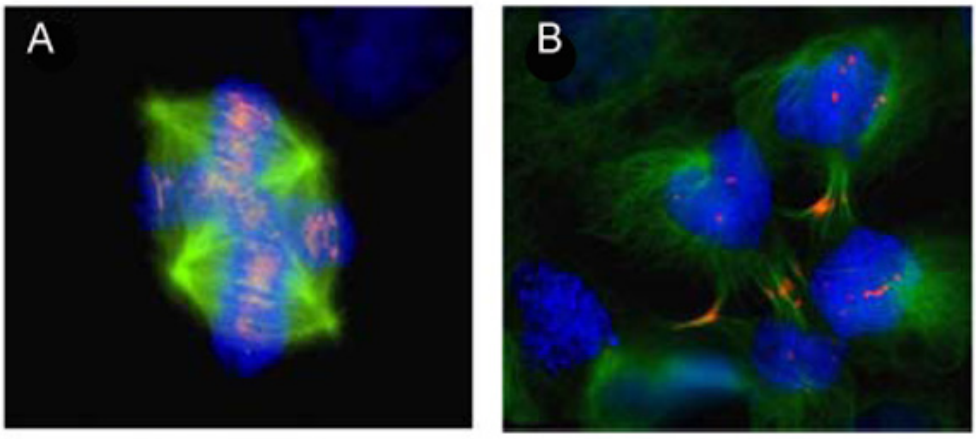

Figure 3 A) multipolar metaphase, and B) multipolar ana-telophase of WiT49 (anaplastic Wilms tumor) cells.[7]

Causing factors of atypical mitosis

Radiation, mitotic toxins and virus are most reported causing factors of atypical mitosis. Radiation is a physical factor can cause DNA damage and induce centrosome amplification, which can result in the formation of multipolar mitotic spindles. High dose of irradiation leads to mitotic catastrophes and consequent cell death.[12] Chemicals are another category of factors causing atypical mitosis. Natural compounds vinblastine and colchicine has been found to be microtubule inhibitors[13,14] and can induce atypical mitosis.[15] These microtubule inhibitors and more mitotic toxins have been used in clinical trials for cancer treatment.[13] Virus and cell fusion are biological factors affecting atypical mitosis. Certain viruses (human adenovirus type 5, human papillomavirus (HPV), hepatitis B etc.) can induce mitotic errors.[10] Multipolar mitoses frequently have been found in lesions caused by HPV.[16] In HeLa cell line, a study found

that about 4% cell fusion led to tripolar mitosis and these cells were viable and had second trivisions and divisions.[17] These causing factors of atypical mitosis are potential carcinogens and better understanding their mechanisms in atypical mitosis will benefit cancer treatment.

Mechanisms of atypical mitosis in cancer cells

The proper attachment and alignment of the chromosomes, which occurs during prometaphase, is the defining aspect of mitosis to keep the fidelity of genome inheritance.[18] However, in cancer cells, an excessive number of centrosomes can give rise to supernumerary spindle poles that may orchestrate a multipolar mitosis, where the chromosome complement is pulled into three or more directions at anaphase. Since the first observations of multipolar mitosis in carcinomas by Hansemann in 1890, multipolar spindles and centrosomal abnormalities have been reported in most common Cancers, such as HEK293 (human embryonic kidney cells), Clone A (colon cancer), MDA-MB-231(breast cancer), WiT49 (Wilms' tumor) cells, HeLa (cervical cancer) cells etc. Some studies have also indicated that multipolar mitosis may be a useful marker for adverse prognosis in tumor disease.

Perturbations in centrosome number and structure have been linked to disturbed function of several cell cycle signalling pathways, such as inactivation of the TP53, RB1, BRCA1, BRCA2, and CDKN1A proteins, as well as AURKA over-expression. Through CCNE and PLK4, centrosomal disturbances have also been associated with exposure to viral carcinogens, most notably high-risk papilloma viruses.[7] Like some cell biologists hypothesize that telomeres control how many generations that somatic cells can divide, there are some polarity control factors in a cell to control its polarity during mitosis. Quite lots of cell polarity proteins, which includes serine/threonine protein kinases, atypical protein kinase C, CRB3, SCRIB, DLG, LLGL, Vang-like protein, PRICKLE1, Wnts, receptor tyrosine-like orphan receptor 2, and FATs, have been found abnormal in multiple cancers.[19]

Polyploid cells with more than two sets of chromosomes are found abundantly in tissues such as the liver, skeletal and cardiac muscle, and bone marrow,[20] which have high regenerative capacity. Some studies propose that polyploids would benefit regeneration by producing injury-resistant, viable progeny.[21] They demonstrate that polyploidization is a cellular mechanism to increase proliferation. At least numerically, multipolar-mitosis is more effective in proliferation than division. However, polyploidization is often a stress response and creates genetic diversity for better stress adaptation. Chromosome segregation during ploidy reduction should not be random but faithful. When chromosome segregation during ploidy reduction turns unfaithful, the increased cell proliferation could become a major driver of tumorigenesis. Unfortunately, multipolar mitoses have mostly been reported in malignant cells,[21] as multipolar-mitoses are more malignant in tumor growth than division, and they genetically keep creating resistance to medication.

Questions need to be answered

It was proposed that loss of control over cell polarity can disrupt normal cell function and lead to cancer.[19] However, it's still short of cell model to prove whether atypical mitosis contributes to initiation and progression of cancer. Except CHO cells, other reported cell lines with tripolar mitosis are cancer cells. Is tripolar mitosis an important step in canceration of a non-cancer cell to a cancer cell? What is the initial event to cause tripolar mitosis? What are the key molecules in controlling mitosis polarity of the cell? During regular mitosis, chromosome congression is already an example of a 'chicken and egg' scenario, with no clear indication of whether bi-orientation is necessary for congression or if chromosome congression promotes bi-orientation.[18] Another challenging question is, during the tripolar mitosis, how does the chromosome align in 120° angle at the spindle equator? These questions still need further study to answer.

Acknowledgments

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

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