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Review Paper

A Review on the Probable Reasons and Effects of Abnormal Mitotic Cell Division in Animal

Riyad Hossen

Lecturer, Faculty of Biosciences, Department of Botany, University of Barisal, Bangladesh.

ABSTRACT

Abnormalities in mitosis refer the deviations of normal mitotic cell division. Many different diseases are occurred in animal due to different types of mitotic abnormalities. Researchers successfully indentified some specific reasons for these types of abnormalities. Some cancers in human and mice is the result of such type of diseases which caused by spindle orientation defects and leads to an imbalance of symmetric and asymmetric cell division. A number of gene deletions or mutations classically associated with impaired spindle orientation in mammals and caused ciliopathies. At the current time scientists also suggest that only spindle orientation defects are not main causes of these diseases it also associated with gene mutations and the mutations linked with defects orientation. Mutant LA is another important causal agent for mitotic abnormality which is responsible for Hutchinson-Gilford Progeria Syndrome. Moreover, trisomy and tetrasomy are produced from abnormal segregation of chromosomes due to multipolarity in mitosis which lead to cancers in human. Gisselsson et al give a model for cancers with trisomies by working on Wilms tumor and this model shows how multiple trisomies can produce in tumor cells maintaining accurate sister chromatid separation at metaphase–anaphase transition. Moreover, micronucleus is formed from a lagging chromosome or fragment of a chromosome that fails to incorporate into the main nucleus and causes cancers in animal.

Key words: Abnormal mitosis, cell division, multipolar mitosis, non-disjunction.

INTRODUCTION

Mitotic cell division is the process by which a parent cell produces two daughter cells which are genetically identical to the parent cell. [1] It is a part of the cell cycle when replicated chromosomes are separated into two new nuclei and it is preceded by the S stage of interphase often followed by cytokinesis, which divides the cytoplasm, organelles and cell membrane into two new cells containing roughly equal shares of these cellular components. [2] Mitosis and cytokinesis together define the mitotic (M) phase of an animal cell cycle. After growth, mitosis allows for continual construction and repair of the organism. [3] The human body experiences about 10 quadrillion cell divisions in a lifetime. [4] It occurs only in eukaryote having five distinct stages (prophase, prometaphase, metaphase, anaphase, and telophase). When any alterations or errors occur in the stages or in the cytokinesis associated with definite cell cycle is indicated as abnormal mitosis or abnormalities in mitosis. Producing three or more daughter cells instead of normal two is an example of mitotic abnormalities (tripolar mitosis or multipolar mitosis). [5] In human, abnormalities can occur during early embryonic development. [6] This type errors can create aneuploid cells that possess few or many of one or more chromosomes which associated with cancer. [7] Some cases sister chromatids fail to separate during anaphase (non-disjunction) also creates abnormal daughter cell having unequal

number of chromosomes. One daughter cell receives both sister chromatids from the nondisjoining chromosome and the other cell receives none. So by the way former cell gets three copies of the chromosome (condition known as trisomy) and the latter will have only one copy (condition known as monosomy). They fail to complete cytokinesis and retain both nuclei in one cell during non-disjunction and form binucleate cells. [8] When the movement of one chromatid is impeded during anaphase caused by a failure of the mitotic spindle to properly attach to the chromosome is called Anaphase lag. [9] The lagging chromatid is excluded from both nuclei and is lost, so one of the daughter cells will be monosomic for that chromosome. Endomitosis is also consider as an abnormality of mitosis in which cells replicate their chromosomes during S phase and enter, but prematurely terminate in the mitosis. Instead of being divided into two new daughter nuclei, the replicated chromosomes are retained within the original nucleus. [10] Besides, these types of errors, other errors during mitosis can induce apoptosis (programmed cell death) or cause mutations and certain types of cancer can arise from such mutations.

Spindle orientation defects associated with mutations

Correct alignment of the mitotic spindle during cell division is very important for cell fate determination, tissue organization, and development. Mutations causing brain diseases and cancers in human and mice have been associated with spindle orientation defects and these defects are thought to lead to an imbalance between symmetric and asymmetric divisions causing reduced or excessive cell proliferation. The orientation of the spindle and the position of centrosomes determine the orientation of the division plane. [11] During cell division the orientation of the division plane usually defines the content, the position, and the fate of daughter cells within tissues. [12] In polarized cells, the division plane orientation determines whether a cell undergoes symmetric or asymmetric cell division. Given the correlation between spindle orientation defects and the appearance of neurological diseases and cancers, it is tempting to postulate that the loss of spindle orientation control is at the origin of these pathologies. Although neurological disorders would be caused by a premature shift from symmetric to asymmetric divisions and consequent reduction in neuron number, cancers would be the results of uncontrolled symmetric and thus proliferative cell divisions. This would reflect the fact that the controlled balance of symmetric or asymmetric cell divisions is essential for development and tissue homeostasis and that the consequences of spindle disorientation strongly depend on the biological context. A causal link between spindle orientation defects and carcinogenesis has been made in *D. melanogaster*. [13,14] Besides, a number of gene deletions or mutations classically associated with this type of disorder like ciliopathies in mammals and they also impair spindle orientation, raising the possibility that spindle orientation defects play an aggravating role in ciliopathies. [15,16] Furthermore, it is difficult to establish a direct causality because mutations affecting spindle orientation can have tissue specific effects. At present it is therefore impossible to determine whether only spindle orientation defects are a cause, an aggravating factor, or just a by-product of these diseases. One way to address this question would be to test whether rescuing spindle orientation defects by reintroducing a separation of function mutant suppresses the corresponding pathology. The C-terminal truncation of ASPM gene in mice is an example for this approach. [17] This truncation does not disrupt spindle orientation, but still leads to microcephaly, indicating that only spindle orientation defects are not essential for primary microcephaly. Another possibility would be to introduce a deletion in a second gene to rescue the spindle orientation defects. For example, to counteract a VHL mutant that

cannot stabilize microtubules, one could delete a gene that destabilizes microtubules, like stathmin-1. [18] Stathmin-1 is an oncogene, but knock-out mice are viable with only minor sociological defects. [19,20] Therefore, one could test whether stathmin-1 deletion suppresses both spindle defects and cancerogenesis in such a background. In the future it will be necessary to closely compare these phenotypes and to combine both mutants for epistasis analysis to investigate the outcome and better understand the role of spindle orientation in this process. However, before drawing strong conclusions, these mice should be analyzed for spindle orientation defects in other tissues. It will be also important to investigate if spindle orientation defects can play an aggravating role in cancer by combining spindle orientation defects with cancer mutations. Ideal cancer mutations could be loss of the tumor suppressor p53, or over expression of the Ras oncogene. [21] The combinations of mutations will be interesting even if spindle orientation defects are sufficient to induce tumor formation, as they can reveal whether spindle orientation defects lead to an earlier onset of tumor formation and/or accelerate the progression of the tumor. Overall, such investigations will allow one to test the attractive hypothesis that spindle orientation is a critical process for abnormal mitotic division or uncontrolled mitotic division and cause of tumorigenesis. It also indicates that the probable reasons behind this are spindle orientation defects associated with mutations.

Alterations in mitosis by mutant

Alterations in mitosis caused by a mutant named LAΔ50/progerin is responsible for abnormal mitotic cell division. The mutant LAΔ50/progerin is also called by mutant LA. The LAΔ50/progerin specially is the result of mutations in the gene encoding nuclear lamin A which cause the premature aging disease Hutchinson–Gilford Progeria Syndrome(HGPS). The patients usually die at an average of 15 years of age from heart attacks or strokes. Lamins are intermediate filament proteins located in the nuclear lamina and throughout the nucleoplasm. This mutation introduces a splice site, resulting in the expression of a mutant LA (LAΔ50/progerin) that is missing or deleting 50 aa near its C terminus according to Thomas Dechat *et al*. in 2007. [22] They demonstrated that the deletion leads to a stable farnesylation and carboxymethylation of the mutant LA. For conducting the whole research they used the techniques including cell culture, lamin expression, synchronization, preparation of mitotic cell extracts, and characterization of farnesylation, carboxymethylation, immunofluorescence and immunoblotting. They collected the dermal fibroblasts from progeria patients and grew in a control conditions. After completing lamin expression and synchronization steps, they prepared mitotic cell extract for performing more next steps of their research. They found that the modifications by gene mutation cause an abnormal association of mutant LA with membranes during mitosis, which delayed the onset and progression of cytokinesis. Furthermore, they demonstrated that the targeting of nuclear envelope/lamina components into daughter cell nuclei in early G1 was impaired in cells expressing LAΔ50/progerin. In the cytoplasm the retention of nuclear components at earlyG1 in HGPS fibroblasts suggests that progression through the cell cycle is altered, which could affect the G1/S transition. To confirm this possibility, they examined the retinoblastoma protein (Rb) in HGPS cell nuclei, because it binds to LA and its hyperphosphorylated form (phosphoRb) is required for the G1/S transition. To be responsible for defects in the retinoblastoma protein(Rb)-mediated transition into S-phase the mutant LA also appears, most likely by inhibiting the hyperphosphorylation of retinoblastoma protein by cyclin D1/cdk4 (cyclin D1 is a cofactor of Cyclin-dependent kinase 4 cell division protein kinase 4). Their discovered

results provided insights into the mechanisms responsible for premature aging and also shed light on the role of lamins in the normal process of human aging and mitotic abnormalities. In interphase cells, the expression of LAΔ50/progerin leads to nuclear lobulation, thickening of the lamina, genome instability, DNA repair defects, changes in histone methylation, and loss of heterochromatin. An initial insight into changes in early G1 came from studies of HeLa cells expressing GFP-LAΔ50/progerin (GFP-tagged LAΔ50/progerin), in which this mutant protein is abnormally retained in cytoplasmic structures after nuclear assembly is completed. They described that with evidences LAΔ50/progerin is stably farnesylated/carboxymethylated and that this leads to its abnormal association with membranes during mitosis. This abnormality delays the onset and progression of cytokinesis and the targeting of nuclear envelope components to daughter cell nuclei in late telophase/early G1. A delay in the progression through cytokinesis also supported by Cao *et al.* HeLa cells expressing GFP- LAΔ50/progerin show increased mitotic index, compared with those expressing GFPLA. These delays undoubtedly have a negative impact on the spatially and temporally regulated sequence of events that represent the hallmarks of normal cell cycle progression. They also proved that the HGPS phenotype may not only be attributable to the abnormal farnesylation of LAΔ50/progerin, but also to the 50 aa that have been deleted near its C terminus. So their observations also extend the previous studies that link normal and accelerated aging to mitotic defects, including impaired chromosome segregation and increases in binucleate and multinucleate cells. They explained that some mitotic cells expressing high levels of LAΔ50/progerin show significant mitotic defects resulting in an even more delayed cytokinesis and in binucleate cells. The ultimate results of their investigations may help to explain the increased numbers of binucleate cells found in HGPS fibroblasts and along with the data presented in the study, indicate that the abnormalities in mitosis, nuclear assembly, and progression through the cell cycle attributable to the expression of the mutant LA responsible for HGPS.

Multipolarity in mitosis

Multipolar mitosis is one of the recent discoveries and it's indicated as a mitotic abnormality which also a reason for chromosomal aberration in daughter cells. Trisomy is the most common type of chromosome aberration although some tetrasomy is also produced at the same way. This type of abnormal segregation of chromosomes at mitosis leads to cancers in human. The exact mechanisms how the trisomies are generated in tumor cells are largely unknown but some researchers suggested that dysfunction of the spindle assembly checkpoint (SAC) leads to an accumulation of trisomies through failure to correctly segregate sister chromatids in successive cell divisions. Moreover, some scientists also suggested that deficiency of the SAC or other key mechanisms controlling sister chromatid separation could promote the generation of trisomies in cancer cells through a continuously elevated rate of non-disjunction at metaphase–anaphase transition. Gisselsson *et al.* [23] showed that trisomic cells can occur even in the presence of a functional SAC through tripolar mitotic cell divisions in which sister chromatid separation proceeds in a regular fashion, but cytokinesis failure nevertheless leads to an asymmetrical segregation of chromosomes into two daughter cells. They showed it by working on Wilms tumor (WT) as a model for cancers with trisomies. Furthermore, their findings provide an experimentally validated model (Figure 1) about how multiple trisomies can produce in tumor cells maintaining accurate sister chromatid separation at metaphase–anaphase transition moment. By using FISH they monitored the segregation process of individual chromosomes in anatelophase

cells then this method they applied to WT which is a prototypical model for cancers. They found polysomies in the majority of cases with abnormal karyotypes having 62% trisomies and 16% tetrasomies. They determined the baseline rate of chromosome missegregation in short-term cultures from normal dermal fibroblast samples then they used cells from patients with mosaic variegated aneuploidy (MVA) syndrome with positive control of SAC deficiency. The rates of chromosome missegregation from MVA patients were more than 10-fold higher compared with normal fibroblasts. The anatelophase cells showing missegregation showed a bipolar orientation with two centrosomes under combined FISH and immunofluorescence observation of the MVA cases. They also examined three colorectal cancer cell lines and found multipolar anatelophase cells coordinated by multiple centrosomes which are similar with previous studies. Then they observed cells from five primaries WT and the WiT49 WTcell lines having hyper diploid-triploid karyotypes with trisomies. A significantly elevated rate of missegregation compared with normal fibroblasts was not observed in bipolar anatelophase configurations in WT cells. However, all examined WTs showed anatelophase cells in multipolar configurations. These cell divisions resulted in unequal copy numbers in sister nuclei at rates that were 16 to 128 times higher than those resulting from missegregation at bipolar mitosis. For more confirmation they did holographic time-lapse imaging of WiT49 cells. And they found many multinucleate single daughter cells with some normal daughter cells. The reason behind this phenomenon is chromosomes nevertheless segregated toward three poles, the latter mitosis resulted in the formation of one binucleate with one mononucleate daughter cell demonstrating that cells having undergone this type of cell division may proliferate further. Most of the cell divisions of this type showed a complete absence of kinetochore indicating that metaphase–anaphase transition had occurred through satisfaction of the SAC and they also showed that trisomies form in the binucleate daughter cells. For supporting their findings in an independent system they then turned to a human embryonic kidney cell line. They conducted transfection technique with an H2B-GFP construct allowing phase contrast and fluorescent imaging. The result is trisomic cells formed through tripolar division coupled to incomplete cytokinesis that strongly support the data from WiT49. Their sequential model predicts the highest probability for the acquisition of tetrasomies, as chromosomes already in a trisomic state would have a higher probability than disomic chromosomes for being involved in any subsequent missegregation, whereas they closely mirrored the ratios predicted by the tripolar mitosis-incomplete cytokinesis model. Furthermore, they also said that the spatial distribution of trisomic clones could be traced in each tumor. Their suggested model (Figure 1) may be of importance for the generation of trisomies in other tumors that frequently show multiple trisomies and is consistent with studies of allele dosages in pediatric high hyper diploid acute lymphoblastic leukemia, showing that hyperdiploidy most probably originates in a single aberrant mitosis and the study adds to several other arguing for the importance of centrosome dysregulation for the generation of aneuploidy. Therefore, it is unique in suggesting an empirically based mechanism directly linking supernumerary centrosomes and spindle multipolarity to trisomy formation.

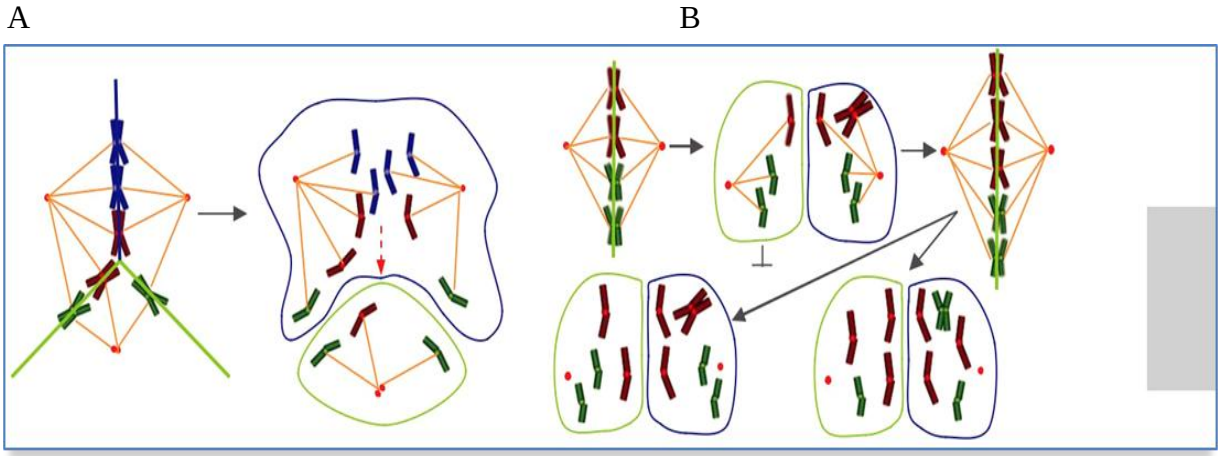

Figure 1. Proposed model for the generation of trisomies and tetrasomies (A) A tripolar nuclear division with amphitelic sister chromatid separation and segregation, followed by incomplete cytokinesis, will generate tetrasomies in one daughter cell (blue membrane, Right) for chromosomes (blue) of which both homologues are located on the metaphase axis (blue line, Left), along which the cleavage furrow fails to ingress completely (red arrow, Right), whereas trisomies will be generated in the same daughter cell for homologues (red) located on this axis and on either of the other axes (green lines, Left); disomies will be retained when both homologues (green) are present on the axes (green) along which cytokinesis is complete. (B) A bipolar mitosis with missegregation of one chromosome (red) will generate one trisomic and one monosomic daughter cell. Another missegregation event in the trisomic cell population involving the same (red) chromosome will result in tetrasomic and disomic daughter cells (Lower Left), whereas missegregation involving another chromosome will result in two trisomies (Lower Right).

Chromosome segregation errors

Micronucleus, a marker of chromosomal instability in aggressive cancers is one kind of very small nucleus which is formed from a lagging chromosome or a fragment of a chromosome that fails to incorporate into the main nucleus. [24] This is the result of chromosome segregation errors**.** When segregated sister chromatids de-condense and the nuclear envelope re-forms around them in telophase, the dispersed chromosomes or chromosome fragments also de-condense forming a small round nucleus with own nuclear membrane. They may be the footprint of chromosome missegregation that persists after mitotic exit and can be visualized in interphase. Moreover, DNA damage in micronuclei occurs in the subsequent interphase is a common phenomenon. The nuclear envelope around micronuclei is abnormal so its nuclear-cytoplasmic trafficking functions are defective, and the nuclear envelope may even undergo catastrophic collapse. The deficient nuclear-cytoplasmic trafficking prevents proper communication of the micronucleus with the rest of the cell, including propagation of the DNA damage signaling. Thus, DNA damage in micronuclei is unable to elicit a robust cellular DNA damage checkpoint response. [25] Failure of the DNA damage checkpoint allows cells with micronuclei containing damaged DNA to re-enter mitosis and also this is linked with a form of genomic instability called chromothripsis. [26,27] A chromosome within a micronucleus first undergoes defective replication or fails to repair DNA damage, then becomes fragmented as the chromosome condenses in early mitosis.

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