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From the Publisher's Desk

Welcome to Biotechnology Kiosk!

This issue includes a letter on the latest advances in Chromothripsis and genomic instability in cancer and editor picks on the positive effects of drugs on reducing obesity and affordable production of antibodies.

We hope our readers will enjoy reading these news and views on the current cutting-edge topics that include latest research breakthroughs in different areas of medicine and biotechnology.

We look forward to receiving your feedback. We do hope that you will enjoy reading this issue of Biotechnology Kiosk. Please do write to us with your comments. Your suggestions are always appreciated.

Dr. Megha Agrawal & Dr. Shyamasri Biswas.

Editors-in-Chief, Biotechnology Kiosk





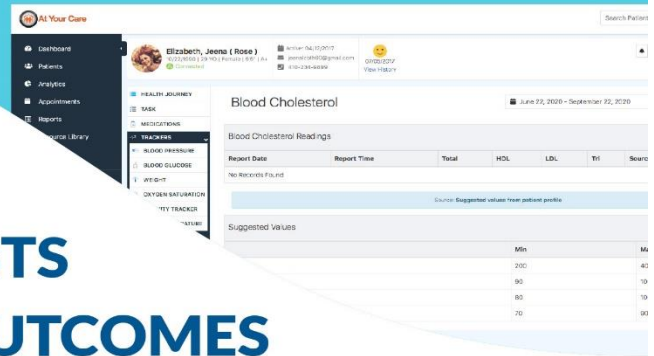
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Chromothripsis: A Cause of Genome Instability in Cancer

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Abstract

Cancer is a term given to uncontrolled cell growth, which is the result of accumulation of genetic changes during cell division. It can occur due to both genetic and environmental reasons. One such genetic cause of cancer discovered recently is known as Chromothripsis. It is defined as the fragmentation and rearrangement of chromosomes. Researchers are still trying to find the true mechanism underlying Chromothripsis. Two models have been significantly described; first one is the 'micronuclei hypothesis', which occurs as a result of chromosome mis-segregation during Mitosis. Second model is based on the 'telomere crisis', which occurs due to faulty telomerase enzyme and cell cycle checkpoint pathway. In this letter, we have tried to give brief information about the mechanisms behind Chromothripsis and their role in causing genome instability leading to cancer.

Keywords: *Genome Sequencing; Chromothripsis; DNA Replication; Chromosomes; Telomere*



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Introduction

Chromosome Shattering & Mechanisms in Chromothripsis

Years of research have shown that cancer is a genetic disorder. However, unlike germline mutations, these disorders are generally caused by somatic mutations in genes such as proto-oncogenes, tumor suppressor genes and DNA repair genes as well. Studies have shown that both environmental factors such as radiation, chemical mutagens and endogenous stressors such as water, reactive oxygen species can interfere with DNA replication, repair, and division pathways and lead to genomic instability which can cause Cancer. Lately, a novel form of genomic instability known as Chromothripsis, discovered in 2011 has been considered as a cause of cancer. Its literal meaning is 'Chromosome shattering'. In the phenomenon involving Chromothripsis, a single catastrophic event leads to breaking of chromosome into numerous short pieces which then rearrange and join randomly by DNA repair processes such as non-homologous end joining [1-7].

Studies to understand the cause of Chromothripsis have proposed two major mechanisms. Most extensively studied model is the 'Micronuclei hypotheses'. Micronuclei are formed due to errors in chromosome segregation [8]. During anaphase stage of mitosis, paired chromosomes aligned at metaphase plate are separated which are then passed onto daughter cells. But, sometimes a chromosome or chromosome fragment lags or fails to align at chromosome plate and remains unattached to the spindle fibers. At the end of mitosis, if this

chromosome is at sufficient distance from the metaphase plate it forms its own nuclear envelope (Figure 1) [9]. This small nucleus like structure formed during interphase is known as Micronucleus. This micronucleus is believed to be a major site of chromosome shattering and rearrangement known as 'Chromothripsis' [9].

Later studies showed that, when cells exit G1 phase nuclear envelope of micronucleus collapses and the fragmented or damaged chromosome gets reincorporated into Primary Nucleus [9]. The collapse of nuclear envelope of micronuclei, leads to lack of nuclear pore because of which important nuclear proteins are absent and replication of chromosomes present is either absent or delayed. On joining with Primary nucleus, these defects cause rearrangement of fragmented chromosomes. This rearrangement then leads to genomic instability and DNA damage [10].

Another proposed model is 'Telomere Crisis', Figure 2 [11]. Telomere are tandem repeat sequences present at the ends of chromosomes and are responsible for protecting the ends of chromosomes and providing genomic stability. Each consecutive cell cycle leads to shortening of chromosomes which is a result of a phenomenon known as end replication problem. An enzyme 'telomerase reverse transcriptase (TERT)' solves this 'end replication problem'. This enzyme activity is seen in germline cells whereas most somatic cells lack its expression. Loss of end repeat sequences or telomerase

enzyme in single chromosome leads to formation of dicentric chromosomes which then undergo Breakage – Fusion Bridge cycles. These damages are generally not

detected as they are identified by Cell cycle checkpoints and spindle check points (SAC) [11].

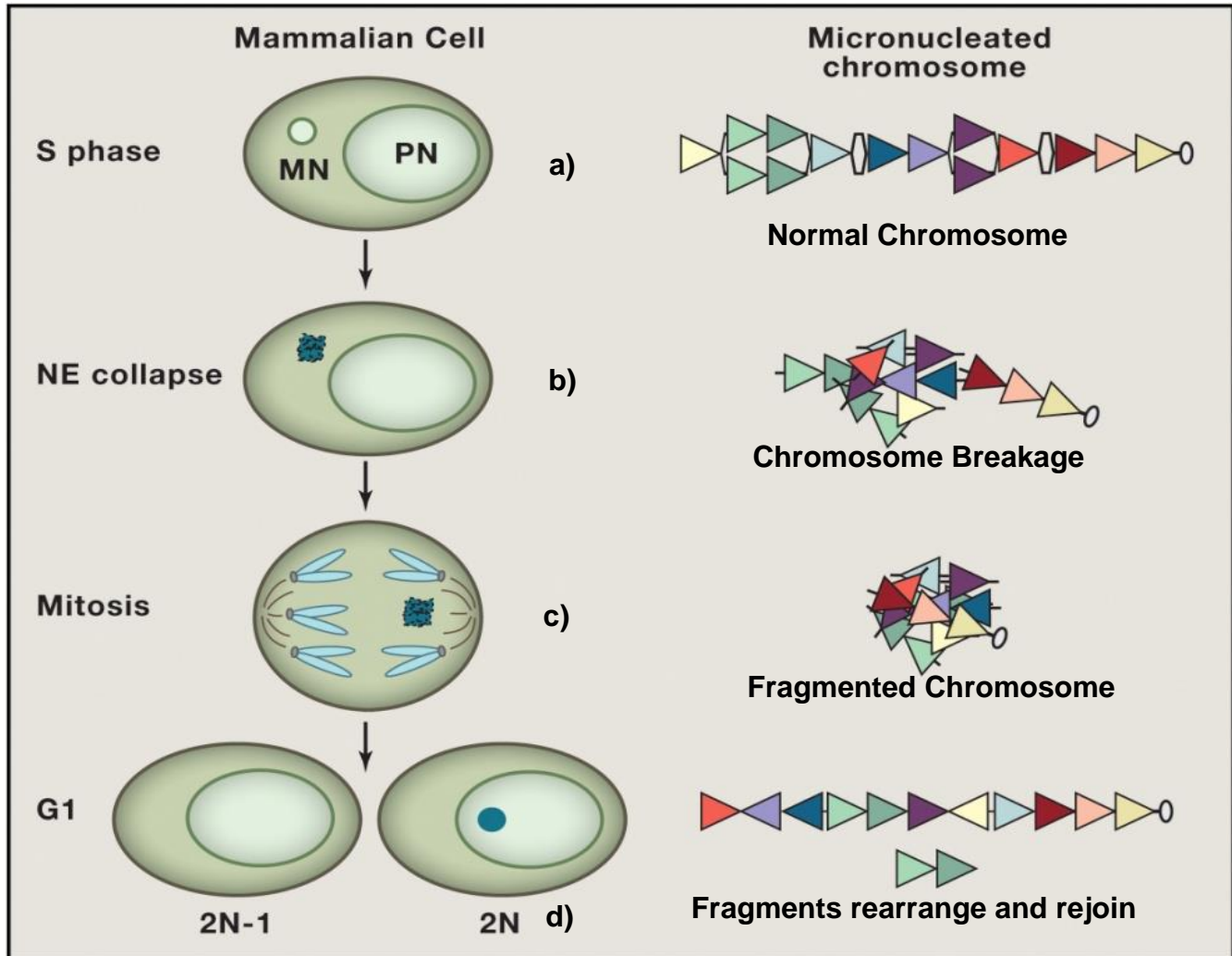


Figure 1: a) Chromosome mis-segregation during mitosis results in cell having two nucleases that correspond to a primary nucleus and a micronucleus which has affected chromosome. b) During replication, nuclear envelope of micronucleus ruptures leading to breaks in chromosome. c) After mitosis damaged chromosome encloses in PN. Subsequently, fragments rearrange and join by DNA Repair mechanisms. d) Fragments that are not joined can form acromeres. One daughter cell is normal while other one which receives damaged chromosome is affected [Source: Cell 161 (2015)].

In tumorigenesis however, due to loss of p53 (a tumor suppressor gene) this telomere shortening leads to telomere dysfunction. In such cases, damaged chromosome bypasses cell cycle check points and telomerase lose the ability to bypass DNA repair mechanisms; the shortened chromosomes are joined via non-homologous end joining mechanism to form Dicentric Chromosomes and form Breakage–fusion bridge (BFB). Researchers showed that cells were made to express TERT; p53 and Rb pathways were inhibited and telomere crisis was induced. This resulted in telomere dysfunction, activation of ATM repair pathway and disabled cell proliferation. Further, on attenuating

telomere protecting gene TRF2, telomere fusion was observed which formed dicentric chromosome as expected [10, 11].

Researchers have also studied interplay of telomere crisis and Kataegis. Kataegis is a process of hypermutation caused by clustering of base substitutions. It does not generally occur in germline cells but in somatic cells. It has been showed that chromatin bridges recruit Replication Protein A (RPA) on extended ssDNA. These ssDNA are considered to be the target region for APOBEC enzyme, which converts cytosine to thymidine or uracil. This leads to the accumulation of substituted bases, which is a process known as Kataegis [11].

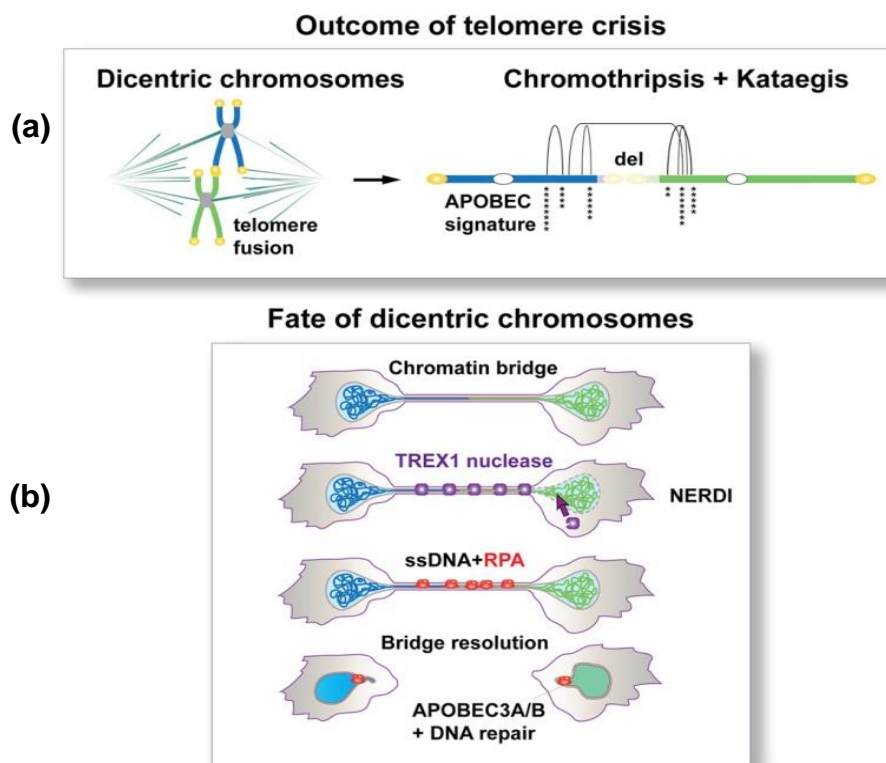


Figure 2: (a) Schematic depiction showing telomere crisis that leads to formation of Dicentric chromosome and Kataegis (b) Dicentric chromosome undergo Bridge formation. The ssDNA gets covered with TREX1 nuclease which recruits RPA. APOBEC enzyme and DNA repair of fragmented bridge DNA results in Chromothripsis and Kataegis [Source: Cell 163 (2015)].

Chromothripsis in Cancer

Normally, damaged DNA is eliminated via apoptosis but in case of Chromothripsis, cells survive based on affected genes present in that chromosome region. If the affected genes are important for pathways such as cell cycle regulation, DNA damage, repair, cell proliferation and apoptosis then, they will inhibit cell death and cell will survive [12].

Understanding the Mechanisms that Cause Cancer

The fragmented chromosomes can form acromeres (small, circular chromosome which lack centromere and telomere). Incorporation of above-mentioned genes in acromeres can cause loss of tumor suppressor genes or can form Oncogenic fusions [12]. This is observed in cases of oesophageal adenocarcinoma and acute myeloid leukemia. In acute myeloid leukemia, this is most prevalent in chromosome 17 [12].

Another mechanism involves DNA Repair: Repair process for joining of fragmented chromosomes is not very accurate in micronuclei and fusion of unwanted chromosome fragments can occur. This can lead to defects in cell proliferation, loss of gene functions and formation of novel oncogene proteins. As detected in cases of pancreatic cancers in which, chromosome 18 and chromosome 12 are most affected [12].

Micronuclei model of chromothripsis has also shown involvement in neochromosome generation. Neochromosomes are functional chromosomes formed by joining of DNA fragments of other normal chromosomes [12]. Involvement of Neochromosomes in cancer is

known since 1950 and commonly observed in certain types of lipocarcinomas.

It has been shown that telomere crisis derived kataegis is involved in certain breast cancers. Base substitutions of C>T, C>G and C>A at TpCpX trinucleotides have been observed in various breast cancer samples which is indicative of the same [13].

Conclusion and Future Perspective

We have presented a short overview of some of the latest discoveries in chromothripsis in cancer that have led to breakthroughs in providing novel insights into cancer genetics. The mechanisms of chromothripsis are discussed, that explain the role of nuclear and somatic genomes in cancer. It shows that formation of micronuclei due to mis-segregation at anaphase stage or telomere loss due to mutated cell cycle checkpoints can lead to tumorigenesis. We have also touched upon the role of nuclear envelope degradation in micronuclei model of chromothripsis.

This can be further used to study if mitochondrial genome also has the potential to cause cancer by fusing with primary nucleus after degradation of nuclear envelope. Kataegis, a phenomenon of clustering of base substitutions have also been shown to occur due to telomere crisis model of chromothripsis and cause cancer development. Chromothripsis related chromosome rearrangement is an early event in carcinogenesis. These findings can be extended for prognosis and detection of cancer at an early stage and further used in therapeutics.

Acknowledgement

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Getting Your Life Back on Track Post-Pandemic

By Gloria Martinez

Creator of WomenLed.org

If you're suffering from pandemic fatigue, it may be time to start looking for ways to increase your confidence so you can re-enter society in a way that feels safe, fulfilling, and personally rewarding. This is the perfect time to reinvent yourself, from getting your fitness back on track, to ensuring your financial health and stability.

Manage Your Health

The pandemic has taken a lot out of everyone from a health perspective. We've all been indulging in comfort foods, limiting our trips to the gym, and wearing stretchy pants while we telecommute. Make a plan to get back on track. Get a head-to-toe physical, clean out the junk food, and start going to outdoor farmer's markets and buying fresh produce. Replace soda with water, limit fast foods, and start meal prepping so you can have nutritious and good-tasting meals on hand. According to the American Heart Association, once you start [fueling your body](#) with healthy foods, you'll start getting your energy back up, and may even see an improvement in your mood!

Start an Exercise Plan

Just like eating well makes you feel good, exercise gets the endorphins pumping and can make you feel stronger, both physically, and mentally. You know yourself best, so make a plan you can stick to. For some, it's just a matter of establishing a routine, like

attending a regular fitness class, or meeting with a neighbor to walk every morning. For others, exercise is best enjoyed when it's mixed with entertainment. For example, you might learn to kayak, rock climb, or take a salsa dance class. Try anything new and appealing that elevates your heart rate and gets you up and moving. If it has been awhile since you were in exercise-mode, [start slow](#) if you need to.

Assess Your Career Path

Are you happy and challenged at work? If not, it may be time for a [career change](#). Consider meeting with an employment counselor, job coach, or headhunter, and take stock of your skill sets and interests. Maybe you need to change companies, go back to school, or even take on a new role with your current employer. Perhaps you've always thought of starting a business, or padding your savings account with a side gig. While it's not wise to make knee-jerk decisions, personal and professional exploration is healthy, and can help you identify both short and long-term career aspirations.

Reduce Your Stress

The pandemic has taken a toll on everyone's mental health, as well as increased stress and anxiety levels. If you find yourself regularly on edge, unable to relax, or

struggle with a [constantly racing mind](#), you aren't alone. The U.S. Department of Health and Human Services recommends working your way [out of this pattern](#) by scheduling regular meditation breaks, or learning yoga, tai chi, or guided relaxation response. Start a gratitude journal, focus on what's good, rather than what's bad, and be kind to yourself. Everyone is learning new coping techniques these days, and it may take a bit of trial and error to learn what works best for you.

Eliminate Financial Stressors

While easier said than done, getting your finances in order can relieve a big mental and emotional burden. Many people have lost jobs or seen hours decreased during the past several months, but you can combat [financial woes](#) by establishing a realistic budget, and

sticking to it. Pay down debt you may have incurred during lockdown so you don't get overwhelmed with high-interest credit card payments. A financial advisor or reputable credit counselor may be able to help. Refinancing your house and [cashing out equity](#) to pay down debt, or create a financial safety net, can all help you sleep better at night.

The pandemic has impacted everyone in different ways, but looking ahead and preparing for better days can provide a much-needed positive mental boost. Be kind to yourself, and to others, and start taking action that will put you back on the road to normalcy.

Footnote -

This article, and others like it, can be found on the [Biotechnology Kiosk](#) website. BK is the monthly peer-reviewed open access international research journal in biotechnology.

Photo by [Pixabay](#)



By: Gloria Martinez creator of WomenLed.org



Biotechnology Advances around the World

Editor's Picks

Every issue of Biotechnology Kiosk presents select latest research news picked by the editors-in-chief on significant research breakthroughs in different areas of biotechnology around the world. The aim is to promote further R&D in all of these cutting-edge areas of biotechnology. The editors have compiled and included the following innovations and breakthroughs to highlight the latest biotechnology advances.



Dr. Megha Agrawal
Co Editor-in-Chief



Dr. Shyamasri Biswas
Co Editor-in-Chief

Antibody

Cost-effective production of antibodies

Antibody injections are considered one of the most sought-after treatment methods for people with chronic diseases such as cancer, psoriasis, Crohn's disease and arthritis. Also, antibody-based treatment methods are very promising for severe cases of COVID-19.

However, very expensive and time-consuming manufacturing processes that are employed to produce antibodies are considered very unfavorable in the wide-scale applications and usage of antibodies. These expensive methods severely limit these treatments from being accessible to most patients who cannot afford the high costs associated with antibody-based treatments. The current methods that are employed to produce antibodies are based on a process called Protein A affinity chromatography. In this process, the antibody binds to Protein A, which is immobilized in a chromatography column. The impurities can then be washed away from the bound antibody. Subsequently, the pH level gets adjusted to recover the purified antibody product.

It is known that a single Protein A chromatography column can cost more than \$10 million. And, it corresponds to just one step in the current manufacturing process. It is therefore, understandable that why

antibody manufacturing is considered so expensive.

Researchers in the US have identified a new cost-effective method to manufacture antibodies, which is believed to drive down the production cost. Their research results were recently published in *Biotechnology Progress* (Enhanced filtration performance using feed-and-bleed configuration for purification of antibody precipitates. *Biotechnology Progress*, 2021; 37 (1) DOI: [10.1002/btpr.3082](https://doi.org/10.1002/btpr.3082)).

In their study, researchers demonstrated new protein purification process that involved adding zinc chloride and polyethylene glycol, a water-soluble polymer, to a solution containing the antibody. This caused the antibody to precipitate so that the impurities can be washed away easily.

While the precipitation process has been employed for 70 years in blood plasma processing, it is demonstrated for the first time in this study commercial production of antibodies. Researchers envision that the precipitation process could be easily scaled up that could potentially enable biopharmaceutical companies to produce lower-cost antibodies for the patients who need them.

Obesity

Drug for treating obesity

The impact of obesity on health is well known and has been studied extensively. Especially, during the current COVID pandemic, obesity is in the focus due to the reason that obesity causes higher risks of dying from the virus. In addition, obesity is considered to increase the risk of many life-limiting serious diseases that include heart disease, type 2 diabetes, liver disease and certain types of cancers as well.

Researchers in U.K. recently published the findings from the large-scale international trial in the New England Journal for Medicine (New England Journal of Medicine, 2021; DOI: [10.1056/NEJMoa2032183](https://doi.org/10.1056/NEJMoa2032183)). The drug developed by the researchers are being hailed as a gamechanging solution to the problem of obesity that could potentially pave the way for improving the health of people with obesity and could play a major part in helping to reduce the impact of diseases, such as COVID-19. The drug, semaglutide was shown to work by hijacking the body's own appetite regulating system in the brain leading to reduced hunger and calorie intake. Researchers developed the drug that possessed a compound structurally similar to (and mimics) the human glucagon-like

peptide-1 (GLP-1) hormone that was released into the blood from the gut after meals.

In this study, the selected average participant in the trial lost 15.3kg (nearly 3 stone) by the administration of the drug. This was accompanied by reductions in risk factors for heart disease and diabetes that included waist circumference, blood fats, blood sugar and blood pressure and they all reported improvements in their overall quality of life.

The findings of this study represented a major breakthrough for improving the health of people with obesity. Researchers showed that three quarters (75%) of people who received semaglutide 2.4mg lost more than 10% of their body weight and more than one-third lost more than 20%. This study paves the way for future breakthroughs for people who can bypass the complex, invasive and expensive weight-loss surgery and achieve weight reductions through drugs.

Compiled and Edited by Dr. Megha Agrawal & Dr. Shyamasri Biswas.



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