Annals of Carcinogenesis

Open Access

Austin Publishing Group

Review Article

Chromothripsis: Introduction and Mechanisms

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Received: October 24, 2025
Accepted: November 11, 2025
Published: November 13, 2025

Abstract

Complex chromosomal rearrangements (CCRs) is a subject of interest since introduction of cytogenetic techniques. Chromothripsis is important and one of the most common mechanisms involved in cancer pathogenesis and progression. Chromothripsis is associated with aggressive tumor behaviour and poor clinical outcome in cancer patients. This mini review is an attempt to explore chromothripsis and understand its causes, implications and gives insights about the emerging literature relevant to it.

Keywords: Genomic instability; Chromothripsis; Genomics; Neoplasia; DNA repair; Chromosomes

Introduction

Genomic instability is characteristic feature of neoplasia. Chromothripsis and cancer has gained significant attention recently as their association with each other has potential implications for pathogenesis of cancer development and progression [1]. Human cells are at the risk of DNA damage which can be caused by both external as well as internal factors. Cells respond to such stimulus and ensures genomic stability [1]. Chromothripsis is derived from the Greek word thrip-sis which means shattering. It was identified and described firstly in a patient of chronic lymphocytic leukemia [4]. Chromothripsis is due to shattering of one or more chromosomes into many small fragments, followed by random re-assembly resulting in multiple breakpoints, deletions without duplications [1]. It involves rapid gain of structural rearrangements within short span leading to complex alterations in affected chromosomes [1]. The affected chromosome bears very less resemblance to the original chromosome and its unique mutation signature has been identified in cancers of brain, blood and bone [1]. When it was discovered, it was thought to be present in 2-3 % genomes but later studies have showed its presence in various types of tumors. It has also been linked with congenital anomalies [4]. Whole genome sequencing (WGS) studies have shown that many tumors are associated with complex structural variations and results of WGS followed by mapping reads against a reference genome has shown us that chromothripsis is based on the process of chromosome shattering which is triggered by double-strand DNA breaks [2]. Chromothripsis is identified by various techniques and are characterized by rearrangement profiles with interleaved structural variants (SVs) with variable loss of heterozygosity (LOH), which result due to random rejoining of DNA fragments arising because of chromosome fragmentation. It is also shown to be more commonly present in specific chromosomes like 17, 12, 8 and 6 [1]. Loss of TP53 gene (17p13.1) was seen in significant number of chromothripsis cases. [1] Also, it is observed that chromothripsis is seen to be coupled with additional mutations in tumor cells for example, IDH mutations [1]. In this mini review we will explore the basics of chromothripsis, its pathogenesis along with implications and future perspectives.

Review of Literature

The complex nature and pathogenesis of chromothripsis has led to suggestion of various causative mechanisms which include abortive apoptosis, telomere erosion, micronuclei formation, p53 inactivation, mitotic errors [1]. Recently, the potential of sub- clonal heterogeneity in chromothripsis patterns were explored which highlighted that such heterogeneity could be the result of a cascade of mutational events occurring within a relatively short period. The inherent genomic instability in rapidly dividing tumor cells lead to therapeutic avenue by targeting DDR pathways [1]. Chromothripsis is not exclusively seen in malignant tumors, but they are seen to occur in benign tumors as well and seen to be present in 13-42% of uterine fibroids [3]. It is also associated more frequently in complex karyotypes, TP53 mutation and monosomal karyotypes [1]. Occurrence of Chromothripsis in tumors is more in patients with inherited genetic disorders that are associated with cell cycle and DNA repair gene mutations. Repair of double stranded breaks occurs either by homologous recombination or by Non homologous end joining (NHEJ) [3]. NHEJ is observed to be the main repair mechanism in cases with chromothripsis. DNA which has been repaired by NHEJ, may sometimes have error in order and orientation of DNA segments [3]. Chromosomes 17, 11, 8, 12 are seen to be more affected by chromothripsis and these chromosomes are most likely seen to be affected by these rearrangements [1]. It is seen that high frequency of chromothripsis on chromosome 17 is due to the presence of TP53 gene [1]. The frequency of chromothripsis is variable across cancers but they are seen to occur more in bone cancers particularly osteosarcoma and chordoma [2]. There is a correlation seen between chromothripsis, micronuclei regeneration and defective DDR and thus there is a possibility that it can be present in cells affected by defects in HR-mediated DNA repair pathways [1]. Past studies have proposed a link between breakage-fusion-bridge cycles and chromothripsis. Micronuclei formation is seen at the start of chromothripsis [1,5].

Discussion

Chromosomes are made up of DNA and proteins organized

Citation: Ashish Arun Wadekar, Nuruddin Mohammad Iqbal and Bharathi Prabakaran N.S. Chromothripsis: Introduction and Mechanisms. Ann Carcinog. 2025; 5(1): 1022.

compactly so as to facilitate accurate and equal division of genetic material to subsequent daughter cells. In spite of the sophisticated cell cycle checkpoints, mis-segregation events occur in cells [1]. Chromothripsis have been shown to be associated with faulty cell division process [1]. Signal pathways which are affected in chromothripsis involve copy number gain and upregulation of oncogenes that promote cancer proliferation [1]. Patients of cancer with chromothripsis exhibit worse overall survival. Chromothripsis has been characterized using high-resolution genomic approaches. Mate-pair and paired-end sequencing, verified by Sanger sequencing, enable precise breakpoint mapping and junction sequence analysis, despite their high cost and technical complexity [3]. Microarray-based comparative genomic hybridisation (aCGH), often combined with SNP arrays, provides sensitive detection of copy number changes and sub microscopic aberrations, though it cannot resolve balanced rearrangements or segment orientation. Fluorescence in situ hybridisation (FISH) techniques—including SKY, M-FISH, and MCB-FISH allow chromosome identification and detailed characterization of derivative structures, with locus-specific probes further refining breakpoint mapping [3]. Conventional karyotyping of metaphase lymphocytes remains useful for detecting numerical and structural abnormalities but requires integration with molecular cytogenetic methods for accurate interpretation of complex chromosomal rearrangements [3]. Thus, comprehensive analysis of chromothripsis necessitates a multimodal approach combining sequencing, microarray, and cytogenetic tools. Korbel and Campbell proposed conceptual criteria to distinguish chromothripsis from stepwise rearrangements, including clustered breakpoints, oscillating copy number states, interspersed loss of heterozygosity, haplotype-specific rearrangements, random fragment order, and the ability to reconstruct the derivative chromosome [3]. Due to sequencing costs, subsequent studies mainly relied on oscillating copy number patterns, defining chromothripsis as ≥10 switches between two or more copy number states on a chromosome [3]. Cytogenetic approaches, including multicolour FISH, multicolour banding and integration with SNP array data, have further illustrated chromothripsis in hematologic malignancies [4]. More recently, optical genome mapping has provided high-resolution structural insights, though it requires long, high-quality DNA, while FISH demands fresh samples [4]. Each technique offers complementary strengths and limitations, underscoring the need for integrated approaches in chromothripsis detection. Understanding the cellular consequences and mechanistic basis of chromothripsis is essential for elucidating the drivers of genomic instability and its broad implications in cancer [4].

Conclusion

Chromothripsis is now recognized across cancers, benign tumours, and constitutional chromosomal abnormalities. While experimental models have clarified its general framework, its precise causes, mechanisms, and clinical consequences remain poorly defined. Constitutional cases typically show fewer breaks and less extensive copy number changes than somatic forms, but both involve complex rearrangements with regions of loss and retention of heterozygosity. Differentiating chromothripsis from other complex rearrangements and understanding its biological relevance remain key challenges. Future studies on chromosome-specific features and the roles of TP53 and related genes may uncover novel therapeutic opportunities.

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