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Mutational game changer: Chromothripsis and its emerging relevance to cancer

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ABSTRACT

In recent years, the paradigm that genomic abnormalities in cancer cells arise through progressive accumulation of mutational events has been challenged by the discovery of single catastrophic events. One such phenomenon termed chromothripsis, involving massive chromosomal rearrangements arising all at once, has emerged as a major mutational game changer. The strong interest in this process stems from its widespread association with a range of cancer types and its potential as a mutational driver.

In this review, we first describe chromothripsis detection and incidence in cancers. We then explore recently proposed underlying mechanistic origins, which explain the curious observations of the highly localised nature of the rearrangements on chromothriptic chromosomes. Detection of chromothriptic patterns following incorporation of single chromosomes into micronuclei or following telomere attrition have greatly contributed to our understanding of the reasons behind this chromosomal restriction. These underlying cellular events have been found to be participants in the tumourigenic process, strongly suggesting a potential role for chromothripsis in cancer development. Thus, we discuss potential implications of chromothripsis for cancer progression and therapy.

1. Introduction

Boveri's hypothesis formulated more than 100 years ago first posited that somatic genetic changes that led to unbridled cell proliferation caused cancers [1]. This seminal finding that cancer is a disease of the genome proved true and drove the pursuit of cancer-causing genes. It is now a paradigm that mutations in the genetic material can cause cancers *via* activation of oncogenes or inactivation of tumour suppressors. Tumour genomes are characterised by increased frequencies of mutations termed genomic instability [2]. Cells possess several surveillance mechanisms that maintain stability of the genome to prevent mutagenesis. When DNA replication is defective or when DNA breaks are induced by external environmental influences such as ultraviolet light or ionizing radiation, the DNA damage checkpoint is activated and enables accurate DNA repair [3]. Epigenetic changes or dysfunctional expression of DNA repair proteins can affect repair efficiencies, potentially resulting in base substitutions (nucleotide instability), high mutations rates in short nucleotide repeats (microsatellite instability) or more complex chromosomal alterations [2]. Another surveillance mechanism, known as the spindle assembly checkpoint (SAC), monitors spindle dysfunction during mitosis [4]. This ensures accurate distribution of chromosomes to daughter cells. Deficient SAC signalling can result in chromosome mis-segregation, potentially leading to an abnormal number of chromosomes, known as aneuploidy [5]. Structural chromosomal rearrangements, including translocations, insertions and deletions, and aneuploidy are collectively known are chromosomal instability [2]. It comes as no surprise that all of these genomic aberrations have been extensively observed in cancers [2]. When these variations occur in genes that confer growth advantage to cells, they can be potential drivers of cancer development [6]. Through selection of these

Abbreviations: SAC, spindle assembly checkpoint; APOBEC, apolipoprotein B mRNA-editing catalytic subunit; SNP, single-nucleotide polymorphism; array-CGH, comparative genomic hybridization; CLTP, chromothripsis-like pattern; SKY, spectral karyotyping; FISH, fluorescent *in situ* hybridization; FoSTeS, fork stalling and template switching; MMBIR, microhomology-mediated break induced replication; CAST, complex alterations after selection and transformation; ATM, ataxia-telangiectasia mutated; TREX1, 3′ repair exonuclease 1; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; BFB, breakage-fusion-bridge; TRF2, telomeric repeat-binding factor 2; RTEL1, regulator of telomere length 1; HR, homologous recombination; NHEJ, classical non-homologous end-joining; MMEJ, microhomology-mediated end joining; indels, insertion and/or deletions; ESCRT-III, endosomal sorting complexes required for transport; LINC, linker of nucleoskeleton and cytoskeleton

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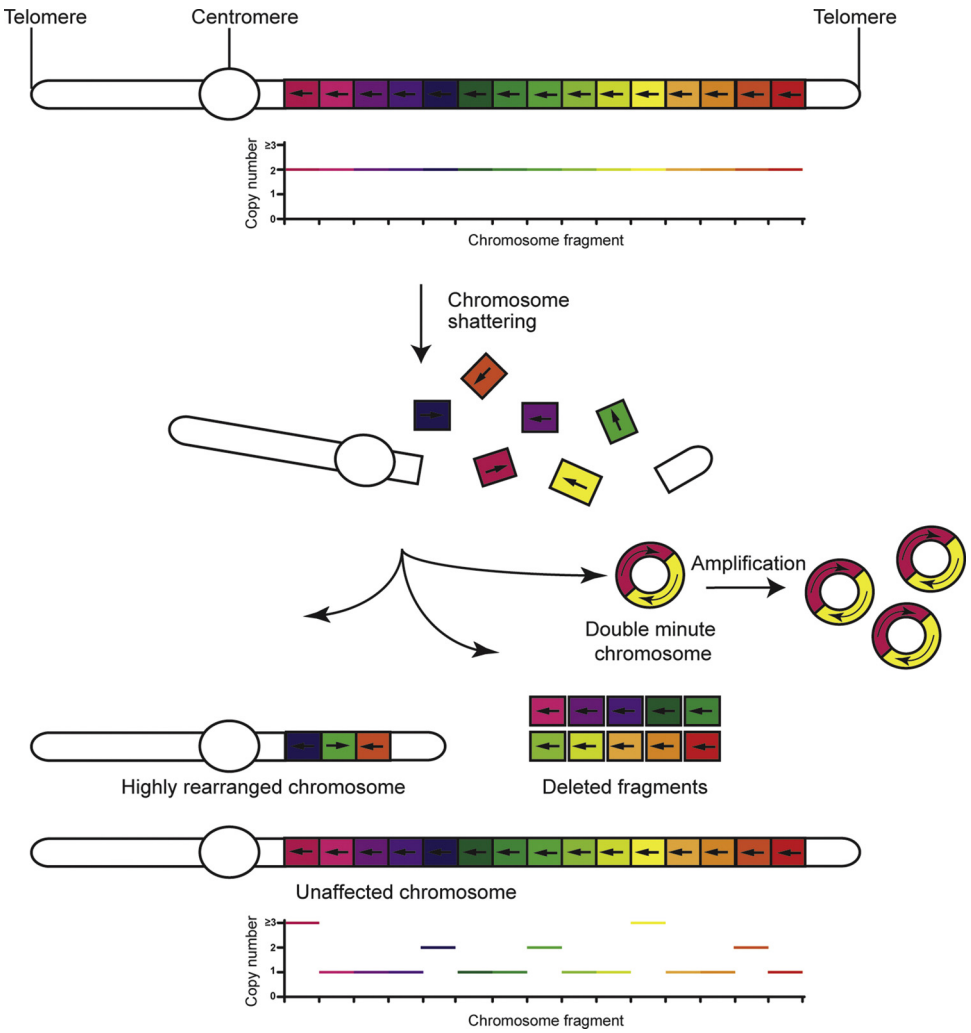

Fig. 1. Schematic overview of chromothriptic chromosomal rearrangements. During chromothripsis, a chromosome or chromosome arm shatters, followed by incomplete and random repair of the fragments. This can result in a highly rearranged chromosome or chromosomal fragment, whereby certain fragment are lost and/or are incorporated into extrachromosomal double minutes, usually present at high copy numbers. As a result, only two, sometimes three, different copy number states can be detected for each fragment of the chromothriptic chromosome.

driver mutations, passenger mutations in genes that are localised in the vicinity of drivers but do not affect the fitness of cells themselves, may also become associated with cancers [7].

Historically, these extensive alterations detected in cancer genomes have been thought to be the result of a stepwise process where driver mutations accumulate progressively over time [7]. However in 2011, work made possible with the advent of next-generation sequencing led to the discovery of massive gene reshuffling achieved within a single step. Stephens et al. discovered unusual chromosomal structural variations confined to chromosome 4 with copy number oscillating between two states in a patient with chronic lymphocytic leukaemia [8]. The authors used a Monte Carlo simulation which demonstrated that this pattern of chromosomal rearrangements could not be simply explained by the "progressive" model of acquisition of mutations and genomic rearrangements [8]. Instead, these rearranged chromosomes were proposed to arise from a single "catastrophic event" resulting in chromosomal breaks at multiple points followed by random reassembly (see Fig. 1). The authors coined the term "chromothripsis" (Greek for chromosome (chromo) shattering (thripsis) to describe this phenomenon [8]. This was proposed to be a consequence of localised shattering of chromosomes followed by aberrant DNA repair [8].

Although there was much initial debate regarding the idea that a subset of cancer genomes might not be due to gradual genome evolution [9,10], it is now well-accepted that chromothripsis is a widespread mutational phenomenon. Chromothriptic rearrangements are not limited to cancer genomes but have also been reported in the germline, mainly in patients with dysmorphic features or developmental delay [11–23]. Furthermore, catastrophic complex rearrangements are not restricted to *Homo sapiens*, but were reported in the Tasmanian devil [24], the nematode *Caenorhabditis elegans* [25], *Arabidopsis thaliana* plants [26], grape (*Vitis vinifera*) [27] and picoplankton *Ostreococcus tauri* (Chlorophyta, Mamiellophyceae) [28], suggesting that chromothripsis can serve as a natural source of genetic variation.

In this review, we present an overview of the association and relevance of chromothripsis in cancers. We describe how to detect chromothripsis, its prevalence in cancers, and we discuss cellular origins and mechanisms underlying chromothripsis, correlation to survival rates and potential influence on treatment outcome.

2. Prevalence of chromothripsis in cancers

2.1. Detection of chromothripsis

After its original description in 2011, one of the initial questions was what is the prevalence of chromothripsis in cancer genomes? Therefore, several attempts have been made to establish characteristics of the