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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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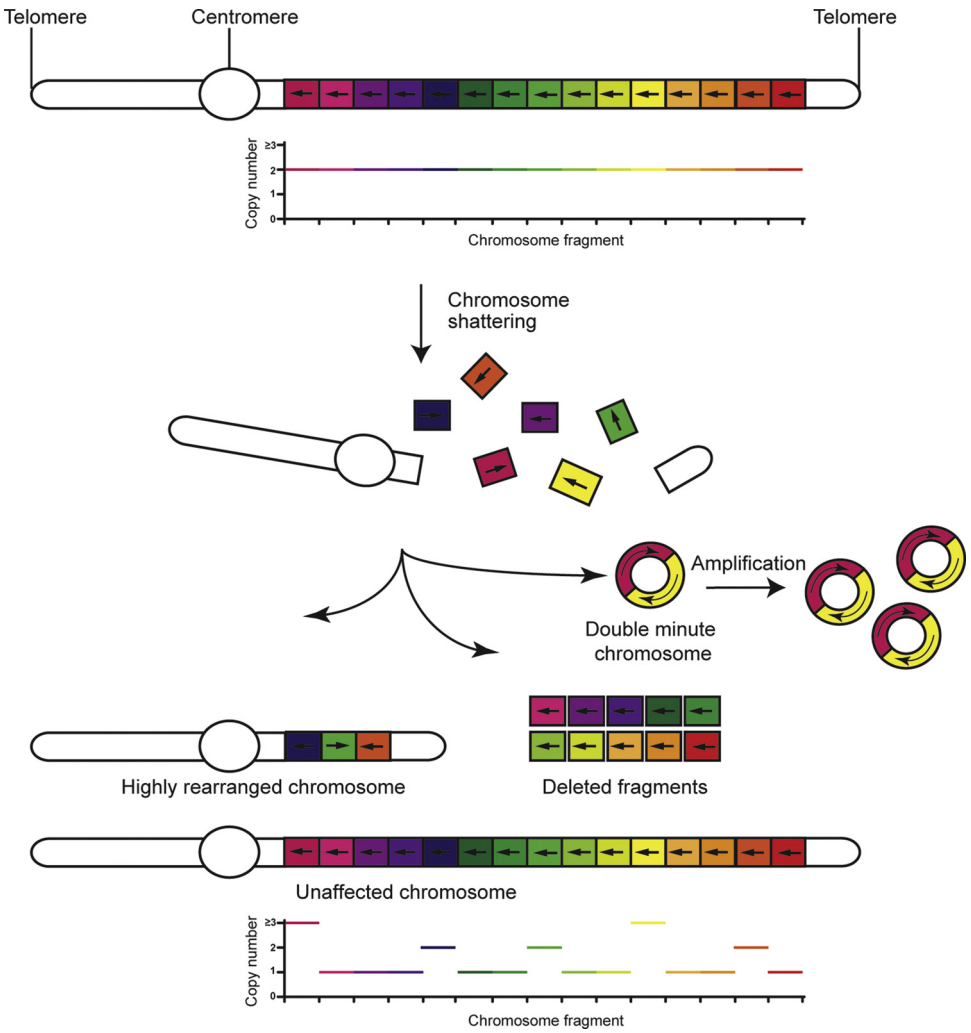

Fig. 1. Schematic overview of chromothriptic chromosomal rearrangements. During chromothripsis, a chromosome or chromosome arm shatters, followed by incomplete and random repair of the fragments. This can result in a highly rearranged chromosome or chromosomal fragment, whereby certain fragment are lost 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

chromothriptic genomic signature that can distinguish gradual accumulation of mutations from a single 'catastrophic' event. In the International System for Human Cytogenetic Nomenclature 2013 chromothripsis is defined as complex patterns of alternating copy number changes (normal, gain or loss) along a chromosome or a chromosomal segment [29]. In general, progressive accumulation of mutations are considered to results in a genomic signature whereby the unique copy number states increases concurrent with the number of breakpoints per chromosome. In 2013, Korbel and Campbell [30] suggested the following criteria to discriminate between rearrangements resulting from chromothripsis and from stepwise DNA alterations.

1 Chromothriptic genome profiles exhibit pronounced clustering of DNA breaks. This clustering is defined by specific chromosomal regions having multiple breaks in close proximity, surrounded by large sections of intact chromosomal sequence.
2 For certain sections of genomic DNA within the chromothriptic profiles, the copy number varies, but there are only two (sometimes three) different copy number states detected.
3 Chromothripsis can result in massive loss of chromosome fragments. The resulting chromothriptic chromosome shows an alternating pattern of retention and loss of heterozygosity between segments.
4 Chromothripsis usually occurs on a single parental copy (haplotype) of the chromosomes.
5 Chromosome fragments are joined together in random order and random orientation. The number of different types of intra- and interchromosomal structural rearrangements are largely equal and the position of the fragments within the chromothriptic region is expected to be random.
6 Following chromothripsis, each fragment is either retained or lost in the resulting chromosome. Thus, when viewed on the reference genome, breakpoints alternate between head and tail paired-end reads, enabling an unambiguous walk through the derivative chromosome.

Additionally, chromothriptic breakpoints were found to sometimes be surrounded by clusters of point mutations, termed kataegis (Greek for "thunderstorm") [31]. Kataegis is hypothesised to be the result of deamination of cytosine to uracil by apolipoprotein B mRNA-editing catalytic subunit (APOBEC) enzymes, whose main functions are believed to be RNA editing and mutation of viral genes as part of the immune response [32,33]. As kataegic regions of hypermutation are known to localise near regions of somatic genome rearrangements [34–36], hypermutated regions can indicate the presence of structural rearrangements.

As suggested by Korbel and Campbell themselves [30], these criteria are not exhaustive but rather intended as evolving guidelines and subject to debate. Chromothripsis was only discovered relatively recently and with maturation of the field new developments will likely generate novel insights that warrant continuous evaluation of definitions. For example, the ability to walk the derivate chromosome as a criterium for chromothripsis was recently challenged by Oesper et al. [37], who instead suggest determining the H/T alternating fraction. However, in practice, the Korbel and Campbell guidelines seem to be predominantly referred to.

Certain of the characteristics of chromothripsis can be detected by genomic array platforms such as single-nucleotide polymorphism (SNP) microarray and comparative genomic hybridization (array-CGH) [38]. Therefore, several studies reported the frequency of chromothripsis in unbiased sets of cancer genomes derived from array data, examples of which are listed in Table 1. However, this data is limited to the detection of clustering of breakpoints within a localised region and variations in copy number states and can therefore not address all above-mentioned criteria. Thus, some studies refer to these array-derived signatures as chromothripsis-like patterns (CLTP), rather than chromothripsis [39–43]. Based on the above-mentioned characteristics, Yang et al. developed an algorithm, named CTLPScanner, for identification of chromothriptic-like rearrangements from genomic array data [44]. Comparison of chromothripsis prevalence from different publications remains challenging as a range of thresholds for these characteristics has been used, as shown in Table 1. Stephens et al. considered a single chromosome to be chromothriptic if at least 50 breakpoints could be detected with a maximum of three different copy number states [8]. However, many publications report less stringent criteria ranging from at least 5 to at least 20 breakpoints per chromosome. In addition, there is clear variation in the amount of copy number states set to define chromothripsis in different studies.

To determine if all the rearrangements occur on the same chromosome as well as whether all rearrangements affect a specific haplotype, spectral karyotyping (SKY) or fluorescent *in situ* hybridization (FISH) can be used [45]. FISH is especially useful to detect centromeres and other regions of highly repetitive DNA. Additionally, SKY and FISH allow detection of variants at single-cell resolution, thereby taking into consideration intratumoral heterogeneity and enabling detection of rearrangements with low abundance in the population.

Although the above-mentioned techniques require less resources, the golden standard for the confirmation of chromothripsis remains paired-end sequencing as this detects rearrangement breakpoints at nucleotide resolution. With this information, the complete chromothriptic region can be pieced together by confirming the orientation of the different breakpoints and connecting the chromosomal fragments. This reconstruction can then be analysed using a Monte Carlo simulation to determine if the observed combination of copy number variation and genomic rearrangements can be produced as a result of one single event as opposed to multiple subsequent events. Even though the reliability of simulations as evidence for chromothripsis has been the subject of debate [10], Govind et al., Notta et al. and Moncunill et al. developed tools for prediction of chromothripsis from next generation sequencing data (Shatterproof, Chrom-AL and SMUFIN, respectively) [46], [47] [48], based on the criteria suggested by Korbel and Campbell [30]. Tables 2 and 3 list examples of studies on the frequency of chromothripsis in unbiased collections of cancer genomes detected using sequencing. Again, a large variation in the designation of what constitutes chromothripsis can be seen amongst these reports, ranging from a match with all criteria suggested by Korbel and Campbell (see Table 2) to a minimum number of breakpoints per chromosome.

2.2. Alternative catastrophic rearrangements

Not all tumour genomes for which the Monte Carlo simulation indicates that they are the result of a catastrophic event rather than a gradual accumulation of mutations, match all criteria for chromothripsis. Kinsella et al. show that adjustment of simulation parameters can result in genomic signatures that are generated as progressively but resemble the chromothriptic ones [10]. In addition, it has become clear that chromothripsis is not the only source of catastrophic complex structural variations. As outlined in more detail below, the majority of chromothriptic cases analysed so far can be explained by chromosome shattering followed by incomplete DNA repair [49]. However, in some cases, sequencing of the breakpoint junctions on rearranged chromosomes revealed patterns that are more compatible with defective DNA replication. For example, in the rearranged genomes of cells with chromothriptic chromosomes induced *in vitro*, microhomology was detected at the breakpoint junctions, suggesting the involvement of erroneous DNA replication through fork stalling and template switching (FoSTeS) and microhomology-mediated break induced replication (MMBIR) [14]. FoSTeS and MMBIR are microhomology-mediated DNA replication mechanisms, which are mutagenic [50]. Presence of a lesion in the DNA prior to replication will cause the replication fork to stall at the lesion. In both FoSTeS and MMBIR, replication of the lesion will be avoided by invasion of a different DNA template using microhomologous regions to establish a new replication fork and restart

Table 1
Examples of studies reporting chromothripsis in cancer genomes detected by array.

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Ref.
SNP array	The rearrangements show geographic localization within the genome Copy number changes oscillate between a maximum of three states Clustering of at least 50 breakpoints across one or multiple chromosome (arms) Random orientation of breakpoints	26 different tumour types	2792	32 (1.1%)	[8]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	11 different tumour types	4934	(5%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Bladder cancer	136	(8%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Colorectal cancer	585	(3%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Glioblastoma	580	(16%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Lung adenocarcinoma	357	(6%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Lung squamous cell carcinoma	344	(1%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Ovarian cancer	563	(5%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Kidney clear cell carcinoma	497	(1%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Breast cancer	872	(7%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Endometrial cancer	496	(1%)	[68]
SNP array	A single chromosome exhibits an unexpectedly large number of copy number alterations Copy number alterations on this chromosome are closely spaced Copy number alterations are non-overlapping and lead to copy number changes of +1 or –1	Head and neck cancer	310	(0%)	[68]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	19 different tumour types	8227	124 (1.5%)	[55]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	Ovarian cancer	336	4 (1%)	[55]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	Neuroblastoma	257	3 (1%)	[55]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	Lung cancer	1012	11 (1%)	[55]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	Lymphoma	740	8 (1%)	[55]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	Melanoma	214	2 (1%)	[55]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	Sarcoma	127	1 (1%)	[55]
SNP array and array-CGH	At least 10 alterations per chromosomes Random occurrence of the breakpoints Copy number oscillates between two states	Leukaemia	911	3 (0.3%)	[55]

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Table 1 (*continued*)

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Ref.
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	132 different tumour types	22347	918 (4.1%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Lipoid tumours	114	61 (54%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Fibroid tumours	59	14 (24%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Sarcoma	48	11 (23%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Bone tumours	123	10 (8%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Myoepithelial tumours	85	5 (6%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Stromal tumours	151	6 (4%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Mesothelial tumours	34	1 (3%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Medulloblastoma	430	17 (4%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Glioma	669	27 (4%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Astrocytic tumours	325	6 (2%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Tumours of peripheral nerves	686	8 (1%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Primitive neuroectodermal tumours	65	4 (6%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Colorectal cancer	923	17 (2%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Uterus carcinoma	101	1 (1%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Cervical carcinoma	261	2 (1%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Head and neck carcinoma	213	4 (2%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Urinary tract carcinoma	166	3 (2%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Renal carcinoma	380	5 (1%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Ovarian carcinoma	801	37 (5%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Hepatic carcinoma	296	7 (2%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Breast cancer	3652	404 (11%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Esophageal carcinoma	135	13 (10%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Bronchoalveolar non-small-cell lung carcinoma	1164	109 (10%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Bronchoalveolar small cell lung cancer	90	6 (7%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Prostate adenocarcinoma	653	41 (6%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Melanocytic neoplasia	621	38 (6%)	[39]

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Table 1 (*continued*)

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Ref.
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Non-melanocytic skin carcinoma	1	1 (100%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Endocrine carcinoma	13	2 (15%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Thyroid carcinoma	17	1 (6%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Gastric carcinoma	160	7 (4%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Nasopharynx carcinoma	8	1 (13%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Leukaemia, not otherwise specified	11	1 (9%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Immature acute lymphoblastic leukaemia	379	1 (0.26%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Acute myeloid leukaemia and myelodysplastic syndrome	1612	16 (1%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Myeloma	731	15 (2%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Hodgkin lymphoma	8	1 (13%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Non-Hodgkin lymphoma, not otherwise specified	125	1 (1%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Diffuse large B-cell lymphoma	441	9 (2%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	Hairy cell lymphoma	126	4 (3%)	[39]
SNP array and array-CGH	Clustering of rearrangements on (part of) one or two chromosomes with a limited number of copy number states	T-cell lymphoma, not otherwise specified	45	1 (2%)	[39]
SNP array and whole genome sequencing	At least 11 copy number state changes per chromosome	Medulloblastoma	1087	139 (13%)	[60]
SNP array and whole genome sequencing	At least 10 copy-number changes involving two or three copy-number states per chromosome	Medulloblastoma	98	13 (13%)	[59]
SNP array and whole genome sequencing	Not reported	Osteosarcoma	37	11 (30%)	[56]
SNP array	All characteristics observed by Stephens et al. 2011	Multiple myeloma	764	10 (1.3%)	[150]
SNP array	At least 10 copy-number changes involving two or three copy-number states per chromosome	Acute myeloid leukaemia	425	34 (8%)	[59]
SNP array	3 out of 6 Korbel and Campbell 2013 criteria	Acute myeloid leukaemia	395	26 (6.6%)	[74]
SNP array	Not reported	Phaeochromocytomas and paragangliomas	40	1 (3%)	[167]
SNP array	At least ten breakpoints per chromosome	Uveal melanoma	249	7 (3%)	[168]
SNP array	Copy numbers oscillate between gains or losses of one and two copies	Neuroblastoma	233	10 (4%)	[169]
SNP array	Not reported	Neuroblastoma	44	1 (2%)	[170]
Array-CGH	At least 20 breakpoints per chromosome	Neuroblastoma	87	10 (11%)	[152]
Array-CGH	Complex patterns of alternating copy number changes along a chromosome or a chromosomal segment	Acute myeloid leukaemia	67	7 (10%)	[171]
Array-CGH	Complex patterns of alternating copy number changes along a chromosome or a chromosomal segment	B-cell acute lymphoblastic leukaemia	19	1 (5%)	[171]
Array-CGH	Multiple oscillations between two copy-number states	Acute lymphoblastic leukaemia	265	3 (1%)	[153]
Array-CGH	At least 7 changes between two or more copy number states detected per chromosome	Chronic lymphocytic leukaemia	180	8 (4%)	[40]
Array-CGH	At least 10 changes in copy number between two or three copy number states per chromosome	Myelodysplastic syndrome and myelodysplastic syndrome/myeloproliferative neoplasm	301	3 (1.2%)	[70]
Array-CGH	Complex patterns of alternating copy number changes along a chromosome or a chromosomal segment	Myelodysplastic syndromes/chronic myelomonocytoc leukemia	19	2 (11%)	[171]

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Table 1 (*continued*)

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Ref.
Array-CGH	At least 10 breakpoint per chromosome Breakpoints are randomly distributed in the chromosome The pattern of copy number states oscillates The sizes of individual segments are not substantially different from their neighbouring segments	Colorectal cancer	5	2 (40%)	[146]
Array-CGH	CTLPScanner with default settings	Breast cancer	229	49 (21%)	[42]
Array-CGH	Not reported	Growth hormone-secreting pituitary adenomas	43	2 (5%)	[172]
Molecular inversion probe microarray	Not reported	Uveal melanoma	25	2 (8%)	[157]
Molecular inversion probe microarray	Not reported	Müllerian adenosarcoma	16	3 (19%)	[41]

synthesis. This generates regions of complex rearrangements with distinguishable junctional microhomology [50], which do not satisfy the classical descriptions of chromothripsis [30,8]. Hence, Holland and Cleveland suggested a different term 'chromoanagenesis' for all catastrophic events leading to complex chromosomal rearrangements involving one or a few chromosomes [51], outlined in Fig. 2. Chromothripsis is a subset of chromoanagenesis. The above-mentioned chromosomal rearrangements characterised by regions of microhomology resulting from FoSTeS and MMBIR are designated 'chromoanasynthesis'. An additional single punctual genome-scrambling event is 'chromoplexy', derived from the Greek word *pleko*, which means 'to weave' or 'to braid'. Chromoplexy is defined as an accumulation of linked translocations involving multiple chromosomes (a maximum of 6 chromosomes simultaneously has been detected so far). The resulting chromosomal rearrangements show little or no copy number alterations, in contrast to chromothripsis, which is generally limited to one or two chromosomes and shows oscillations between two different copy number states. Chromoplexy was first detected in prostate cancer, where it affects up to 40% of cases [52] and is thought to primarily result from deletion/rejoining mechanisms [53].

The relatively subtle differences in the genetic signatures of the chromoanagenetic subtypes require mate-pair sequencing to distinguish chromothripsis from alternative forms of complex chromosome rearrangements generated by catastrophic events [54].

2.3. Frequencies of chromothripsis in cancer genomes

Despite the lack of consensus on the exact definition of the chromothriptic genomic signature, several general deductions on the frequencies of chromothripsis in cancer genomes have been made. Initially, chromothripsis was considered a relatively rare event in the development of cancers, as the seminal paper from the Campbell group reported chromothripsis to occur in approximately ~2%–3% of all cancers, with a high incidence particularly in bone tumours (25%) [8]. In a different study, 124 out of 8227 tumour samples (1.5%) were suspected to contain chromothriptic patterns as detected by array-CGH [55]. Cai et al. detected chromothripsis in 918 samples from database of 20,000 oncogenomic arrays from 132 different cancer types [39]. From the studies listed in Tables 1–3 on unbiased sets of genomes from various cancers it is rapidly becoming evident that tumour cell types display a range of frequencies of chromothripsis. For example, a high incidence of chromothripsis is found in osteosarcomas [8,56], oesophageal adenocarcinomas [57,58], medulloblastoma [59,60], uterine leiomyomas [61,62] and glioblastomas [55,63,64], while there are relatively few cases reporting chromothripsis in renal [65] and hepatocellular carcinoma [55].

Interestingly, particular chromosomes have been reported to be more sensitive to chromothripsis compared to others. Chromothriptic-like patterns were detected more frequently on chromosomes 8, 11, 12 and 17 in a 2014 screen of 22,347 cancer genomes [39]. In acute myeloid leukaemia, chromothripsis was observed in almost all chromosomes, with chromosome 7 being most frequently affected [66]. Among the chromothripsis events detected in pancreatic cancers, 11% occurred on chromosome 18 while 8% occurred on chromosome 12 [47]. In osteosarcomas, chromothripsis amplification affected mainly chromosomes 5, 12 and 17 [56]. Chromothripsis events were concentrated on chromosome 17 in all breast cancer subtypes [38,67] and on chromosomes 9 and 12 in glioblastomas [68]. 54% (81 of 150) of chromothripsis detected in bladder cancer involved chromosomes 4, 5, and 6 [69]. Chromothripsis on chromosome 13 is a recurrent abnormality in high-risk myelodysplastic syndromes [70]. A possible explanation for the increased occurrence of chromothripsis in particular chromosomal regions could be that these regions are structurally more fragile. Alternatively, certain chromothriptic rearrangements might be selected for because they result in a proliferative advantage for tumour development.

Table 2
Examples of studies reporting chromothripsis in cancer genomes detected by sequencing that fulfil all criteria suggested by Korbel & Campbell.

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Ref.
Whole genome sequencing	The rearrangements show geographic localization within the genome. Copy number changes oscillate between a maximum of three states Clustering of at least 50 breakpoints across one or multiple chromosome (arms) Random orientation of breakpoints	Chronic B cell lymphocytic leukaemia	10	1 (10%)	[8]
Whole genome sequencing	The rearrangements show geographic localization within the genome. Copy number changes oscillate between a maximum of three states Clustering of at least 50 breakpoints across one or multiple chromosome (arms) Random orientation of breakpoints	Osteosarcoma & chordoma	20	5 (25%)	[8]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	7 different tumour types	64	11 (9%)	[173]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	Basal-like breast cancer	12	0 (0%)	[173]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	Colon Adenocarcinoma	3	0 (0%)	[173]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	Glioblastoma	18	7 (39%)	[173]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	Lung adenocarcinomas	6	2 (33%)	[173]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	Lung squamous cell carcinoma	13	2 (15%)	[173]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	Ovarian cancer	11	0 (0%)	[173]
Paired-end sequencing	Bedtools cluster to determine breakpoint clusters and Monte Carlo simulation	Renal adenoma	2	0 (0%)	[173]
Paired-end sequencing	1) Affected locus comprises a region exceeding 10 Mb 2) At least 13 breakpoints within the region 3) Breakpoints comprising the cluster involved one or two chromosomes 4) Breakpoints comprising the cluster include alternating copy number states, insertions and loss of heterozygosity	Prostate cancer	132	19 (14%)	[145]
Whole genome sequencing	Clustering of breakpoints, oscillating copy number state, randomness of DNA fragment joins and ability to read the derivative chromosome	Supratentorial ependymoma	9	9 (100%)	[143]
Whole genome sequencing	Clustering of breakpoints, oscillating copy number state, randomness of DNA fragment joins and ability to read the derivative chromosome	Posterior fossa ependymoma	32	0 (0%)	[143]
Whole genome sequencing	Shatterproof software - hallmark score of 0.37	Glioblastoma	12	9 (75%)	[63]
Whole genome sequencing	Korbel and Campbell 2013 criteria At least ten changes in segmental copy number involving two or three distinct copy-number states on a single chromosome	Esophageal squamous cell carcinoma	31	17 (55%)	[58]
Whole genome sequencing	Chrom-AL algorithm	Pancreatic cancer	191	120 (63%)	[47]

Table 3
Examples of studies that report chromothripsis in cancer genomes detected by sequencing with more relaxed criteria.

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Ref.
Whole exome sequencing	At least ten alternating switches within 50 Mb per chromosome	Leiomyosarcoma	49	17 (35%)	[174]
Whole genome sequencing	At least 20 breakpoints per chromosome	Uterine leiomyomas	36	15 (42%)	[61]
Whole genome sequencing	At least 20 breakpoints per chromosome	Uterine leiomyomas	38	5 (13%)	[62]
SNP array and whole genome sequencing	At least 10 transitions between 2 or 3 copy number states, with loss and preservation of heterozygosity in one or few chromosomes	Esophageal adenocarcinoma	123	40 (32%)	[57]
Whole genome sequencing	At least 31 rearrangements and 11 translocations per chromosomal arm	Hepatocellular carcinoma	88	5 (5.7%)	[76]
Whole genome sequencing	Not reported	Hepatocellular carcinoma	4	1 (25%)	[175]
Whole exome sequencing	Not reported	Anal squamous cell carcinoma	6	1 (17%)	[176]
Whole genome sequencing	Not reported	Small cell lung cancer	110	2 (2%)	[177]
Whole genome sequencing	Not reported	Glioblastoma	110	18 (16%)	[64]
Whole genome sequencing	Not reported	Glioneuronal tumours	114	3 (3%)	[156]
Whole genome sequencing	Not reported	Meningioma	11	1 (9%)	[178]
Whole genome sequencing	Not reported	Medulloblastoma	1022	14 (1%)	[72]

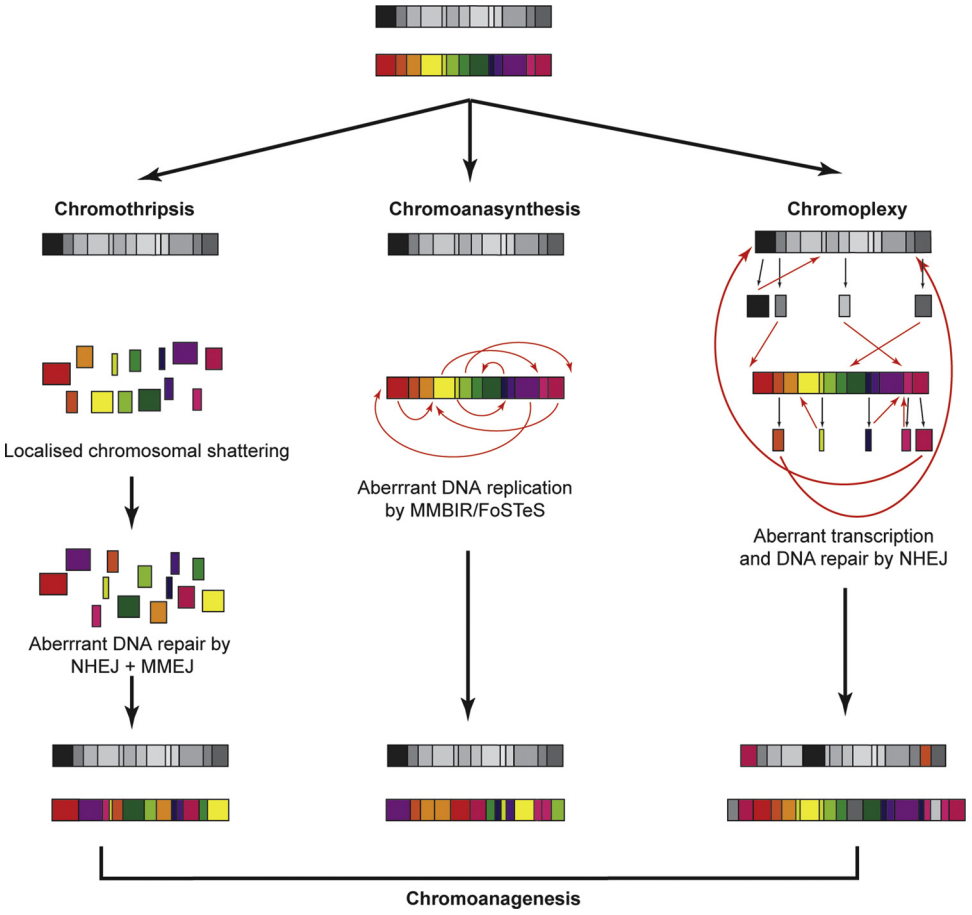

Fig. 2. Schematic overview of catastrophic chromosomal rearrangement phenomena collectively known as chromoanagenesis. Chromoanagenesis refers to all catastrophic events leading to complex chromosomal rearrangements involving one or a few chromosomes. Chromothriptic rearrangements can result from shattering of one chromosome or chromosome arm followed by incomplete DNA repair through non-homologous end-joining (NHEJ) and microhomology-mediated end joining (MMEJ), generating complex rearrangment of a single chromosome (arm). Chromoanasynthesis is the result of erroneous DNA replication of a single chromosome through fork stalling and template switching (FoSTeS) and microhomology-mediated break induced replication (MMBIR) which generates regions of complex rearrangements with distinguishable junctional microhomology. Chromoplexy involves linked translocations of multiple chromosomes, thought to result from aberrant transcription and DNA repair by NHEJ.

2.4. Factors linked to chromothripsis

A few studies have linked signalling proteins to the occurrence of chromothripsis. The Korbel lab was the first to report that tumour genomes from patients with Li-Fraumeni syndrome (OMIM #151623) carrying germline TP53 mutations, showed massive genomic rearrangements consistent with chromothripsis [59]. Further analysis of additional tumour entities further confirmed a strong association between mutations in TP53 and chromothripsis in childhood cancers [71], medulloblastoma [60,72], acute myeloid leukaemia [59,73,39,66,74], myelodysplastic syndromes [70], glioblastoma [75,63], hepatocellular carcinoma [76] and bladder cancer [69]. In support of this, in an unrelated study, rats heterozygous for TP53 knockout developed osteosarcomas in which chromothripsis and other complex structural rearrangements were detected [77]. As TP53 is required for the induction of cell cycle arrest, DNA repair and apoptosis following DNA damage [78], TP53 inactivation will allow uncontrolled proliferation of cells with DNA damage from chromothripsis. Therefore, a mutation in TP53 could be predicted to be accompanied by increased incidences of chromothripsis. However, this association is not fully penetrant, as chromothriptic rearrangements have been detected in tumours with wild-type TP53 [75] and not all tumours with aberrant TP53 show

chromothripsis [61,76].

Chromothripsis has also been associated with amplification of EGFR, MDM2 and MDM4 in glioblastoma [63] as well as deletions of CDKN2A, PTEN and SETD2 in leukaemia [74,79].

Increased frequencies of chromothripsis has also been associated with hyperploidy (an increase in modal chromosome number). This was uncovered by the Korbel lab, where an elegant integrative cell-based method termed "complex alterations after selection and transformation" (CAST) was utilised to detect the mechanistic basis of chromothripsis. CAST combines induction of double-strand DNA breaks with soft agar selection followed by massive parallel sequencing [80]. The CAST analysis revealed a significant increase in chromothriptic events in hyperploid compared to diploid cells *in vitro* [80]. In addition, the occurrence of chromothripsis was found to be higher in hyperploid Sonic-hedgehog pathway-driven medulloblastomas [80] and in childhood cancers [71] compared to diploid equivalent tumours *in vivo*. The patterns of somatic alteration in these tumours were consistent with hyperploidization preceding the chromothripsis event [80,81]. Using the algorithm ChromAL, Notta et al. also confirmed the higher incidence of chromothripsis in polyploid pancreatic tumours than diploid tumours [47]. However, in contrast to the findings from the Korbel lab, the majority of chromothriptic events were observed prior to polyploidization. This suggests that in these tumours, polyploidization exacerbated the pre-existing genetic instability after the one-step chromosomal rearrangements, thereby driving tumourigenesis [47].

The association between age and chromothripsis has been controversial. Chromothripsis did not seem to correlate with age in osteosarcomas, as it is detected throughout all stages of life with incidence being highest at adolescence and old age [56]. Similar findings were also observed for prostate cancers [82]. However, in acute myeloid leukaemia [74] and 132 tumour types studied in a screen [39], chromothripsis incidence seemed to increase with advanced age.

3. Molecular mechanisms underlying chromothripsis

As is evident from the previous sections, chromothripsis has been found in different cancer types and may represent one mechanism by which mutations engender tumourigenesis. Chromothripsis was first hypothesised to result from the localised shattering of chromosomes followed by aberrant DNA repair [8] (see Fig. 1). Several observations suggested that chromothripsis was a consequence of double-strand DNA breaks. Individuals with ataxia telangiectasia (OMIM #208900), caused by homozygous inactivating mutation of the key DNA damage response protein ataxia-telangiectasia mutated (ATM), showed increased frequencies of chromothriptic events [83]. Furthermore, complex genomic reorganisation similar to chromothripsis was also detected after integration of transgenes into the genomes of various transgenic animals *via* double-strand DNA breaks [11]. These observations raised a number of questions, including: What causes shattering of the genetic material? How is shattering confined to one or a few chromosomes? Why is the shattered DNA not lost to the cell? Which DNA repair mechanisms are involved?

In recent years, several mechanisms have been proposed to answer these questions and are beginning to shed light on the origins of chromothripsis. Here, we aim to provide an integrated overview of the non-mutually exclusive cellular mechanisms that can potentially lead to chromothripsis.

3.1. Chromothripsis from DNA damage in micronuclei

The micronucleus model has been proposed as an explanation for chromothriptic rearrangements (see Fig. 3). Micronuclei (previously known as Howell-Jolly bodies) are small, round, extra-nuclear structures consisting of a lipid bilayer surrounding DNA [84]. For years, micronuclei have been used as indicators of genotoxicity and chromosomal instability [85,86]. Indeed, micronuclei are known as highly reliable markers for risk prediction, screening, diagnosis and prognosis as well as treatment management in cancers [87]. There are two types of micronuclei; whole-chromosome or centric micronuclei form around whole chromosomes with an intact centromere that lag during mitosis (lagging chromosomes) [88], while acentric micronuclei contain chromosome fragments without a centromere resulting from exposure to radiation [89]. Whole-chromosome micronuclei were found to incur massive DNA damage, leading to severe chromosomal breaks [90,91]. Coupled with the finding that the micronuclear chromosomes could be reincorporated into the main nucleus [90], the micronucleus with its spatially-restricted chromosome(s) provided an elegant explanation for the chromothripsis phenomenon.

How does DNA damage occur in the micronuclei? It has been demonstrated that certain processes taking place in the main nucleus are dysfunctional in the micronuclei, including transcription and DNA replication [90,92–94]. This was hypothesised to generate double-strand DNA breaks due to stalled or slowed replication forks [49]. Furthermore, it was shown that micronuclear chromosomes harboured persistent DNA damage due to defective recruitment of DNA repair proteins [90,92]. In addition, DNA replication in the micronucleus was found to be asynchronous relative to the main nucleus [90,95,94]. If the replicating DNA within the micronucleus is exposed to cytoplasmic "mitotic signals" when the main nucleus is in mitosis, the micronuclear chromosomes could potentially undergo premature chromosome compaction. Premature chromosome compaction was reported to cause chromosome pulverisation [96]. Indeed, Crasta et al. found evidence of premature chromosome compaction and pulverised chromosomal fragments that originated from a single chromosome [90].

Hatch et al. reported defects in the structure of the micronuclear lamina to be the dominant factor leading to micronuclear DNA damage [91]. As early as 1989, using electron microscopy, the micronuclear envelope was shown to be incomplete [97]. This could be a result of increased curvature of the micronuclear membrane, as it has been shown that rupture of the nuclear envelope in migrating cancer cells occurs mainly at sites of high membrane curvature [98]. It was recently found that soon after nuclear envelope rupture, DNA damage appears at a region immediately adjacent to the rupture site [98,99]. However, Hatch & Hetzer [100] suggested that curvature might not play a critical role micronuclei, based on the observation that micronuclei of all sizes have similar frequencies of rupturing [91]. Alternatively, it was shown that micronuclear membranes have lamin B1 defects [101,102] and disruption of nucleopore complex proteins NUP153, TPR, SEC61B, LBR and Lap2beta [91,93]. Indeed, very recently it was shown that only "core" nuclear envelope proteins, and not the "non-core" nuclear envelope proteins, including nuclear pore complex proteins, assemble efficiently on lagging chromosomes that can be encapsulated within micronuclei [103,104]. The Vagnarelli lab demonstrated loading of nuclear pore complex proteins onto the lagging chromatin to be inhibited by CDK1, PLK1 and Aurora B kinase [103], while the Pellman lab has found the spindle microtubules to inhibit proper recruitment of these "non-core" envelope proteins, independent of Aurora B, when the micronuclear membrane is assembled around mis-segregated chromosomes during mitotic exit [104]. Consistent with this, lagging chromosomes that are a distance away from the spindle midzone, restored envelope formation and displayed concomitant decrease in DNA damage [104]. While spontaneous rupture of the main nuclei in cancer cells is rapidly repaired [105], defective assembly of the micronuclear envelope is mostly irreversible [91].

Since micronuclear chromosomes are exposed following rupture, it is possible that certain cytoplasmic components, such as endo- or exonucleases can induce DNA damage when they come into contact with the contents of the micronucleus. Indeed, the cytoplasmic 3′ repair exonuclease 1 TREX1 has been found to cleave chromosomal DNA outside the nucleus [106].

Unequivocal experimental evidence linking chromothripsis to lagging chromosomes and micronuclei encapsulation was demonstrated by

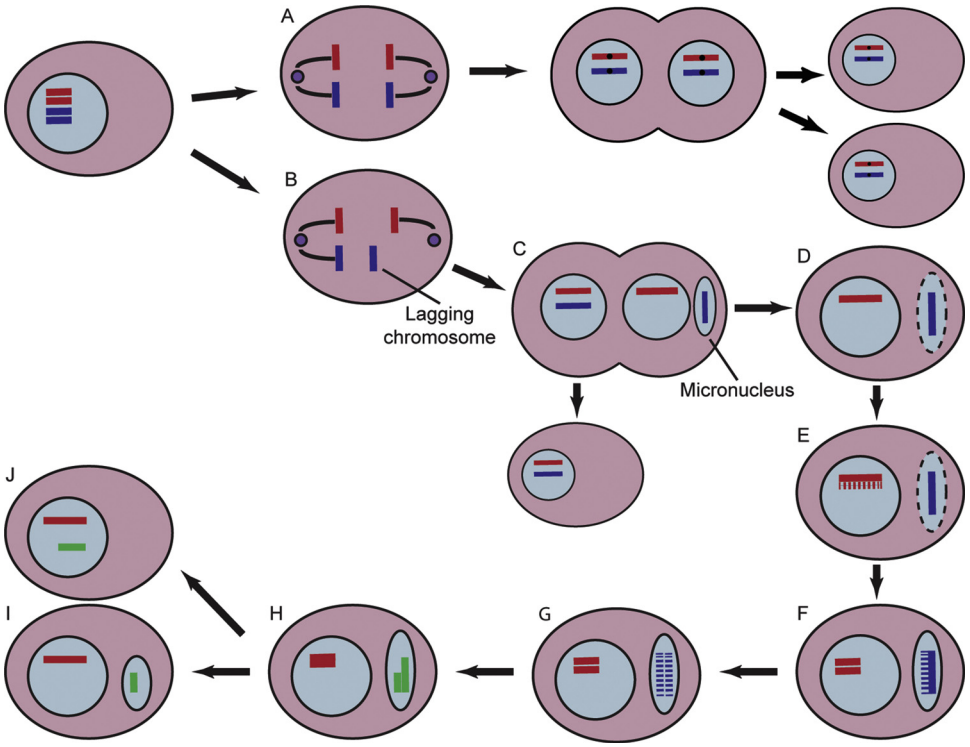

Fig. 3. Chromothripsis can result from spatial isolation of chromosomes into a micronucleus. (A) During mitosis, the mitotic spindle segregates chromosomes to two daughter cells. (B) As a result of kinetochore-microtubule mis-attachments of the mitotic spindle, whole chromosomes can lag during mitosis. (C) This leads to encapsulation of the lagging chromosome into a micronucleus when the nuclear envelope is reformed during telophase. (D) The micronuclear envelope (dotted line) is defective compared to main nucleus (black line), which affects nucleocytoplasmic transport within the micronucleus. (E) Therefore, DNA replication in the micronucleus (shown in blue) is asynchronous relative to the main nucleus (shown in red). (F) When the main nucleus enters mitosis, the micronucleus is still undergoing DNA replication. (G) This uncoordinated replication can lead to premature chromosome condensation of the genetic material within the micronucleus, causing the DNA to shatter. (H) The decreased micronuclear integrity also compromises the recruitment of DNA damage-response factors, leading to incorrect assembly of chromosomal fragments (shown in green). The micronucleus and its content can be degraded or extruded from the cell, (I) distributed to daughter cells or (J) be reincorporated into the main nucleus, thereby contributing to chromosomal instability.

Zhang et al. [107]. Here, the authors used an elegant combination of live-cell imaging to track cells after induction of micronuclei by nocodazole-mediated microtubule depolymerisation [108], followed by single cell sequencing of the daughter cells [107]. The genetic material within the micronucleus is under-replicated and could therefore be identified through its asymmetric distribution in the daughter cells. Genomic analysis of these cells revealed *de novo* chromothriptic rearrangements on chromosomes that were previously encapsulated in a micronucleus [107].

Additionally, micronuclei might contribute to the development of chromothripsis through alternative mechanisms. In prostate cancer, chromothripsis was associated with dysregulation of several immune genes [82]. Recently, it has become clear that rupture of the micronuclear envelope can lead to activation of the immune response through cyclic GMP-AMP synthase (cGAS) signalling [109]. cGAS is a cellular DNA sensor, originally discovered as a part of the innate immune system, whose localisation is normally restricted to the cytoplasm [110,111]. After rupture of the micronuclear envelope [109], cGAS gains access to the encapsulated genetic material [112,113], binds the DNA and catalyses the formation of cyclic GMP-AMP (cGAMP). cGAMP then triggers phosphorylation and activation of stimulator of interferon genes (STING) [110,111] and downstream signalling [109,112]. These studies revealed a potential role of micronuclei in the mechanism behind the association of chromothripsis and aberrant expression of immune genes.

3.2. Telomere attrition can facilitate chromothripsis

Telomere loss is known to cause shattering of the genetic material, through breakage-fusion-bridge (BFB) cycles [114]. Several additional observations increased speculation about a role for telomeres in chromothripsis. Particular subtypes of chronic lymphocytic leukaemia showed significantly shorter telomere lengths in cases with chromothripsis compared to those without [115]. Tumours with chromothriptic patterns have also been reported to show increased activity of mechanisms responsible for telomere maintenance [116]. Chromothriptic breakpoints are frequently located within the telomeric regions of a chromosome, suggesting a possible role of telomere erosion in breakpoint clustering [53]. Experimental evidence supporting this hypothesis was recently provided by the Korbel, De Lange and Boulton labs [80,106,117], schematically depicted in Fig. 4.

Human telomeres consist of (TTAGGG)n tandem repeats capped by shelterin proteins [116]. This shelterin complex prevents recognition of the telomeres as double-strand DNA breaks, thereby preventing activation of the DNA damage response [31]. During normal somatic cell division, the telomeres shorten due to inactivation of the telomerase enzyme required for replication of the telomeres. After several rounds of proliferation, the telomeres reach a critical length and cellular senescence is activated in a TP53- and pRB-dependent manner, to prevent undesirable cellular proliferation. Loss of TP53 and pRB prevents activation of cell cycle arrest in response to shortening telomeres. This leads to continuation of cell proliferation and telomere shortening, eventually resulting in dysfunctional and unprotected telomeres. When the protective effects of the telomeres are lost, DNA repair mechanisms can generate end-to-end telomere fusions resulting in dicentric chromosomes. These dicentric chromosomes are notorious for entering BFB cycles [118]. During anaphase, the centromeres of the dicentric chromosome may be pulled in different directions of the diving cell [93]. The ends of the chromosomes then remain connected between the two daughter cells, preventing the completion of segregation during mitosis and creating a chromatin bridge. Indeed, it has been suggested that the telomere attrition-related BFB cycles could lead to chromothripsis [8,119]. For instance, following formation of dicentric chromosomes, breaks can occur at a region between the two centromeres. The damage may occur at the cleavage furrow during cytokinesis [51,120], or accrue over repeated BFB cycles [119]. The latter does not strictly fit into the existing chromothripsis criteria of “a single event”, also pointed out by Sorzano et al. [119]. In fact, work done by Bignell et al. [121] has shown that BFB cycles create inverted duplications. This is inconsistent with the typical random chromosome rearrangement observed for chromothripsis [30].

Indeed, chromothripsis was detected *in vitro* after depletion of either

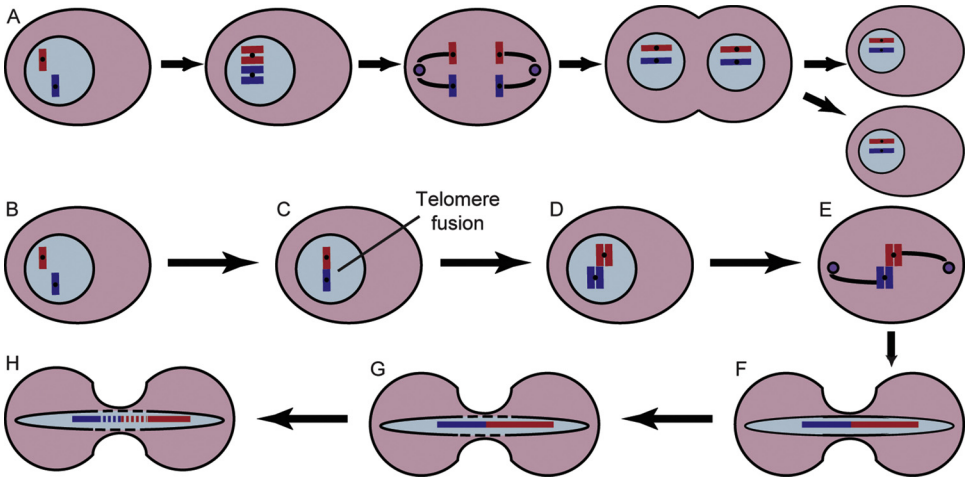

Fig. 4. Chromothripsis can result from telomere attrition. (A) During mitosis, the mitotic spindle segregates chromosomes to two daughter cells. (B) When the protective ends of the telomeres are lost, (C) DNA repair mechanisms can generate end-to-end telomere fusions resulting in dicentric chromosomes. (D) After DNA replication, (E) the various centromeres of one dicentric chromosome may be pulled in different directions of the diving cell, (F) creating a chromatin bridge. (G) The nuclear membranes surrounding the chromatin bridge can rupture, (H) which exposes the chromatin in the bridge to cytoplasmic exonucleases that resolve the bridge by converting it into single-stranded DNA fragments.

the shelterin complex protein TRF2 [80] or the telomere maintenance protein regulator of telomere length 1 (RTEL1) [117]. Maciejowski et al. provide a mechanistic explanation for how telomere crisis could lead to chromothripsis [106]. The authors induced chromatin bridges in hTERT-RPE-1 cells with disabled TP53 and pRB, by expressing a dominant negative allele of TRF2, thereby inducing telomere fusions [106]. They observed that the nuclear membranes surrounding the chromatin bridge rupture, thereby exposing the chromatin in the bridge to the cytoplasmic exonuclease TREX1. TREX1 resolves the chromatin bridge by converting it into single-stranded DNA. Whole-genome sequencing of cellular clones post-telomere crisis identified hallmarks of chromothripsis [106], confirming a causative relationship between telomere attrition and chromothripsis. These studies also explain the localised appearance of genomic rearrangements observed in chromothripsis, as only the DNA residing within the chromatin bridge is exposed to TREX1 activity.

3.3. DNA repair mechanisms involved in chromothripsis

After shattering of the chromosomes, either through micronuclei incorporation or telomere dysfunction, the genetic material needs to be repaired for it not to be lost to the cell. Mammalian cells have three main double-strand DNA break repair mechanisms at their disposal, namely homologous recombination (HR), classical non-homologous end-joining (NHEJ) and alternative non-homologous end-joining or microhomology-mediated end joining (MMEJ) [122]. HR only occurs after DNA replication during S and G2 phase, because it requires the replicate DNA as a template to accurately repair a double-strand DNA break in an error-free manner. NHEJ has a higher capacity for repair and is active throughout the cell cycle, but is error-prone because it introduces insertion/deletions (indels). MMEJ relies on microhomologous sequences on either side of the break [123]. As MMEJ is also error-prone but always results in deletions, each of these repair mechanisms leave their own characteristic signature. NHEJ can offer an explanation for the presence of deletions, insertions, inversions and translocations on the resulting rearranged chromosomes following chromothripsis. However, chromothriptic chromosomes can also have extra copies of DNA fragments, in the form of duplications or triplications [12], which are most likely not the result of NHEJ. This suggests involvement of additional DNA break repair mechanisms in chromothripsis. Sequencing of the chromothriptic breakpoints revealed a lack of homology surrounding the breakpoints in the majority of cancer patients [8,57,63], congenital diseases [13,124,125] and in cells with induced chromosome segregation errors *in vitro* [107]. It is therefore highly unlikely that break repair involves HR. Out of the three repair mechanisms, only the role for NHEJ in chromothripsis has been confirmed experimentally. Inhibition of NHEJ resulted in decreased genome reorganisation following chromosome fragmentation induced by either chemotherapeutic treatment [126] or Y chromosome centromere inactivation *in vitro* [127].

3.4. Integration of proposed mechanisms underlying chromothripsis

In summary, various cellular mechanisms have been shown to generate chromothriptic genomic rearrangements *in vitro*. These different mechanisms may give rise to different chromothriptic signatures. Some chromothriptic patterns show rearrangements along the entire chromosome, which is considered indicative of shattering after chromosome incorporation into a micronucleus. Alternatively, some cases report chromothriptic rearrangements restricted to a particular chromosome arm or terminal region, suggesting they originate from BFB cycles as the result of telomere attrition [128,106]. This could include inverted repeats, large heterogeneous duplications on the end of the chromosome, the lack of a telomere, anaphase bridges, and extensive amplification of subtelomeric DNA [129]. We speculate that since these rearrangements occur in particular chromosomal regions containing specific genes, this may result in discernible molecular signatures. For example, telomeres have been shown to influence gene expression through the telomere position effect [130,131]. Genes located near telomeres can undergo reversible transcriptional silencing, which is relieved as the telomeres shorten during cellular aging. In the chromothriptic cases attributed to telomere malfunction such genes could become relocated and/or reactivated. Additionally, genes associated with deficiencies in replication or repair of telomeres can also increase the rate of telomere loss. Similarly, molecular signatures associated with homologous recombination deficiency may be linked with micronuclei resulting from unrepaired double-stranded breaks. Therefore, it would be interesting to study the gene expression profiles from chromothripsis with separate underlying causes. We envision it may be possible to detect an association between cellular signalling pathways and different causative mechanisms for chromothripsis.

Both cellular mechanisms that have been experimentally shown to result in chromothriptic rearrangements could also explain why chromothripsis is linked to polyploidization [80,71,47]. Progressive telomere dysfunction is known to cause cytokinesis failure leading to polyploidization [132]. Additionally, tetraploid cells are known to frequently mis-segregate chromosomes, giving rise to lagging chromosomes and micronuclei due to extra centrosomes [133]. Hence, telomere dysfunction and micronuclei could potentiate chromothripsis through ploidy variation as well.

It is also possible that the mechanisms described above are non-mutually exclusive. For example, telomere attrition and micronuclei formation may exist in the same mechanistic model underlying chromothripsis origin. For instance, although telomere dysfunction induced

by TRF2 depletion did not lead to increased number of micronuclei [80], the resolution of chromatin bridges in cancer cells has been shown to give rise to micronuclei [93]. Additionally, telomere crises induced tetraploidisation [106], which can promote chromosome mis-segregation and micronuclei formation.

Mechanisms linking cellular processes and molecular pathways to chromothripsis have only recently been elucidated. One can envision that additional studies will provide definitive insights into its role in cancer development. Unlike nuclear rupture in micronuclei and cells with fragmented dicentric chromosomes that have been shown to promote chromothripsis [91,106], the consequences of transient nuclear envelope rupture have not been addressed. Interestingly, nuclear envelope rupture that occurs transiently during interphase is enhanced by the loss of TP53 [134]. It is possible that tumour suppression by TP53 prevents nuclear rupture thereby protecting the cell from genomic rearrangements. Incidentally, cells can also be protected from the deleterious consequences of nuclear envelope rupture by the endosomal sorting complexes required for transport (ESCRT-III) complex by facilitating nuclear envelope repair [99,98]. Nuclear envelope rupture relies on contractile actin bundles that interact with the nucleus *via* the linker of nucleoskeleton and cytoskeleton (LINC) complex [135]. Although loss of actin bundles or the LINC complex did not rescue nuclear envelope it decreased chromatin hernia number and size. Additionally, nuclear rupture in micronuclei is not based on actin-based compression as they are not confined by perinuclear actin; gradual disorganization of the lamin network of the micronucleus may be responsible for rupture instead [91]. It remains to be seen whether nuclear envelope rupture holds consequences for tumour progression as well.

4. Potential contribution of chromothripsis to carcinogenesis

Intuitively, one could envisage that cells undergoing chromothripsis would most likely undergo apoptosis as a consequence of the massive DNA damage incurred [51]. However, cells might survive chromothripsis depending on which specific genes are affected. For example, chromothripsis is more frequently detected in particular genomic regions [38,47,39,66,56,67–70], which potentially contain critical genes for the regulation of cell cycle control, DNA damage, proliferation and/or apoptosis. We anticipate that rearrangements of these genes might lead to a decreased induction of cell death upon DNA damage, resulting in cell survival. Chromothripsis may then promote tumour progression through incorporation of genetic material into double minutes, loss of tumour suppressor genes, and/or construction of oncogenic fusions.

Repair of the shattered chromosomal fragments through the above-mentioned mechanisms is thought to be incorrect and incomplete, leading to incorporation of genetic material into double minute chromosomes [107]. These are small, circular chromosomes without centrosomes, which are distributed asymmetrically to daughter cells during cell division. Double minutes can therefore be present at very high copy numbers. If they contain oncogenes, as reported for *MYC* in oesophageal adenocarcinoma [57,58] and acute myeloid leukemia [136], cells with more copies will have selective growth advantage, supporting uncontrolled cellular proliferation.

The formation of double minute chromosomes by chromothripsis, involving the micronucleus model, was recently suggested as the initial event in the generation of neochromosomes [137,107]. In contrast to double minutes, which are typically only a few megabases in size and do not contain centromeres or telomeres, neochromosomes are giant, circular or linear, functional chromosomes including centromere and telomeric domains composed of DNA fragments derived from various normal chromosomes [138]. Neochromosomes have been detected in cancers as early as the 1950s [139] and their contribution to cancer development was suggested in 1999 [140]. They are generally found in 3% of cancers, but particularly common in certain types of cancer, including WD/DDLPS subtype of liposarcoma [138]. For a long time it was unclear how neochromosomes are formed, but a recent study examining neochromosomes enriched by FACS using high-depth pair-end sequencing has revealed that the initial double minutes resulting from chromothripsis can assemble and amplify into much larger neochromosomes through additional catastrophic events [137].

Incorrect repair of shattered chromosomes can also lead to a complete loss of gene function. 11% of the chromothripsis events detected in pancreatic cancers occurred on chromosome 18, resulting in the loss of the key tumour suppressor gene *SMAD4* [47]. It has also been reported that rearrangement patterns in 16% of pancreatic cancer cases combined allelic alterations in preneoplastic driver genes *KRAS*, *CDKN2A*, *TP53* and *SMAD4* [47]. In osteosarcoma, tumour suppressor genes including *TP53*, *RB1*, *WWOX*, *DLG2* and *LSAMP* are situated in chromothriptic regions [141].

Additionally, incorrect repair of shattered chromosomes can generate undesirable chromosomal fusions, leading to novel oncogenic proteins. For example, in a primary colon cancer sample, a novel fusion involving USP9X-ERAS was detected that was formed by chromothripsis. This USP9X-ERAS fusion appeared highly oncogenic based on its ability to activate AKT signalling [142]. In the majority of supratentorial ependymomas, chromothripsis caused an oncogenic fusions between *RELA* and *C11orf95* which was shown to have tumourigenic potential both *in vitro* and *in vivo* [143].

In summary, there are multiple ways in which extensive rearrangements of the genetic material by catastrophic events can affect genes essential for normal cellular functioning, thereby creating a tumour-promoting environment.

5. Is chromothripsis a driver or passenger of oncogenesis?

So far we have described how chromothripsis has the potential to generate a genetic environment in favour of tumour development. However, the question remains as to whether chromothripsis is an initiating event or a passenger of the general state of chromosomal instability known to characterise many cancer genomes.

In some tumours, chromothripsis has been suggested as a late event. For example, chromothripsis was only detected in a subset of multiple biopsies from the same primary glioblastoma [144]. Chromosomal catastrophe was present in prostate tumours of different stages [145] suggesting that it can occur at any stage of prostate tumourigenesis.

However, there are many studies that point to chromothripsis being an early event or selectively propagated during tumourigenesis. It has been reported that chromothripsis-related rearrangements are observed at high frequency in tumours [8,51]. For example, the chromothriptic breakpoints from different regional biopsies of one primary colorectal tumour overlapped exactly [146] while in pancreatic cancer, the copy number changes from chromothripsis are essentially clonal [47]. FISH experiments in paediatric medulloblastoma showed both chromothriptic rearrangements and double minutes in the vast majority of tumour cells, not limited to particular subclones [59]. Analysis of multiple tumour samples taken at different time points from one chronic lympocytic leukaemia revealed that chromothripsis appeared years after the diagnosis and was therefore not the tumour-initiating event but it participated in the increase of aggressiveness [147]. Similarly, chromothripsis was detected in pre-neoplastic stages of myeloid leukemogenesis [66] and prostate tumourigenesis [145], suggesting it can contribute to malignant transformation. Analysis of paired samples from primary and metastatic pancreatic [47] or breast [148] cancers revealed that if chromothripsis was present in the primary tumour, it was conserved in the metastasis. This suggests that chromosomal rearrangements arise early during the development of cancer and remain stable during metastatic progression.

In addition, the cellular mechanisms underlying chromothripsis also contribute to cellular invasion and metastasis. It was recently shown that the activation of cGAS-STING signalling, resulting from rupture of the micronuclear membrane following chromosome mis-segregation, can drive invasion and tumour metastasis *in vitro* and *in vivo* [113].

Suppression of chromosome mis-segregation by overexpression of KIF2B or KIF2C/MCAK decreased metastatic burden, reduced spontaneous metastasis and prolonged survival *in vivo*, through inhibiting the formation of micronuclei and the accompanying cGAS-mediated non-canonical NF-kB signalling [113].

In conclusion, accumulating evidence points towards an early occurrence of chromothripsis in the development of cancer, therefore likely driving malignant transformation. It would be interesting to experimentally determine the malignant potential of cells containing chromothriptic chromosomes, for example using xenograft assays. In addition, after induction of either micronuclei formation or telomere dysfunction chromothriptic cells could be subjected to assays investigating both their intrinsic cancer hallmark characteristics as well as their influence on the environment.

6. Clinical relevance of chromothripsis

Apart from particular tumour entities with high incidence of chromothripsis [8,57,55], the overall percentage of tumours showing chromothriptic patterns seems to be relatively low [55,39,8]. This raises questions about the importance of chromothripsis as a tumourigenic mechanism. Yet, it is becoming increasingly clear that there is a substantial contribution of both intra- as well as inter-tumoural heterogeneity in the therapeutic response of individual patients. Increased availability of low-cost sequencing and additional tools to genetically characterise individual tumours (*e.g.* next-generation FISH probe mapping [149]) has enabled development of personalised treatment options based on their genetic profiles. Identification of particular genetic phenomena such as chromothripsis can aid in the stratification of patient subgroups. In particular, chromothripsis seems to strongly correlate with more aggressive tumours and poor prognosis in various types of cancer, including pancreatic cancer [47], multiple myeloma [150], melanoma [151], neuroblastoma [152], osteosarcoma [141] and different leukaemia subtypes [66,59,73,153,115,40,154,74]. Indeed, as shown in Table 4, studies in which samples are preselected for more aggressive cases report a high incidence of chromothripsis. Thus, chromothripsis detection can be used as a prognostic or predictive biomarker for patient outcome.

The association of chromothripsis with poor prognosis may be tumour-specific. Chromothripsis was frequently detected in clinically-insignificant grade 6 tumours of the prostate [145]. In epithelioid glioblastoma, chromothripsis was associated with intermediate prognosis [155]. All three patients with chromothripsis in a cohort of 114 glioneuronal tumours survived without progressive disease after extended follow-up [156]. This was also observed in uveal melanomas where chromothripsis did not necessarily indicate a poor prognosis [157]. For metastatic colorectal cancer, an increased progression-free survival was associated with chromothripsis [158], although this report defines chromothripsis as high breakpoint instability index, which may include alternative mechanisms of chromosomal rearrangements.

Chromothripsis has been found to be associated with the inactivation of TP53 [39,69,59,60,73,75,76]. It has been reported that paediatric tumours with chromothriptic rearrangements were relatively more likely to be the result of Li-Fraumeni syndrome, caused by germline TP53 mutation, than those without chromothripsis [159]. Therefore, it may be highly advisable to perform additional genetic testing in these patients.

Identification of chromothriptic rearrangements not only contributes to determining patient prognosis, but also positively affects treatment outcomes. The rearranged regions can potentially indicate vulnerabilities in chromothriptic tumours, thereby revealing targets for therapies. For example, MDM2-inhibitors might prove more effective in glioblastoma with chromothripsis-generated MDM2-containing double minutes [149]. Chromothripsis can also influence therapeutic outcomes by modulating the selection of particular clonal populations. Genetic characterisation of paired samples from primary and relapsed tumours has revealed that the chromothriptic rearrangements detected in the primary tumours can be stabilised, in which case there is highly significant overlap in the genetic signatures of the primary and the relapsed samples [116]. Alternatively, they may be lost by clonal selection in the relapsed samples. For example, analysis of multiple samples collected pre- and post-treatment from one case of chronic lymphocytic leukaemia demonstrated that chromothripsis was reversible by treatment and did not participate in tumour development and subsequent relapses [147]. This suggests that in some cases, although chromothripsis may drive formation of the initial tumour, it is not required for tumour maintenance [116]. These effects may be tumour-specific however as therapy-resistant clones were observed as a result of chromothripsis in gliomas and multiple myelomas [64,160]. Taken together, these studies highlight the instability of the cancer genome, thereby emphasising the need to genetically characterise individual clinical recurrence or progression.

Depending on the chromosomal regions affected, chromothriptic events can also be beneficial. For instance, chromothripsis has been reported as a spontaneous cure for a case of WHIM syndrome, by deletion of the dominant negative disease allele [161].

Due to the large number of rearrangements, chromothriptic tumours may potentially display higher sensitivity to immune therapies [162]. Chromosome mis-segregation and consequential formation of micronuclei not only provide a confined environment for chromothriptic events but can also be considered as triggers of the innate immune response, through activation of cGAS-STING signalling [113,109,112]. STING appears to be an essential component in the recruitment of immune cells to the tumour microenvironment, which is paramount to immune clearance of the tumour [163]. Many cancer cell lines have lost cGAS-STING signalling [164] and reactivation of STING signalling in these cell lines resulted in regression of various mouse tumour models through a systemic immune response [165]. It would be of interest to examine whether therapeutic activation of cGAS-STING signalling might generate a more pronounced immune response against tumour cells with increased levels of genomic rearrangements and chromosomal instability.

7. Concluding remarks

We have witnessed the emergence of a mutational game changer in this decade. The seminal discovery of chromothripsis in cancer genomes in 2011 not only challenged the long-standing concept of progressive genetic events driving tumourigenesis, but also redefined scientific views on its underlying cellular mechanisms. Chromothripsis has the potential to generate massive pro-tumourigenic mutational changes in a relatively short period of time. The nucleus has come to the forefront as being an organelle that can potentiate mutagenesis in cancers and we envision future studies to uncover detailed mechanisms regarding the role of nuclear envelope integrity in chromothripsis. For example, micronuclei have emerged not only as markers of genotoxic damage, but also as a source, thereby contributing to genomic instability and carcinogenesis.

There has been a recent flurry of research activities into nuclear envelope rupture since it was found that the resultant DNA damage may be lead to chromothripsis particularly in micronuclei and cells with telomere loss. It remains to be seen whether transient nuclear envelope rupture can also lead to chromothripsis *via* DNA damage generated, potentially *via* cytoplasmic nucleases such as 3′ repair exonuclease 1 TREX1 that come into contact with the nucleoplasm. Elucidating why cancer cells, especially metastatic cells, are more prone to rupture than normal cells, and whether these cells have evolved mechanisms to overcome repeated transient nuclear rupture, pose important implications for tumourigenesis. Another exciting area of research worth exploring is whether frequent mitochondrial-nuclear genome fusion sequences present in cancer cells [166] is associated with chromothripsis. Mitochondrial DNA fragments incorporated into micronuclei could fuse

Table 4
Examples of studies describing chromothripsis in sets of cancer genomes with clinically biased sample selection.

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Sample selection	Ref.
Array-CGH	At least 10 copy number changes involving up to three distinct copy number states per chromosome	Melanoma	20	2 (10%)	Biased: malignant melanoma	[151]
Array-CGH	Clustering of rearrangments on (part of) one or two chromosomes combined with a limited number of copy number states	Breast cancer	29	12 (41%)	Biased:High-risk breast cancer patients defined as at least stage 2 or higher breast cancer and/ or < 50 years old.	[67]
SNP array	CTLPScanner Copy number aberration status change events of ≥11 and Log10 of likelihood ratio of ≥8. To exclude artifacts, only chromosomal segments of size ≥50 kb were considered.	Pancreatic intraepithelial neoplasia	11	4 (36%)	Biased: high grade	[43]
SNP array	At least 5 switches between 2 and more copy number states on an individual chromosome	Chronic lymphocytic leukaemia	97	48 (39%)	Biased: High-risk, relapsed/refractory CLL in the phase II trial CLL2O trial	[115]
SNP array and paired-end whole genome sequencing	Clustering of rearrangments on (part of) one or two chromosomes combined with two copy number states	Colorectal cancer	4	4 (100%)	Biased: Metastatic cases	[179]
Whole genome sequencing	At least 20 breakpoints per chromosome	Neuroblastoma	75	18 (24%)	Biased: High stage neuroblastoma with poor prognosis	[180]
Whole genome sequencing	Shatterproof software - score over 0.517	Prostate cancer	186	38 (20%)	Biased|: Localised, non-indolent prostate tumour	[82]
Whole genome sequencing	Not reported	Bladder cancer	5	3 (60%)	Biased: Muscle-invasive transitional cell carcinoma of the urinary bladder	[69]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Childhood cancer	528	73 (14%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Burkitt lymphoma	15	1 (7%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Adrenocortical carcinoma	8	5 (63%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	B-cell acute lymphoblastic leukaemia (hypodiploid)	16	1 (6%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	B-cell acute lymphoblastic leukaemia (non-hypodiploid)	22	1 (5%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing		Childhood atypical teratoid rhabdoid tumour	18	0 (0%)	Biased: Excluding adult cancers	[71]

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Table 4 (*continued*)

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Sample selection	Ref.
	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.					
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Embryonal tumours with multilayered rosettes	8	2 (25%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	High-grade glioma	51	25 (49%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Paediatric medulloblastoma (all subtypes)	202	20 (10%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Paediatric medulloblastoma (WNT)	19	1 (5%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Paediatric medulloblastoma (SHH)	38	8 (21%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Paediatric medulloblastoma (group3)	54	5 (9%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Paediatric medulloblastoma (group4)	91	6 (7%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Neuroblastoma	20	0 (0%)	Biased: Excluding adult cancers	[71]

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Table 4 (*continued*)

Method of chromothripsis detection	Definition of chromothripsis	Tumour	Sample size	Number (%) chromothripsis positive	Sample selection	Ref.
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Osteosarcoma	14	14 (100%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Paediatric acute myeloid leukaemia	15	0 (0%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Paediatric supratentorial ependymomas	18	0 (0%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Pilocytic astrocytoma	105	0 (0%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Retinoblastoma	4	0 (0%)	Biased: Excluding adult cancers	[71]
Whole genome sequencing	At least ten copy-number switches on one chromosome Oscillating copy number variation (usually with changes of +1 or −1, but also between other levels where additional large-scale copy-number changes interfere), and many more of such copy-number variations in one chromosome or chromosome arm compared to the remaining genome.	Rhabdomyosarcoma	12	4 (33%)	Biased: Excluding adult cancers	[71]
Microarray	Multiple chromosomal fragmentations/high breakpoint instability index	Colorectal cancer	19	10 (52.6%)	Biased: Metastatic colorectal cancer receiving FOLFOX first-line palliative chemotherapy between August, 2011 and October, 2012	[158]
Molecular inversion probe microarray	(1) copy number oscillations of 2 or 3 copy number states. (2) copy number oscillation involve 10 or more potential breaks. (3) localised copy number oscillation within 20 Mb of a chromosomal segment. (4) copy number states alternate between heterozygosity and LOH.	Breast cancer	42	23 (61%)	Biased: Primary invasive breast carcinoma of intermediate or high nuclear grade and Nottingham histological grade 2 or 3	[38]

to broken nuclear fragments, offering a potential mechanism by which the mitochondria could pose as another “mutator” organelle besides the nucleus.

We anticipate elucidation of additional mechanistic pathways and cellular processes that underlie chromothripsis, insights of which could lead to strategies for development of novel preventive and therapeutic measures to battle cancer.

Conflict of interest

All authors confirm that there are no known conflict of interest associated with this publication.

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