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IN BRIEF

In Brief: Chromothripsis and cancer

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Abstract

Chromothripsis is a one-step catastrophic event which plays an important role during cancer development. During chromothripsis, tens to hundreds of genomic rearrangements can occur within localized regions of the genome, and lead to the simultaneous creation of multiple cancer-driving aberrations. Given that chromothripsis has a cancer-wide incidence of 2–3%, its recent discovery has significant implications for our understanding of tumour biology and evolution.

Keywords: chromothripsis; cancer; sequencing; genome rearrangement

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Introduction to chromothripsis

In the past 5 years, global genome sequencing efforts have confirmed that the majority of cancers develop through a progressive series of accumulating genetic aberrations. Gradual alteration to DNA repair mechanisms, cell survival processes and cell fate specification collaborate to produce increasingly aggressive malignancies. However, in 2011 Stephens *et al* surprised the genomics world by revealing that tens to hundreds of genetic rearrangements can occur in a one-step cataclysmic process which they termed 'chromothripsis'.

Similar to the implication of its name ('chromo' from chromosome; 'thripsis' for shattering into pieces), chromothripsis is analogous to the massive fragmentation and haphazard repair of one or a few chromosomal regions. During this process, many of the 'fragments' are lost to the cell, and the remaining pieces are reassembled into an incoherent haplotype. Amazingly, not only can cells survive such genomic devastation but, through the simultaneous disruption of tumour suppressor genes and activation of oncogenes, they can emerge with a selective advantage. Furthermore, although chromothripsis was first discovered in a patient with chronic lymphocytic leukaemia, a chromothripsis signature has subsequently been identified in a diverse range of different cancers at an average incidence of 2–3%. Conceptually, therefore, the discovery of chromothripsis suggests a punctuated equilibrium model for the evolution of a significant fraction of cancers.

Key features

There are several features of chromothripsis which differentiate it from other types of complex genomic rearrangements. Firstly, chromothripsis typically affects only one or a few chromosome regions, meaning that hundreds of rearrangements will be spatially localized within the genome. Even within affected chromosomes there is also a characteristic clustering of genomic breakpoints, affecting a single parental haplotype. Secondly, a distinctive oscillation between two copy number states arises across affected regions, with regions exhibiting a 'lower' copy number state, representing fragments 'lost' to the cell. Thirdly, within the regions at the 'higher' copy number states (ie those fragments that were reassembled), there is retention of heterozygosity. This feature, combined with the observation that chromothripsis is normally evident in all tumour cells (not merely subclones), suggests that it predominantly occurs prior to other genome rearrangements and may represent an early driving event in cancer development.

Potential causes

The cause of chromothripsis is hotly debated, and several mechanisms are currently proposed, including localized ionizing radiation, aborted apoptosis or dicentric chromosome formation with telomeric erosion. To date, the most attractive hypothesis stems from an exquisite study investigating the fate of chromosomes contained within 'micronuclei'. Micronuclei, which contain one or more chromosomes, can form due to errors in mitotic chromosome segregation. Crasta *et al* demonstrated that defective DNA replication within micronuclei can then result in those chromosome(s) being pulverized, with derivative chromosomes eventually reabsorbed into the main nucleus and distributed to daughter cells. This study therefore

provides a compelling explanation for exactly how such massive DNA damage can be localized to specific genomic regions.

Given the genetically catastrophic nature of chromothripsis, it is highly probable that the outcome is almost always cell death. However, since chromothripsis is observed in 2–3% of cancers, nascent tumour cells affected by chromothripsis must be regularly escaping programmed cell death *and* emerging with a strong selective benefit. This suggests that, at the cellular level, chromothripsis must be unnervingly common. In theory, DNA damage occurring within micronuclei has the potential to be frequent enough to explain this apparent quandary.

A high frequency of chromothripsis has been identified in tumours from patients with Li–Fraumeni syndrome (germline mutations in the TP53 tumour suppressor). Given the well-documented role of *TP53* in genome stability, it is possible that *TP53* mutation is a predisposing factor for chromothripsis, perhaps by facilitating errors to chromosome segregation and causing micronuclei formation. Furthermore, in the wake of massive DNA damage, *TP53* loss may be important to disrupt feedback mechanisms, leading to cell death. Interestingly, somatic *TP53* mutations are also strongly associated with chromothripsis in acute myeloid leukaemia, suggesting that chromothripsis must occur in combination with progressively acquired defects.

Consequences and clinical relevance

It is not difficult to imagine how the shattering of entire chromosome regions and chaotic repair (reportedly through non-homologous end-joining) can cause major disruption to tumour suppressor genes (notable examples include recurrent deletion of *FBXW7*). However, chromothripsis can also promote oncogene activation through the creation of double minute chromosomes (small circular DNA fragments) or fusion genes. The former can harbour oncogenes (eg MYC, MYCN, EGFR) and over time become highly amplified in daughter cells, due to the selective advantage conferred. An example of the latter is observed in

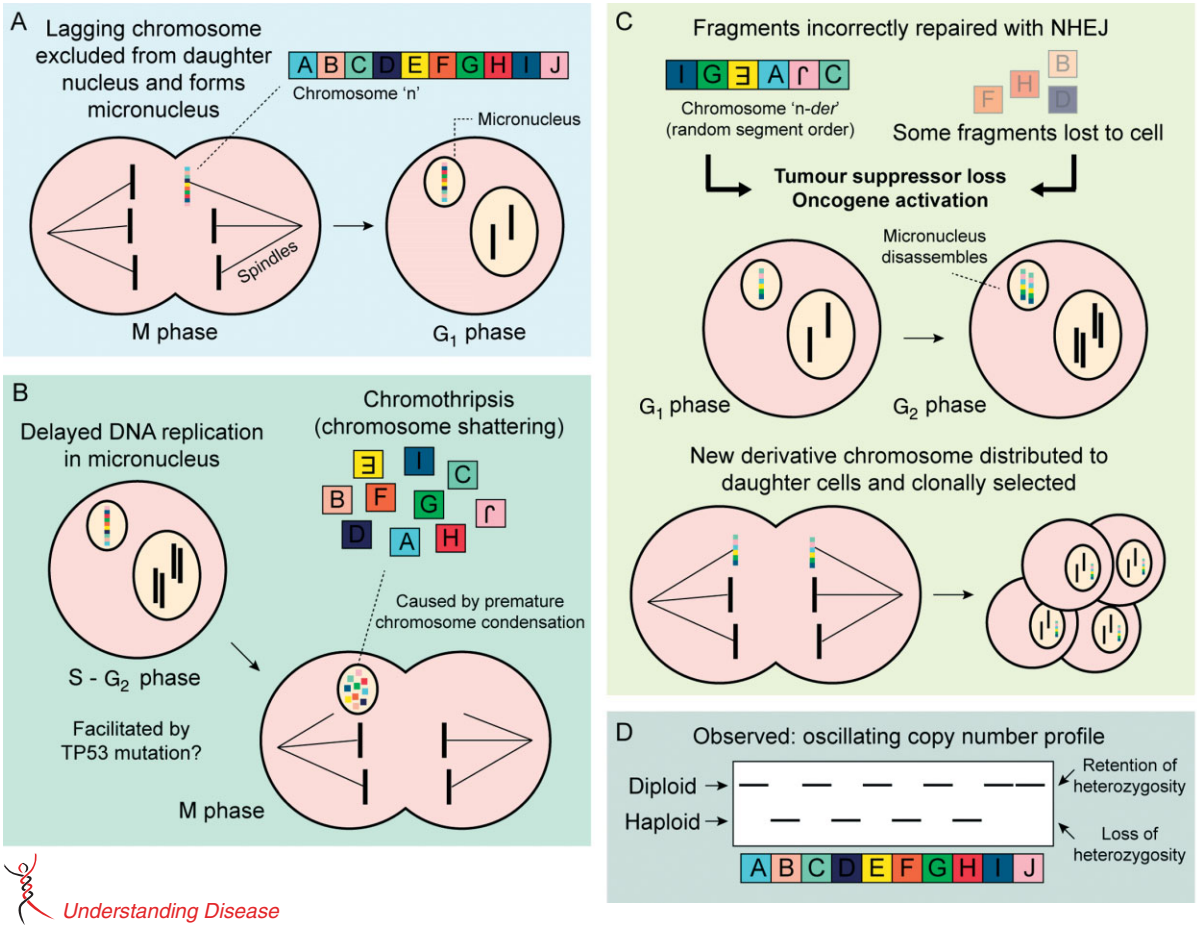

Figure 1. Chromothripsis overview. This schematic illustrates the fate of chromosome ('n') during chromothripsis, according to the 'micronuclei hypothesis'. A) Chromosome 'n' lags behind due to errors in mitosis and is incorporated into a micronucleus outside of the main nucleus. B) DNA replication within the micronucleus is delayed, and the cell enters mitosis before replication has completed. Chromosome 'n' is prematurely compacted, causing it to shatter into fragments (represented by coloured blocks). C) The shattered fragments are haphazardly repaired by non homologus end-joining (NHEJ) within the micronucleus. Some fragments are lost to the cell (lighter blocks). The new derivative chromosome 'n-der' is eventually reincorporated back into the main nucleus and distributed to daughter cells. D) The characteristic copy number profile that would be observed across chromosome 'n'.

medulloblastoma, where chromothripsis leads to the recurrent creation of *PTV1* fusion genes, driving oncogenic expression of MYC or NDRG1.

Chromothripsis has been strongly linked to poor survival in acute myeloid leukaemia, neuroblastoma and multiple myeloma. Therefore, chromothripsis diagnosis has potential to aid prognostication or stratification. Furthermore, since chromothripsis disrupts a large numbers of genes, tumours bearing the scars of chromothripsis may be susceptible to rationally targeted therapies, or drugs targeting the DNA damage response pathway (to which they may be more sensitive than normal cells).

Future directions

Chromothripsis is garnering significant interest as an important pathogenetic phenomenon and, as such, its prevalence in major cancers is likely to be rapidly determined. In light of the high frequency of chromothripsis reported in bone cancers (25%), particular focus should be given to identifying distinct cancer subtypes exhibiting high prevalence. This is likely to facilitate the discovery of collaborating genomic abnormalities, similar to TP53 mutations, which may play a mechanistic role in chromothripsis development. Once we have a larger compendium of chromothripsis genomes, it may be possible to identify common functional consequences and the relationships of any of these to clinical variables. Finally, we need to define the contribution of chromothripsis to human disease outside of cancer, since constitutionally-acquired chromothripsis has been reported in developmental disorders (albeit arising through DNA replication-based mechanisms).

The discovery of chromothripsis was completely unanticipated, and its revelation begs the question: what other surprises does next-generation sequencing have in store?

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Author contributions

Both authors contributed to preparing the manuscript and figure.

Suggested further reading

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