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GENOMIC INSTABILITY

Shattered details

Chromothripsis — extensive DNA rearrangements that are typically focused on single chromosomes or chromosome arms — is thought to occur in 2–3% of cancers. Two new papers provide intriguing insights into possible mechanisms for chromothripsis.

Crasta *et al.* investigated micronuclei as possible sites of chromothripsis; micronuclei are formed around lagging chromosomes or chromosome fragments that result from chromosome segregation errors during mitosis. The authors induced chromosome mis-segregation and micronucleus formation in human cell lines and tracked the subsequent properties of both types of nucleus using fluorescence microscopy. They noticed a spike in the number of DNA damage foci that occurred specifically in the micronuclei after the following S phase. This damage was dependent on DNA replication, which was shown in the micronuclei to take longer and to be defective in recruiting crucial replication factors.

Cell fusion experiments have previously shown that coincident DNA replication and chromosome condensation can cause chromosome shattering. Indeed, karyotyping revealed that micronuclear-derived chromosomes were frequently shattered, indicating that replication of DNA in micronuclei might persist into M phase. Importantly, the sequestration of chromosomal DNA in micronuclei and subsequent shattering provides an elegant explanation for why chromothriptic rearrangements are focused on particular chromosomal regions.

If micronuclear events underlie chromothripsis, an explanation must be found for how the shattered pieces are re-ligated in a rearranged manner and reincorporated into the nuclear genome. Live-cell imaging showed that 38% of the time, chromosomes from micronuclei rejoin the main nucleus following nuclear envelope breakdown at mitosis. Although translocation events were rarely observed (<1 translocation per 100 cells), rare oncogenic rearrangements might be positively selected during tumorigenesis. It remains to be seen whether micronuclei have an important role in chromothripsis and tumorigenesis in the absence of enforced defects in chromosome segregation.

In a separate study, Rausch *et al.* carried out whole-genome DNA sequencing on four medulloblastoma cases of the sonic hedgehog (SHH) subtype. They identified chromothripsis in all four cases, although different chromosomes were affected in each sample. By detecting regions of microhomology at the junctions of the rearrangements, these authors proposed that DNA repair by non-homologous end joining was responsible for the re-ligation. Importantly, these four samples were all from patients with Li–Fraumeni syndrome caused by *TP53* germline mutations. To assess whether the status of *TP53* correlates with chromothripsis, Rausch *et al.* analysed 98 medulloblastoma samples of diverse subtypes. They carried out *TP53* DNA sequencing and used a microarray-based DNA copy number analysis to detect chromothripsis. They found a striking correlation between *TP53* loss-of-function mutations and chromothripsis that occurred specifically in the SHH subtype: 10 out of 10 SHH-subtype *TP53* mutant tumours displayed chromothripsis compared with 0 out of 22 SHH-subtype *TP53* wild-type tumours. Furthermore, an analysis of 311 samples of acute myeloid leukaemia also revealed a considerable enrichment for chromothripsis in *TP53* mutant samples. Because p53 is involved in a multitude of cellular processes, dissection of the role or roles of p53 loss-of-function in chromothripsis will require further research, as will the connection between *TP53* loss, chromothripsis and SHH-driven medulloblastoma.

Although both of these papers provide details on potential causes of chromothripsis, more work is needed to characterize fully the underlying mechanisms and their impact on tumorigenesis.

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ORIGINAL RESEARCH PAPERS Crasta, K. *et al.* DNA breaks and chromosome pulverization from errors in mitosis. *Nature* 18 Jan 2012 (doi:10.1038/nature10802) | Rausch, T. *et al.* Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with *TP53* mutations. *Cell* **148**, 59–71 (2012)