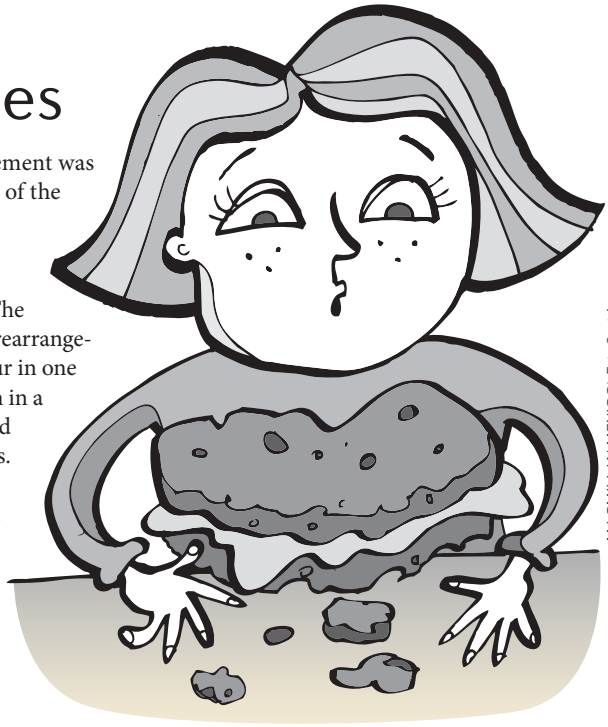
GENOME INSTABILITY

Chrombling into pieces



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It is generally assumed that tumours evolve through a progressive acquisition of mutations in the genome that allow cells to evade apoptosis, proliferate, invade and metastasize. However, in some instances one single event can lead to multiple coexisting mutations — the loss of telomeres results in end-to-end chromosome fusions that lead to chromosomal rearrangements. In a recent study published in *Cell*, Peter Campbell and his collaborators have identified a new phenomenon in which tens to hundreds of genomic rearrangements are acquired in one step. They have termed this process chromothripsis.

Using paired-end sequencing, the authors first sought to identify genomic rearrangements in ten patients with chronic lymphocytic leukaemia. In one of the patients the position of these rearrangements revealed an unusual pattern: the vast majority of the rearrangements were in one single chromosome; the copy number of the chromosomal segments was never higher than two; those regions with only one copy number were not originated by one single deletion but by multiple rearrangements; and all the alterations were clustered together in certain regions of the chromosome. When the analysed sample was compared with a sample obtained after the patient had undergone treatment, the authors found the same alterations and no new genomic rearrangements. A combination of genome re-sequencing and analysis of single nucleotide polymorphism (SNP) arrays in a large number of cell lines and primary tumours determined that this unusual pattern is present in 2–3% of cancers; in bone cancer, this extreme rearrangement was observed in up to 25% of the analysed samples.

How is the chromosome restructured in such a dramatic way? The authors argue that the rearrangements are likely to occur in one single event rather than in a series of progressive and independent alterations. Sequential rearrangements would lead to an increasingly altered genomic structure with more than two copy number states of chromosomal fragments and mutations that would be unlikely to cluster together. In the one-single-event model proposed, the chromosome (chromo) shatters (thripsis) into tens to hundreds of pieces, and some of those pieces are subsequently glued back together in a random order by the DNA repair machinery.

Now, how does chromothripsis contribute to tumorigenesis? A possible explanation was obtained by genomic analyses and fluorescence *in situ* hybridization (FISH) in a small-cell lung carcinoma cell line. This showed a normal copy of chromosome 8 and a derivative copy that was highly rearranged by chromothripsis. In addition, this cell line also contained multiple double-minute chromosomes — small fragments of extrachromosomal DNA — that were composed of numerous copies of 15 segments of chromosome 8; these segments were not in the derivative chromosome and were aligned in such a way that they led to the amplification of the oncogene *MYC*.

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Another example of the contribution of chromothripsis to tumorigenesis is the simultaneous disruption of the three tumour suppressor genes *CDKN2A* (which encodes p16), *WRN* (which encodes Werner syndrome ATP-dependent helicase) and *FBXW7* by chromothripsis that was observed in a chordoma tumour sample.

This study raises many important questions: what triggers these dramatic changes in the chromosome? By which mechanism does the chromosome break down? How are the pieces stitched together? As the authors emphasize, whatever the mechanism involved, this phenomenon seems to have an important role in chromosomal remodelling in cancer.

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ORIGINAL RESEARCH PAPER Stephens, P. J. *et al.* Massive genomic rearrangement acquired in a single catastrophic event during cancer development. *Cell* **144**, 27–40 (2011)