

disks. The fluid immediately adjacent to an end cap also rotates uniformly and therefore must make a sharp transition, within a narrow region, to join onto the shearing rotation in the bulk of the flow. The transition causes additional stresses to be present throughout the fluid, which in turn drive vertical circulation patterns (technically known as Ekman flow) that would not be present in astrophysical disks. To avoid this unwanted Ekman flow, the authors¹ work with long cylinders, so that near the midplane of the apparatus these effects are minimized.

Schartman *et al.*¹⁰ use instead a Couette system with split end caps comprised of two sliding annuli, so that four velocities can be adjusted: those of the two confining cylinders, and the rotation rates of the annuli. The Ekman circulation may thus be directly controlled. The experiment¹⁰ is also equipped to measure the internal velocity of the fluid directly. This ability serves to verify that the correct rotation profile has been achieved, as well as to detect the characteristic fluctuations in velocity that accompany a breakdown into turbulence. Paoletti and Lathrop's experiment¹, by contrast, is designed to measure only the enhanced torque, not the velocity field itself.

The two approaches have led their respective investigative teams to exactly opposite conclusions. Paoletti and Lathrop argue that their results show that astrophysical disks would be unstable to large-amplitude disturbances (as opposed to the infinitesimal perturbations assumed in Rayleigh's mathematical analysis) and become turbulent. By contrast, Schartman *et al.* maintain that there are no significant dynamical instabilities in which the Keplerian rotation field of the Couette flow — or, presumably, of an astrophysical disk — is the driving source of energy for the onset of turbulence.

By way of support, Paoletti and Lathrop can point to a recent fluid experiment by van Gils *et al.*¹¹ that finds the same quantitative relationship between the rotation parameters of the cylinders and the ensuing turbulent torque. It must be noted, however, that in the study by van Gils and colleagues, the unstable profiles are not near the Keplerian regime. On the other hand, the null result of Schartman *et al.* is itself supported by direct numerical simulations^{12,13} showing stability of the flows in question. Here, the caveat is that the simulations do not yet have viscous effects controlled at the same level that the laboratory experiments can now achieve.

Because of its central importance to astrophysics, the possibility that disks may be turbulent for purely hydrodynamical reasons will probably excite another round of intense investigative activity, both in the laboratory and on the computer. For the time being, however, we must wait a little longer for a laboratory consensus on whether Keplerian disks are, after all, intrinsically unstable, or whether, as

is currently suspected by most accretion-disk theorists, magnetic effects have an essential role in the destabilization process. ■

Steven A. Balbus is at the *Laboratoire de Radioastronomie, École Normale Supérieure, 75231 Paris Cedex 05, France.*
e-mail: steven.balbus@lra.ens.fr

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CANCER

When catastrophe strikes a cell

In 2–3% of cancers, a single genetic event may have led to hundreds of genomic rearrangements confined to just one or a few chromosomes. This finding challenges the conventional view of how mutations accumulate in oncogenesis.

JOSE M. C. TUBIO & XAVIER ESTIVILL

How do the mutations that lead to cancer come about? The traditional view¹ is that a gradual process involving continual acquisition of heritable genetic changes by cells causes cancer. There is, however, an alternative view that single catastrophic events can lead to multiple mutations. In a paper published in *Cell*, Stephens *et al.*² provide evidence for the concept of chromothripsis in cancer.

Our understanding of oncogenesis has benefited greatly from next-generation

sequencing technology. Stephens and colleagues combined next-generation sequencing² and single nucleotide polymorphism (SNP) array data^{3,4} to analyse the patterns of somatic (non-germline) genomic rearrangements in tumours. Intriguingly, they found that in some cases the changes consist of tens to hundreds of rearrangements, confined to one or a few chromosomes. The authors² coin the term chromothripsis (from 'chromo', for chromosome; and 'thripsis', for breaking into small pieces) to designate this phenomenon². Although they observed evidence of a high incidence of chromothripsis in bone tumours, it

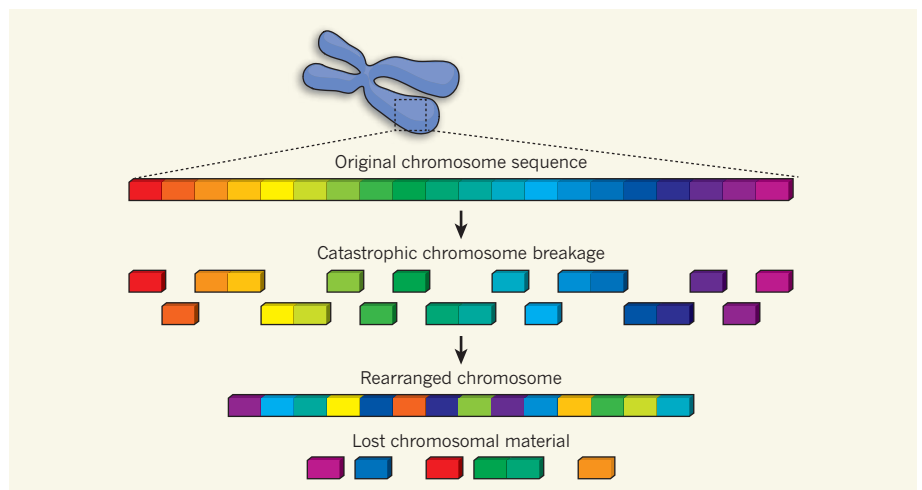


Figure 1 | Chromothripsis. Stephens *et al.*² report that, when a catastrophic event causes DNA fragmentation, its subsequent repair leads to chromosomal rearrangements, as well as the loss of some sequences. They call this phenomenon chromothripsis. (Adapted from ref. 2.)

seems to occur in at least 2–3% of all cancers.

Rearrangements are common in cancer, so how can Stephens *et al.* tell whether such mutations were caused by a single event? They argue that the final configuration of the rearrangements they observed could be explained only by a single catastrophic episode, rather than by a series of independent events. Rearrangements due to chromothripsis are usually restricted to a few chromosomes, within which breakpoints show a non-random distribution.

In a patient with leukaemia, for example, the authors found seven rearrangements clustered within a region spanning just 30,000 nucleotides. Stephens and co-workers propose that when a chromosome or chromosomal region shatters into tens or hundreds of fragments, the DNA-repair machinery reassembles some of the fragments incorrectly, leading to rearrangements (Fig. 1).

Another of the authors' observations also favours chromothripsis as the initiating event — in the final configuration, the copy number varies along each affected chromosome arm, usually alternating between just one and two copies. By contrast, statistical simulations showed that, if the rearrangements had been acquired gradually, tandem duplications should have increased the copy number of the associated genomic segments several-fold.

The potential implications of chromothripsis as a cause and/or mediator of cancer are evident. As Stephens *et al.* point out, the generation of so many rearrangements in a single genomic crisis makes it likely that more than one cancer-causing lesion would occur. Indeed, in their samples they describe several cancer-related genes that are affected by the rearrangements. In one patient, for instance, they found that a single catastrophic event resulted in the disruption of three tumour-suppressor genes — *CDKN2A*, *FBXW7* and *WRN*. In addition, on the basis of several cases, it seems that chromothripsis rearrangements can produce potentially oncogenic fusion genes, by juxtaposing coding regions of two different genes.

Stephens *et al.* clearly establish the hallmarks of chromothripsis, but the mechanism and the cause of such DNA fragmentation remain open for discussion. Because chromothripsis rearrangements are strictly limited to one chromosome or chromosomal region, the authors posit that catastrophe strikes when chromosomes condense for mitotic cell division. They assume that if the damage occurred during the interphase stage of the cell cycle — when the DNA structure is more relaxed — it is unlikely that it would lead to clusters of breaks within such well-circumscribed genomic regions. An alternative explanation for spatially restricted chromothripsis could simply be that several damaged chromosomes would decrease the probability of the cell's survival (Fig. 2).

As for the cause of chromothripsis, Stephens

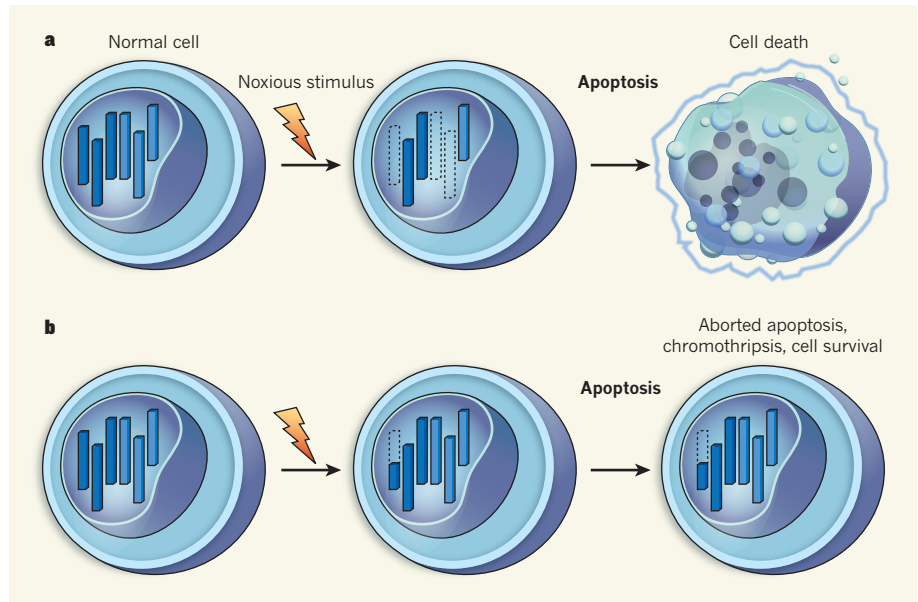


Figure 2 | Severity of damage matters. On exposure to a noxious stimulus, programmed cell death (apoptosis) probably commences, triggering DNA fragmentation (dotted regions). **a**, Consequently, most cells die. **b**, If the damage is not too severe, however, abortion of apoptosis could occur, and incorrect repair of DNA fragments could lead to the chromosomal rearrangements characteristic of chromothripsis. The surviving cells could eventually become cancerous.

et al. suggest two possibilities. For one, ionizing radiation could induce chromosome breaks. Depending on how the radiation affects chromosome structure, breaks could occur in a short or a long stretch of the chromosome. Another possibility is dysfunction of telomeres — cap-like nucleoproteins at the tips of chromosomes. Telomere dysfunction is known⁵ to promote chromosomal abnormalities that often typify cancer cells, including end-to-end chromosome fusion, anaphase bridges, aneuploidy and polyploidy. This possibility is appealing given that, in most cases, chromothripsis involves regions that extend to telomeres.

We propose a third possibility: aborted programmed cell death (apoptosis) might cause chromothripsis (Fig. 2). There is evidence⁶ that the abortion of apoptosis in its initial stages may lead to chromosomal rearrangements in cancer. Accordingly, it could be that noxious stress stimuli (such as radiation, nutrient deprivation, infection or oxygen shortage) induce apoptosis in a cell population, initiating higher-order fragmentation of chromatin (DNA–protein complexes). For most of the population, the outcome would be relentless cell death. But somehow one or a small subset of cells may not complete apoptosis and so may survive. The surviving cells would then need to repair the cleaved DNA, but some might do so incorrectly, leading to rearrangements.

This alternative hypothesis could explain the complex chromosomal configuration that characterizes chromothripsis². As for the significant non-random distribution of breakpoints along chromosomes, this could be due to targeted cleavage and/or cleavage

in the most exposed DNA regions^{7–9}.

What could drive the abortion of apoptosis? Many members of the γ -herpesvirus family can cause cancer, possibly by inhibiting apoptosis¹⁰. Could such viruses also be involved in chromothripsis? With the large amount of unbiased data that can be generated through sequencing in cancer projects, testing this possibility should be feasible.

The authors' results² indicate that chromothripsis can have cancer-promoting genomic consequences, but could equally be interpreted as implying that chromothripsis is a consequence of the initial stages of tumorigenesis. These observations are probably a snapshot of the cellular changes that occur in some cases of oncogenesis. ■

Jose M. C. Tubio and Xavier Estivill are in the Genes and Disease Programme, Center for Genomic Regulation (CRG) and Pompeu Fabra University, Barcelona, Catalonia 08003, Spain.

e-mail: xavier.estivill@crg.cat

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