News & views

Cancer

A mitotic glue for shattered chromosomes

Yibo Xue & Daniel Durocher

Two studies now shed light on how chromosomes that undergo catastrophic shattering are transmitted to daughter cells during cell division, thereby enabling them to be reassembled for the benefit of cancer cells. **See p.1041 & p.1049**

Chromosomes, like Humpty Dumpty in the nursery rhyme, can shatter into pieces. But unlike poor Humpty Dumpty, who could not be put back together by all the king's men, shattered chromosomes can be reassembled, albeit imperfectly, generating extensively rearranged chromosomes. This phenomenon is termed chromothripsis, and such chromothriptic chromosomes are frequently observed in tumours, possibly because they drive the evolution of cancer cells[1]. Exactly how chromosomes are pulverized, how they are put back together and what consequence these events have for shaping genome evolution are burning questions in chromosome biology.

Writing in *Nature*, Lin *et al.* (page 1041)[2] and Trivedi *et al.* (page 1049)[3] report that the fragments produced by chromosome shattering are held together during cell division by a complex composed of the proteins CIP2A and TOPBP1. This clustering allows for the en masse inheritance of pulverized chromosomes, which is probably fundamental to chromothripsis.

Chromothriptic chromosomes originate from mis-segregated chromosomes (those that have not reached the correct daughter cell when a cell divides in two) or from chromosomal fragments that are encapsulated outside the nucleus into abnormal nuclear structures called micronuclei (Fig. 1). These micronuclei are prone to rupture, and this is associated with chromosome fragmentation before, or on entering, the stage of cell division called mitosis[1].

The presence of chromosome fragments during cell division poses a challenge, because most fragments do not contain a specialized chromosome region called a centromere that is essential for accurate chromosome segregation. This leads to the prediction that these micronucleus-derived fragments would be randomly segregated into daughter cells. However, using a combination of microscopy approaches to examine live cells or cells preserved through a 'fixation' process, both teams observed that shattered chromosomes originating from ruptured micronuclei are clustered together throughout mitosis and, instead of being randomly partitioned into daughter cells, are inherited collectively by a single daughter cell (Fig. 1). In other words, pulverized chromosomes are held together during segregation, pointing to the existence of a 'glue' that binds them.

The peculiar challenge of segregating chromosome fragments that lack a centromere was recognized as long ago as the 1930s[4,5]. This problem is compounded by the fact that DNA repair is mainly, although not entirely, suppressed during cell division[6,7], which means that mitotic cells are unable to use the DNA-repair toolkit to reassemble broken chromosomes before mitotic exit.

An intuitive solution to the problem posed by the segregation of such chromosome fragments would be to physically link them to their corresponding centromere-bearing fragment during division – and, indeed, evidence for such tethers has been described or hinted at over the years[5]. To find the proteins responsible for gluing shattered chromosomes together, both teams tested a set of candidate proteins and identified the same complex, formed by the proteins CIP2A and TOPBP1, as being responsible for fragment tethering in mitotic cells. The finding is exciting, because this complex is implicated in the segregation of chromosome fragments lacking centromeres[8,9], strongly supporting the idea that CIP2A and TOPBP1 physically bridge broken chromosomes during cell

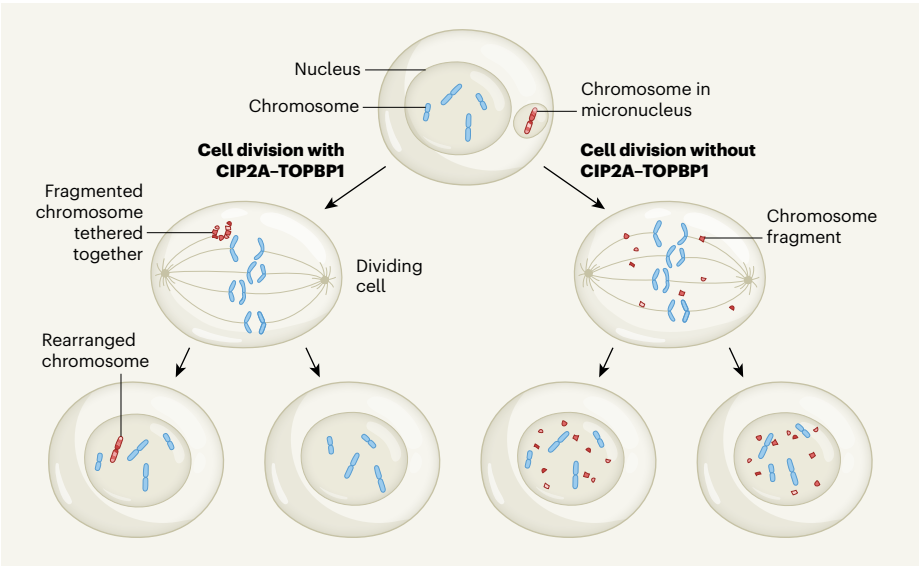

Figure 1 | Handling fragmented chromosomes during cell division. Lin *et al.*[2] and Trivedi *et al.*[3] examined what happens to shattered chromosomes during a stage of cell division called mitosis. Chromosomes can be abnormally encapsulated outside the nucleus in a structure called a micronucleus. Such a chromosome is shown here in a micronucleus that is about to rupture. Near or at the start of mitosis, this chromosome shatters. In cells with normal levels of the proteins CIP2A and TOPBP1, the chromosome fragments are tethered together. This enables the fragments to be inherited together and a rearranged chromosome forms subsequently. In cells that are deficient in the CIP2A–TOPBP1 complex, the chromosome fragments are dispersed and segregate randomly, causing loss of genetic information and affecting cell viability.

division.

Cells lacking CIP2A or TOPBP1, or that are deficient in the interaction between CIP2A and TOPBP1, are unable to cluster shattered chromosomes, leading to the dispersion of chromosomal fragments into the nuclei and cytoplasm of daughter cells. The presence of these fragments triggers a defence response (involving signalling pathways of innate immunity) after DNA is sensed in the cytoplasm.

Furthermore, both teams showed that this CIP2A–TOPBP1 complex not only accumulates on chromosome fragments but also acts specifically during mitosis, consistent with its having a tethering function at this stage of the cell cycle. Both studies also demonstrate that the loss of CIP2A-dependent chromosome tethering reduces the viability of micronucleus-bearing cells, possibly owing to the loss of genes essential for the cell's viability. Indeed, Lin *et al.* found that CIP2A-dependent clustering prevents loss of genetic material after chromosome pulverization, and Trivedi *et al.* carried out whole-genome sequencing and report that transient depletion of CIP2A results in a higher number of types of genetic alteration (deletions and inversions).

The typical chromothripsis seen in most cancer genomes is characterized by variations in the number of copies of DNA sequences (copy number)[1] arising from the loss of DNA fragments. However, the existence of a mitotic chromosome-end-tethering system suggests that this copy-number oscillation might not be a necessary outcome of chromosome shattering. Indeed, Lin *et al.* reanalysed cancer-genome sequencing data and found that they could detect a type of chromothripsis that they called balanced chromothripsis. This displays chromosomal rearrangement but without an oscillation in copy number that is typical of chromothriptic chromosomes.

Although the results of both studies are remarkably consistent, they differ in some details. Perhaps the most notable divergence pertains to the conclusion about the role in chromosome-fragment clustering of a protein named MDC1. Trivedi *et al.* conclude that MDC1 has a key role upstream of CIP2A–TOPBP1 in promoting shattered chromosome tethering, whereas Lin *et al.* observed only a minor contribution from MDC1. CIP2A–TOPBP1 has two modes of recruitment to mitotic DNA damage[8,9]: an MDC1-dependent mode that responds to chromosome breaks, and an MDC1-independent mode associated with defective DNA replication. Therefore, understanding how CIP2A–TOPBP1 associates with shattered chromosomes might help to reveal the origins of chromosome shattering, or to identify the elusive factor that recruits CIP2A–TOPBP1 to mitotic chromosomal DNA that has not replicated normally.

The results from Trivedi *et al.* and Lin *et al.* suggest that chromothripsis might be profoundly altered in the absence of CIP2A–TOPBP1-dependent clustering of shattered chromosomes, but this remains to be confirmed. Nevertheless, the identification that CIP2A–TOPBP1 acts as a mitotic chromosome tether is sure to unleash a flurry of further investigations. First and foremost on the to-do list is defining the biochemical basis of chromosome tethering by CIP2A–TOPBP1, which remains, for now, a complete mystery. The poor viability of micronucleus-bearing cells on CIP2A depletion, and the activation of innate-immune signalling caused by chromosome-fragment dispersion, suggest that it might be worth testing whether inhibition of CIP2A–TOPBP1 offers an attractive strategy for the treatment of some cancers, or a way of limiting chromothripsis-driven tumour evolution.

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Condensed-matter physics

Widespread waves spark superconductor search

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Periodic waves of changing electron density are linked to the ability of some materials to conduct electricity without resistance. Four studies reveal that such waves could emerge in more materials than expected. **See p.921, p.928, p.934 & p.940**

Superconductors are materials that exhibit zero electrical resistance when cooled to temperatures of just a few kelvin. But harnessing this remarkable property for practical applications — in energy transmission and electronics, for example — requires materials that superconduct at higher temperatures. And to induce such behaviour, it must first be understood. A particular class of high-temperature superconductor has shown an intriguing phenomenon that involves a periodic modulation of electron density, known as a pair density wave[1]. Now, writing in *Nature*, four research groups[2–5] report that pair density waves are actually more prevalent than was previously thought, with evidence for these waves in three separate materials.

Electrons in superconductors form what are known as Cooper pairs, which were first thought to move together with zero momentum and condense into a state that allows them to traverse the material without electrical resistance[6]. However, around 60 years ago, two teams of physicists independently predicted that strong magnetic fields could be applied to give these pairs non-zero momentum and make them oscillate spatially as they moved through the material[7,8]. This prediction was confirmed experimentally[9], and subsequent work[10–12] suggested that such oscillations could occur even in the absence of a magnetic field in systems that are characterized by strong interactions between electrons. These oscillations are referred to as pair density waves — but observing them is not a trivial task.

A powerful tool in the search for pair density waves is known as scanning tunnelling microscopy (STM) — a technique that visualizes the quantum states in a material with atomic resolution. There are different ways of looking for pair density waves using STM. One approach involves searching for signatures of superconductivity at low temperatures, and simultaneously observing another phase known as a charge density wave, in which the concentration of electric charge varies periodically through a material. This is because pair density waves are expected to transition into a charge-density-wave phase, which can persist at high temperatures. Another approach is to detect a periodic variation in the 'superconducting gap', which is a gap in the allowed energies of electrons in a material that directly relates to the density of Cooper pairs.