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Biophysics

A phase transition for chromosome transmission

Kazuhiro Maeshima

An analysis of chromosomes during mitotic cell division reveals that DNA and associated histone proteins condense through a process called phase transition, which helps them to resist the pushing forces involved in mitosis. **See p.183**

The faithful transmission of matching copies of DNA from a dividing mother cell to its two daughters requires the DNA to be tightly compacted. This process is fundamental to the mitotic cell divisions needed for an organism's development and maintenance, but the underlying physical principles of chromosome compaction remain unclear. Schneider *et al.*[1] provide evidence on page 183 that a key aspect of accurate chromosome transmission is condensation into a more solid-like state through a process called phase transition.

The packaging of DNA into the condensed, rod-like shape characteristic of mitotic chromosomes involves multiple levels of organization. On a local scale, negatively charged DNA is wrapped around positively charged histone proteins to form bead-like structures called nucleosomes that are linked by DNA 'strings' – this irregularly folded, beads-on-a-string structure is known as chromatin[2]. Long tails on the histones, enriched with positive charges, bind to nearby nucleosomes and mediate nucleosome–nucleosome contacts, thus compacting the chromosomes. On a larger scale, a ring-like protein complex called condensin forms an axis around which chromatin packs in loops to form a compact, rod-like shape[3].

Separating these tightly packaged mitotic chromosomes into daughter cells involves two opposing forces. First, fibres called microtubules pull the two sister chromosomes apart. Second, other microtubules make contact with the chromosome arms and push them in the opposite direction through a 'polar ejection' force (Fig. 1a)[4]. These two forces first align chromosomes around the centre of the cell and then accurately divide them into two daughters. Condensins are known to confer the mechanical stability needed for chromosomes to remain intact despite being pulled[5]. Do they also confer mechanical resistance to the polar ejection force, or is another factor involved?

Schneider *et al.* first showed that chromosomes remained resistant to the polar ejection force even when condensin was depleted (Fig. 1b). The authors confirmed that, as previously observed[6], the mitotic-chromatin density (an indicator of compaction state) was similar in condensin-depleted and control cells. However, they also found that chromosomes in the condensin-depleted cells adopted abnormal shapes.

The authors therefore investigated another possible factor – 'deacetylation' of the histone tail. Acetyl groups can modify histones, changing the physical properties of local chromatin through loss of positive charges in histone tails and so loss of nucleosome–nucleosome contacts. Histone tails are deacetylated in mitotic chromosomes[7], leading to a greater increase in nucleosome–nucleosome contacts and subsequent global chromatin compaction. Could this deacetylation explain how mechanical resistance to polar ejection forces is obtained?

Schneider *et al.* treated human cells with a drug called trichostatin A (TSA), which inhibits the histone deacetylase enzymes that remove acetyl groups from histones. As expected, TSA treatment led to histone-tail hyperacetylation,

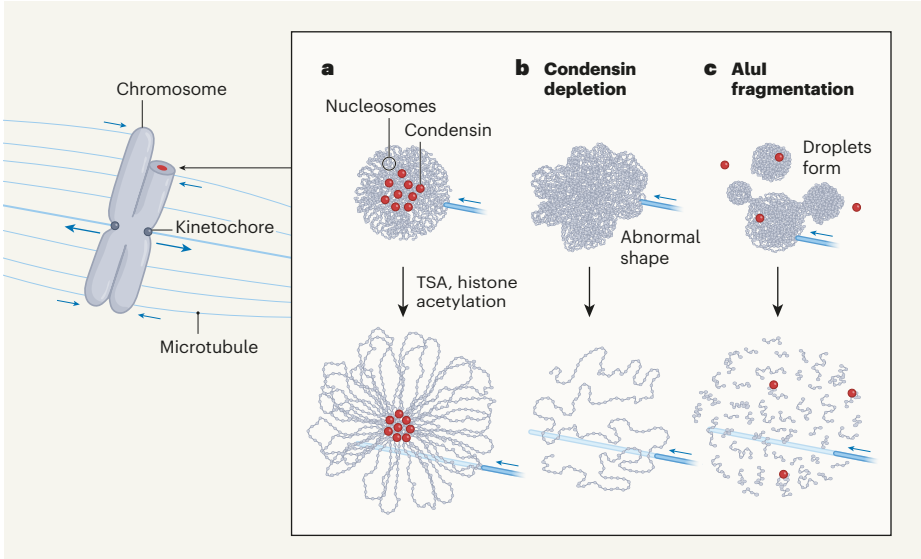

Figure 1 | Resisting pushing forces during mitotic cell division. a, Chromosomes undergoing mitosis form a rod-like shape, with an axis of condensin protein at the centre, surrounded by nucleosomes (bead-like complexes of DNA wrapped around histone proteins). Fibres called microtubules attach to kinetochore structures to pull halves of the chromosome to opposite poles of the dividing cell, and other microtubules push the chromosome arms in the opposite direction (the polar ejection force). Proper chromosome separation requires that the chromosome arms resist the polar ejection force, preventing microtubules from penetrating them. Schneider *et al.*[1] show that an absence of acetyl groups on histone tails is key to this resistance. Treatment with the drug trichostatin A (TSA), which induces histone acetylation, leads to puncturing of the chromosome surface by microtubules. **b**, When condensin was depleted, chromosomes adopted an abnormal shape, but resisted the polar ejection force until treated with TSA. **c**, When DNA was fragmented using an enzyme called AluI, round bodies formed and fused to one another like liquid droplets. A stiff surface still prevented microtubules from penetrating the round bodies, but TSA treatment dissolved these bodies.

and weakened nucleosome contacts. The chromosomes in TSA-treated cells seemed less compact than in their untreated counterparts, particularly towards the periphery, and microtubules grew extensively through the chromosome surface. This suggests that chromatin compaction, mediated by histone-tail deacetylation, is necessary to prevent microtubules from penetrating chromosomes.

Next, the researchers treated condensin-depleted mitotic cells with TSA. The result was striking. The chromatin in these cells became greatly decondensed and was distributed throughout the cytoplasm. This indicates that histone deacetylation causes complete compaction of mitotic chromosomes in the absence of condensin. Condensin is thus neither necessary nor sufficient for complete chromatin compaction during mitosis.

The team that performed the current study had previously found evidence that short strings of nucleosomes can condense into liquid-like droplets *in vitro*, in a process called liquid–liquid phase separation (LLPS)[8], and that these droplets dissolve after acetylation. In LLPS, a solution of macromolecules separates into two or more liquid phases that have different physico-chemical properties[9]. To investigate whether a similar phenomenon might occur *in vivo*, and have a role in chromosome compaction, Schneider *et al.* injected a restriction enzyme called AluI into living mitotic cells. This treatment fragmented chromatin to relieve the physical constraints imposed by long strings of interacting nucleosomes.

Indeed, AluI-treated chromosomes lost their rod shape, and instead formed round bodies that fused to one another (Fig. 1c). These bodies looked like the liquid droplets formed by LLPS, and the fragmented chromatin within them was highly mobile, supporting the idea that they are liquid droplets. AluI injection alone did not change chromatin density or compaction state, and did not perturb the stiff chromatin surface that prevents microtubules from penetrating. However, treatment of cells with TSA before AluI injection suppressed LLPS and resulted in uniformly dispersed chromatin with almost no local condensation.

The mobility of AluI-fragmented mitotic chromatin might relate to that seen in an earlier phase of the cell cycle, interphase[10,11] (the period between divisions). In interphase, chromatin shows some histone acetylation[7] and has liquid-like motion on a scale of about 200 nanometres, which is mainly driven by thermal fluctuations[10,11], arising from collisions with water and other molecules in the cell. Schneider and colleagues' work therefore implies that a phase transition between interphase and mitosis makes mitotic chromatin more condensed and more constrained than interphase chromatin[12] – these constraints probably suppress its motility. The key to this phase transition seems to be global histone deacetylation. As histones are deacetylated, chromosomes become more solid-like, immiscible in the cell cytoplasm, and so able to resist microtubule perforation. Together, the study offers mechanistic insight into the processes of mitotic chromosome condensation and transmission.

The current study could have implications for our understanding of how condensin is involved in chromosome packaging. Although the team shows that histone deacetylation can induce complete compaction of mitotic chromosomes in the absence of condensin, the shape of the chromosomes is aberrant. To make a proper rod-like chromosome shape, then, loop formation by condensin seems crucial. It is thought that genomic DNA is pushed through the ring-shaped condensin complex to form loops[13] – but one could imagine that the compacted nucleosome clusters that form when histones are deacetylated would get stuck in the ring. We might therefore need to consider alternative possibilities[14,15] that would make sense in the context of mitotic chromatin. Future work combining sophisticated imaging techniques, computational modelling and a technique called Hi-C that captures information about chromosome conformation could shed light on the mechanism of loop formation required to make the rod-like shape of mitotic chromosomes.

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Earth science

Search for eruption signals in volcanic noise

Emily K. Montgomery-Brown

A volcano that erupted with few precursory signals offers a test bed for seeking out ways of forecasting disaster – and a reminder that analysis on a global scale is necessary for a comprehensive understanding of volcanoes. **See p.83**

The beginnings of volcanic eruptions are often heralded by changes in observable features such as seismic activity, gas chemistry and the shape of the volcano. That wasn't the case, however, on 22 May 2021, when Mount Nyiragongo in the Democratic Republic of the Congo erupted. As Smittarello *et al.*[1] report on page 83, the volcano had been undergoing low-intensity eruptive activity since 2002 and had remained mostly unchanged from this condition until its striking and destructive eruption. The authors' analysis provides clues to how such eruptions can be forecast in the absence of the usual precursors.

Nyiragongo is an open-vent volcano, which means that it continually emits products, such as gases and lava, in this case from a lava lake in its summit crater that has existed since at least 1928 (ref. 1) (Fig. 1). Eruptions had previously occurred on the flanks of the volcano in 1977 and 2002, but the 2021 eruption began with fissures opening high on the volcano, with other fissures at progressively lower levels. Over a period of around 6 hours, lava covered an area of about 10 square kilometres. Some 6,000 households were displaced, according to Smittarello and colleagues' analysis, and electrical, telecommunications and water facilities were destroyed, as well as schools, health centres and churches. At least 31 people were killed and more than 750 injured, during the eruption and evacuation.

Before the 2021 eruption, a local seismic network installed in 2015 had detected a persistent, low-level tremor in both seismic and acoustic frequencies, suggesting that