Cell biology

Nuclear location foretells chromosome anomalies

Krishnendu Guin & Tom Misteli

A single-cell analysis suggests that the 3D location of chromosomes in the cell nucleus contributes to their likelihood of being involved in genomic rearrangements associated with cancer. **See p.604**

Normal human cells have two copies of each chromosome. By contrast, many cancer cells have abnormal numbers of chromosomes, either having extra copies or lacking some. The most common reason for such abnormalities is the result of defective cell division, specifically, a failure to distribute the cell's chromosomes equally between the two newly forming daughter cells. Klaasen *et al.*[1] report on page 604 that the 3D location of chromosomes in the nucleus before cell division affects their likelihood of being incorrectly partitioned in the daughter cells.

The authors set out to answer a simple question. Do all chromosomes have the same chance of being mis-segregated during cell division? To address this, Klaasen and colleagues turned to several types of human cell grown under conditions that promote chromosome mis-segregation during division. They used DNA sequencing of single cells to globally monitor the sets of chromosomes in all daughter cells. Strikingly, their results indicate that not all chromosomes mis-segregate at the same frequency. Some were more likely than others to be incorporated incorrectly into the daughter cells, or to be found in structures called micronuclei, which are aberrant, nucleus-like structures that often contain only one chromosome and can form during defective cell division.

The authors asked what makes chromosomes particularly prone to mis-segregation, but found no clear relationship to several chromosomal features, such as the size of a region called the centromere or the length of the chromosome 'arms'. However, they identified a robust correlation with the 3D location of a chromosome in the nucleus before cell division. Chromosomes that were generally positioned more peripherally and closer to the membrane of the nucleus were more prone to be mis-segregated than were chromosomes residing at the centre of the nucleus. Klaasen *et al.* used several methods to show that a chromosome's location can determine its fate. Most tellingly, artificial tethering of a chromosome that was normally centrally located, so that it was relocated to the nuclear periphery, resulted in its more frequent mis-segregation.

A hint about the mechanism responsible for the higher segregation defects of peripheral compared with central chromosomes came from the imaging of live cells. The authors monitored individual central and peripheral chromosomes in dividing cells, and found that peripheral chromosomes took longer to align properly in the middle of the dividing cell – at what is known as the metaphase plate – than central chromosomes did.

Together, these observations suggest a model for the mechanism that is based on what we know about how chromosomes behave during cell division (Fig. 1). As the cell begins to divide during the prometaphase stage of the cell cycle, an elongated structure called the mitotic spindle develops, formed of protein filaments called microtubules; this attaches to the centromere of each chromosome, helping to align chromosomes in the middle of the dividing cell. Subsequently, during the anaphase stage of cell division, the spindle pulls chromosomes to the two newly forming daughter cells. Klaasen *et al.* propose that peripheral chromosomes are more likely to be mis-segregated than are central chromosomes because they take longer to travel to the middle of the cell to align, and also take longer to orient themselves, as was observed in the imaging experiments. The resulting delay in getting chromosomes ready for division might increase the likelihood of their mis-segregation.

Klaasen and colleagues' results build on, and expand, several previous observations about genome organization. It has long been known that chromosomes are non-randomly positioned in the cell nucleus during the interphase stage of the cell cycle, which occurs before division[2]. The location of chromosomes relative to the nuclear periphery correlates with chromosome size and overall transcriptional activity, with smaller and transcriptionally active chromosomes preferentially located at the centre of the nucleus[3]. Consistent with those findings, Klaasen *et al.* observe a contribution of chromosome size to mis-segregation frequency. The new results suggest that chromosome position also has a role in ensuring proper chromosome segregation.

An aberrant number of chromosomes, or aneuploidy, is associated with conditions such as Down syndrome, but is also a particularly prominent hallmark of certain types of cancer[4].

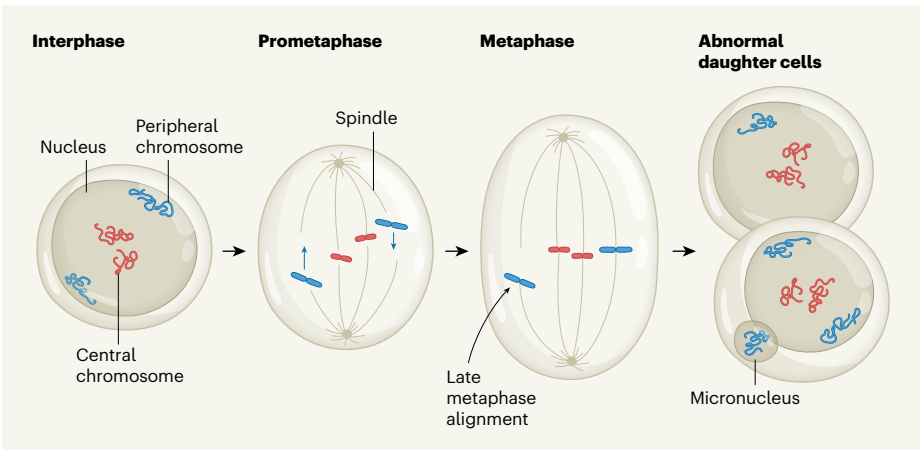

Figure 1 | Consequences of a chromosome's nuclear position. Klaasen *et al.*[1] analysed human cells, and report that chromosomes found at peripheral locations of the nucleus at the interphase stage of the cell cycle are more likely to give rise to abnormalities than are chromosomes located in central nuclear regions. The spindle is a structure that enables chromosomal partitioning into daughter cells at cell division. The authors' observations indicate that peripheral chromosomes might take longer than central chromosomes when moving (blue arrows) to make proper contact with spindle components at a stage of the cell cycle called prometaphase. The data also suggest that peripheral chromosomes take longer than central chromosomes to align in the middle of a dividing cell at metaphase. These abnormalities can result in peripheral chromosomes not being correctly included in the newly forming nucleus of a daughter cell. Defects might therefore arise, such as abnormal numbers of nuclear chromosomes and the formation of a chromosome-containing structure called a micronucleus.

Furthermore, a role for the 3D positioning of chromosomes in cancer has previously been demonstrated for another common type of cancer-related genome rearrangement, known as a chromosome translocation[5]. Such rearrangements occur when chromosome fragments generated by two breaks in DNA are incorrectly rejoined to form hybrid chromosomes. Live-cell tracking showed that translocations preferentially form between chromosomes that are close together in the nucleus at interphase[5]. It thus seems that the 3D location of chromosomes can contribute to cancer-promoting genome rearrangement in multiple ways.

Finally, it is well established that the types of genomic rearrangement and the chromosomes involved in nuclear defects often vary between tumours in different tissues. This phenomenon is caused, in part, by growth selection — the preferential proliferation of cells that have growth advantages as a result of the specific genetic rearrangements they contain[6]. Klaasen and colleagues' work suggests that, in addition, the 3D position of chromosomes might contribute to such tissue specificity of genomic rearrangements in cancer, by affecting which chromosomes are involved in aneuploidy. This idea is consistent with the observation that the arrangement of chromosomes in 3D space is often tissue-specific[2,3]. How much of the observed tissue specificity of genome rearrangements is due to growth selection compared with mis-segregation driven by chromosome location is an intriguing and important question. Regardless of the answer, Klaasen and colleagues' study demonstrates yet another functional role of 3D genome organization in cells and tissues.

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Climate change

Heating and stirring the global viral soup

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Simulations show that rising global temperatures and changes in land use will drive new encounters between mammalian species. This could lead to an increase in virus-sharing events that might threaten both wildlife and humans. **See p.555**

The year 2020 will remain a defining one of recent history — for, not one, but two, reasons. While the world's attention was focused on the emergence, spread and evolution of the SARS-CoV-2 virus, by January 2021, atmospheric scientists had reported another stark fact: 2020 was the second-warmest year on record globally, and the warmest ever recorded in the Northern Hemisphere (see go.nature.com/3wywzmd). Could these two distinct crises of our time — pathogen emergence and anthropogenic climate change — be linked? Carlson *et al.*[1] conclude on page 555 that they could. Theirs is one of the first systematic analyses to explore the implications of climate change for cross-species virus sharing — a key step in pathogen emergence.

Most pandemics are driven by zoonoses: diseases that leap from animal populations into humans. As the COVID-19 pandemic exemplifies, pinning down the location and timing of such a jump is extremely difficult. Identifying the possible role of climate change in driving a specific emergence event is therefore all but impossible. The deep complexity of the biological, social and environmental processes that might link climate change to pathogen emergence, as well as the difficulties in gathering data on pathogen emergence in general[2], has limited research in this area. Consider the scales involved: greenhouse-gas emissions drive temperature changes at the planetary scale, whereas the microbiological processes that govern pathogen evolution occur at nanometre or even smaller scales, in an individual host.

Carlson and colleagues provide a robust, quantitative advance in this complicated but crucial research area. Rather than tackling the intractable, vast, multiscale chain from climate change to pathogen emergence, the authors focus on a subset of steps, specifically looking at how climate change will alter the geographical ranges of 3,870 species of wild mammal by 2070. To summarize, they find that changing environments will drive mammals to enter new areas, interact with species that they have not encountered before — and ultimately share viruses, with a probability that previous work[3] indicates will depend on factors such as evolutionary relatedness.

The authors predict that most mammalian species will have a range that overlaps with that of at least one previously unfamiliar species, and that more than 300,000 new cross-species encounters will occur globally — especially in tropical Africa and southeast Asia. This will lead to a doubling in the number of cross-species contacts, the authors calculate. Carlson *et al.* also find that even modest changes to the climate will lead to new virus-sharing events (around 15,000), and that some might already be happening: their model predicts that most new encounters will have occurred between 2011 and 2040.

Given the wide range of uncertainties involved, the authors stop short of quantifying the likelihood of pathogen emergence into human populations, and remain focused on wildlife. They do, however, project the future overlap between virus-sharing events and the distribution of human populations, finding that new cross-species encounters are more likely to occur in human-inhabited or agricultural areas, especially highly populated ones — a hint at the implications for zoonoses.

Carlson *et al.* argue that virus sharing between wild mammal species is an important outcome in its own right, with consequences for wildlife and general ecosystem health. However, given recent global events, the spectre of emergence and the implications for future pandemics loom large. It remains unclear how changes to this wildlife–virus evolutionary soup will shape prospects for the next event similar in nature to an outbreak of SARS-CoV-2 or Ebola. This is an inevitable area for caution given the state of the science, but the question is tantalizing because this is where the key public-health questions lie.

The treatment of uncertainty is exemplary in the current study. Exploring uncertainty in climate-change projections is the bread and butter of atmospheric scientists. But it