Journal club

THE MANY SIDES OF CIN

Surveillance mechanisms, such as the spindle assembly checkpoint (SAC), have evolved to ensure chromosome segregation fidelity. When these quality control mechanisms fail, aneuploidy ensues. This condition of an abnormal chromosome number has long been linked to disease, developmental abnormalities and death. Many spontaneous abortions are associated with single chromosome aneuploidies, which indicates that aneuploidy compromises the viability of an organism. However, most solid cancers also exhibit multiple aneuploidies. As cancer is defined by unrestrained cell proliferation, this implies that aneuploidy can confer fitness advantages at the cellular level. Clearly, the effects of aneuploidy on cells and organisms are complex, and cell and animal models need to be developed to fully understand their impact.

To directly characterize the consequences of chromosome missegregation and aneuploidy, collectively called chromosome instability (CIN), Baker *et al.* induced chromosome missegregation in mice by disrupting the SAC. The authors generated mice homozygous for a hypomorphic mutation in the checkpoint component BUBR1 and obtained viable animals in which chromosomes were continuously missegregated. As a result, approximately one-third of cells harboured one or more whole-chromosome aneuploidies. One may have expected that some of these cells would have a proliferative advantage and that the mice would develop tumours. However, quite the opposite occurred. Cells senesced prematurely, and the mice exhibited a progeroid phenotype. BUBR1 hypomorphs developed cataracts, skeletal abnormalities and tissue atrophy at a young age, and the median lifespan was reduced to 6 months. Consistent with this, the same group later found that reducing chromosome missegregation by overexpressing BUBR1 was sufficient to delay signs of ageing and extend lifespan.

A paper is interesting when it changes your perspective — when you put it down and say "I did not see that coming." The study by Baker *et al.* in 2004 did this for us. This paper causally implicated, for the first time, CIN and aneuploidy in yet another phenomenon — ageing. They suggested that most aneuploid cells can survive in somatic tissues, but they become senescent rather than initiate oncogenic transformation. We must now understand how CIN and aneuploidy can be associated with the disparate phenotypes of limitless proliferation and accelerated senescence. Further investigations into the genetic and cellular context in which aneuploidy occurs should help to resolve this paradox.

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The authors declare no competing financial interests.

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FURTHER READING Musacchio, A. & Salmon, E. D. The spindle-assembly checkpoint in space and time. *Nature Rev. Mol. Cell Biol.* **8**, 379–393 (2007)