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The many sides of CIN

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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 associated with death, disease and developmental abnormalities. Many spontaneous abortions are found to harbor single chromosome aneuploidies, indicating that aneuploidy compromises viability when present throughout the 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 we must develop cell and animal models to fully understand their impact.

To directly characterize the consequences of chromosome mis-segregation and aneuploidy, collectively called chromosome instability (CIN), Baker and colleagues induced chromosome missegregation in mice by disrupting the spindle assembly checkpoint. By generating mice homozygous for a hypomorphic mutation in the checkpoint component BubR1, Baker and colleagues obtained viable animals in which chromosomes were continuously missegregated. As a result, approximately one-third of cells harbored one or more whole-chromosome aneuploidies. One may have expected some of these cells to have a proliferative advantage and for the mice to develop tumors. However, quite the opposite occurred. Cells senesced prematurely and 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 six months. Correspondingly, the same group subsequently found that reducing chromosome mis-segregation by overexpressing BubR1 was sufficient to delay signs of aging and extend lifespan.

A paper is interesting when it changes your perspective—when you put it down (or press apple-quit) and say, “Hmm, did not see that coming.” This paper did this for us. The studies by Baker and colleagues implicate CIN and aneuploidy in yet another phenomenon—aging. They suggest that the majority of aneuploid cells can survive in somatic tissues, but they become senescent rather than precipitate transformation. We must now understand how CIN and aneuploidy can be associated with the disparate phenotypes of limitless proliferation and accelerated senescence. Further investigation into the genetic and cellular context in which aneuploidy occurs should help to resolve this paradox.

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