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Genomic instability switch identified

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The observation that age and cancer are inextricably linked is clear from the exponential increase in the cases of cancer at the end of human life. Chromosomal abnormalities are seen in all older individuals, cancerous or not, and this genomic instability is considered one of the hallmark prerequisites of cancer. In addition to the mutations that may cause cancer accumulating over time, the rates at which they occur also increase with age. The explanations for this observation are plentiful and hotly debated, but it has been difficult to adequately test these theories. In the September 26 Science, Michael A. McMurray and Daniel Gottschling from the University of Washington used *Saccharomyces cerevisiae* to study this hallmark of cancer and discovered an age-related switch to genomic instability (*Science*, **301:**1908-1911, September 26, 2003).

McMurray and Gottschling created yeast strains in which they could monitor the loss of marker genes and thus the genetic history of a strain during aging. To test whether genetic instability - visible as the lost of a marker gene that affected colony color - was affected by a yeast (mother) cell's age, they sampled every daughter cell produced by micromanipulation and allowed it to form a colony. Examination of the color of the colonies revealed that daughter cells from old mothers were approximately 40 to 200 times more likely to lose a marker gene. Once a marker gene was lost in a pedigree, subsequent loses were much more frequent. These results suggest a switch occurred during aging that resulted in increased genetic instability. The authors then attempted to identify the mechanism causing the loss of markers, revealing the chromosomal damage in old mothers was likely the cause, with large DNA double-stand breaks resulting in the loss of markers being repaired by break-induced replication (BIR). This genetic instability was predominately observed in daughter cells, seemingly protecting the mother's "genomic integrity" for future generations.

"Our results provide predictions about the mechanisms that underlie age-related genomic stability in eukaryotic cells, as well as a model system in which to test them," conclude the authors.

In an accompanying preview article, David Sinclair from Harvard Medical School comments, "Only when we truly know the under lying causes of this phenomenon, can we truly predict how relevant it will be to humans. But if history is anything to go by, we can look forward to learning more lessons about aging and cancer from this tiny fungus."

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