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How aging affects stem cells: A fly's tale

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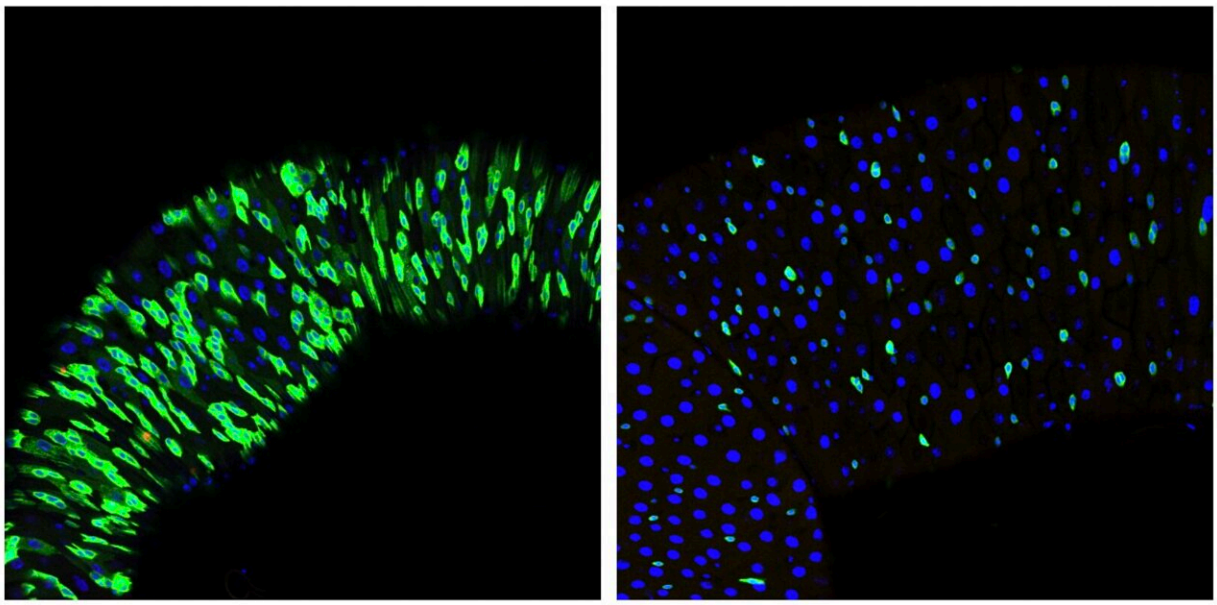

Excessive cell proliferation (left) and stem cell exhaustion (right) during aging. Credit: RIKEN

Scientists from the RIKEN Center for Biosystems Dynamics Research (BDR) have identified key changes to both chromosome structure and gene expression that affect stem cell function during aging. Using fruit flies, they found that these changes led to stem cell exhaustion, which prevents stem cells from multiplying.

The findings, published in *iScience* on September 9, provide the first evidence of an independent exhaustion signal and enhance our

understanding of how the delicate balance between stem cell exhaustion and proliferation is disrupted in normal aging.

When organs like the kidneys or intestines are damaged, the stem cells within them multiply and transform into the specific parts of the organ that need replacement. As animals—including humans—age, this process can malfunction.

Sometimes, the stem cells may continue to divide uncontrollably, resulting in excessive numbers that can lead to cancer. In other cases, they can become depleted and lose their ability to divide, preventing any tissue repair. This condition is referred to as stem cell exhaustion.

In humans, while stem cell proliferation at the molecular level is relatively well-understood, exhaustion remains largely a mystery. Previously, Sa Kan Yoo at RIKEN BDR identified how intestinal stem cells of fruit flies become cancerous as they age. By using the same experimental system, in the new study, the team tested their theory that a proliferation-independent mechanism for stem cell exhaustion also exists.

They analyzed the chromatin structure in fruit fly intestinal stem cells and found a region of chromatin that often closed up during aging, preventing the regulator encoded by this region of DNA from being made. Because ced-6 is a gene whose expression is normally controlled by this regulator, they next evaluated ced-6 expression using RNA sequencing. As expected, they found that ced-6 expression decreased with aging.

To determine whether there is a relationship between this gene and stem cell exhaustion, they next blocked its expression. This intervention effectively halted age-related stem cell proliferation, indicating that normally these genes work to prevent stem cell exhaustion.

They also discovered that blocking ced-6 could trigger stem cell exhaustion at any age. When intestinal cells are damaged, the stem cells normally proliferate, differentiate, and replace the damaged tissue. However, when the researchers intentionally damaged intestinal cells and blocked ced-6, they did not see any stem cell proliferation.

This indicates that the exhaustion caused by blocking ced-6, or other genes controlled by the same regulator, is not limited to times of advanced age, but is likely a general process that could be active any time to help maintain balance when proliferation is too high.

"Our findings will lead to new advances in aging research," says Yoo. "Understanding the mechanisms of stem cell exhaustion in fruit flies provides valuable insights into the aging process more broadly and could offer clues about how aging impacts stem cells in humans. The next step is to determine if similar changes occur in human stem cells as they age."

More information: Insidious chromatin change with a propensity to exhaust intestinal stem cells during aging, *iScience* (2024). DOI: 10.1016/j.isci.2024.110793. www.cell.com/iscience/fulltext … 2589-0042(24)02018-2

Provided by RIKEN

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