Effects of aging in stem cells

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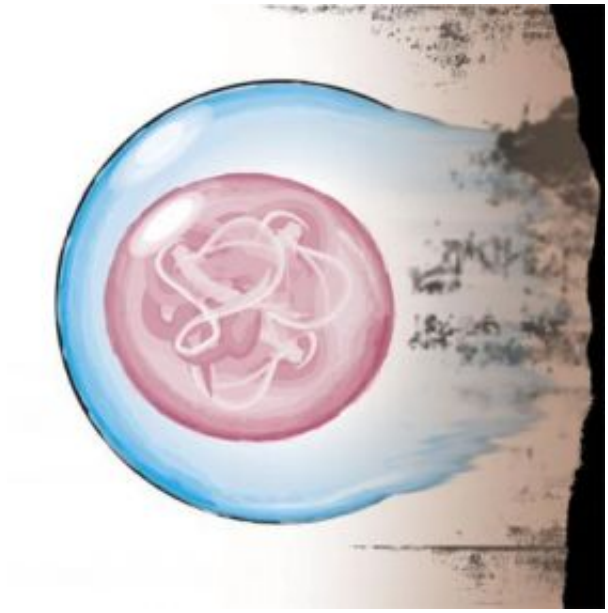

Aging HSCs exhibit a functional decline (yet an increase in cell number) and display a heightened stress and inflammatory response along with signs of epigenetic erosion. Credit: Image: S. M. Chambers

There is little disagreement that the body's maintenance and repair systems deteriorate with age, even as there is plenty of disagreement as to why. Stem cells combat the aging process by replenishing old or damaged cells—particularly in the skin, gut, and blood—with a fresh supply to maintain and repair tissue. Unfortunately, new evidence published in the open-access journal *PLoS Biology* suggests that this regenerative capacity also declines with age as stem cells acquire functional defects.

Stuart Chambers, Margaret Goodell, and their colleagues investigated the molecular mechanisms underlying aging of stem cells by looking at the gene expression profiles of aging hematopoietic stem cells (HSCs), the precursors of blood cells. They found that genes involved in the inflammatory and stress response became more active with age, while genes important for regulating gene expression and genomic integrity became less active. These results lend strong support to the notion that HSCs succumb to the wear and tear of aging, just like other cells, and shed light on the mechanisms of aging.

To study HSCs' regenerative capacity over time, Chambers et al. isolated HSCs from young (aged 2 months) and old (aged 21 months) mice and then transplanted either young or old cells into mice whose bone marrow cells had been destroyed by radiation. The young and old HSCs gave rise to new marrow cells at roughly the same pace 4 weeks after transplantation. But at 8 and 16 weeks after transplantation, the old HSCs' contributions had dropped considerably, suggesting that aging HSCs lose their repopulating capacity. Yet, because HSCs increased in number, overall blood production from HSCs remained stable.

The finding that genes involved in the inflammatory response are expressed more (called up-regulation) as HSCs age fits with evidence linking inflammation and aging in the kidney, brain, and arteries. It may also help explain why HSCs lose function. One of the up-regulated genes, P-selectin, encodes a cell surface adhesion molecule. Because transplanted HSCs depend on cell adhesion to colonize bone marrow properly, the researchers explain, inappropriate up-regulation of genes encoding P-selectin may interfere with this process.

The markedly reduced expression (or down-regulation) of genes involved in chromatin remodeling, an "epigenetic" regulator of gene expression, suggested that transcriptional activity might be dysregulated across the genome.

Though the dominant model attributes the physical effects of aging to an accretion of isolated genetic insults, these results link age-related decline to global mechanisms operating across the genome. In the researchers' "epigenetic view of aging," chromatin dysregulation provides a logical explanation for the numerous and diverse age-related changes observed at the molecular, cellular, and organismal levels. Over the normal course of aging, chromatin dysregulation leads to dysregulation of many genes, which in turn leads to a loss of normal cellular functions and a loss of growth regulation. These changes ultimately increase the risk of cancer, which, in many of its forms, increases dramatically with age. Future studies can investigate how epigenetic regulation, inflammation, and the stress response interact to better understand the molecular mechanisms of aging, and why so many of us face a high risk of cancer in our later years.

Source: Public Library of Science