Old neurons can block neurogenesis in mice

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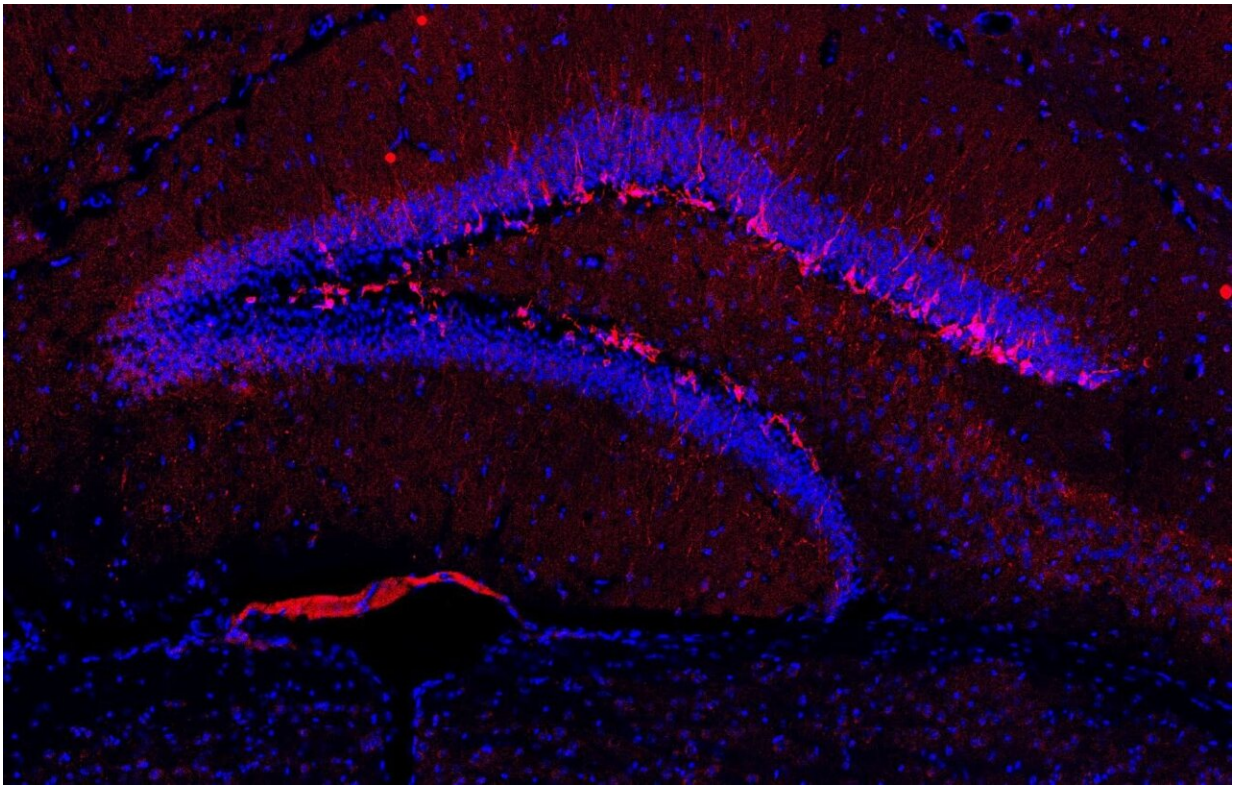

Thisis a high-resolution image of the large number of new neurons being produced (in red) in the hippocampus of middle-aged mice, treated with the drug that ablates senescent neural stem cells in the stem cell niche. Credit: Michael Fatt

Destroying senescent cells in the aging stem cell niche enhances hippocampal neurogenesis and cognitive function in mice, researchers report January 20 in the journal *Stem Cell Reports*.

"Our results provide further support for the notion that excessive senescence is a driving factor behind aging, and even late-life reduction of these cells can rejuvenate and restore the function of the stem cell niche," says senior author David Kaplan of The Hospital for Sick Children (SickKids) in Toronto, Canada. "Moreover, they identify stem cells as a key cellular target, potentially explaining the widespread effects of senescent cells on tissue decline."

Senescent cells, which are permanently arrested because of chronic stress, are partly responsible for tissue decline during aging. Several studies indicate that senescent cells also play a negative role in age-related neurodegenerative disorders. But the cellular mechanisms responsible for tissue failure during aging are still not entirely clear.

Some research has pointed to stem cells as targets for aging and senescence-associated functional decline. The adult mammalian brain contains stem cells that continuously generate new neurons that are important for cognition. The generation of new neurons in the hippocampus declines rapidly with age, and this decline is associated with reduced stem cell activity. This raises the possibility that age-dependent senescent cell accumulation may deregulate neural stem cells and thereby negatively impact brain function.

"Stem cells last throughout life and, like us, are subjected to the ravages of aging, environmental stressors, and deterioration of the machinery that enables them to function optimally," Kaplan explains. "To survive, many stem cells revert to a dormant, unresponsive, and inactive state. Our goal was to wake up these dormant cells and, in doing so, enable them to carry out their biological functions that facilitate learning, memory, and brain repair."

In the new study, Kaplan teamed up with Freda Miller and Paul Frankland of SickKids to test the idea that increased senescence within

the neural stem cell niche negatively impacts adult neurogenesis, focusing on the middle-aged mouse brain. They observed an aging-dependent accumulation of senescent cells, largely senescent stem cells, within the hippocampal stem cell niche coincident with declining adult neurogenesis. Pharmacological ablation of the senescent cells via a drug called ABT-263 caused a rapid increase in normal stem cell proliferation and neurogenesis, and genetic ablation of senescent cells similarly activated hippocampal stem cells.

This burst of neurogenesis had long-term effects in middle-aged mice. One month after treatment with ABT-263, adult-born hippocampal neurons increased and hippocampus-dependent spatial memory was enhanced. "The surprise for us is that only one injection of the drug was sufficient to mobilize the normal stem cells in the hippocampus, and it did so after only 5 days," Kaplan says. "The newly awakened stem cells continued to function well for the next 30 days."

These results support the idea that the aging-dependent accumulation of senescent cells, including senescent stem cells in the hippocampal niche, negatively affects normal stem cell function and adult neurogenesis, contributing to an aging-related decline in hippocampus-dependent cognition. Moreover, the results provide a potential explanation for the previously observed age-related decreases in hippocampal stem cells and neurogenesis. A large proportion of stem cells becomes senescent, making them unavailable to generate new neurons, and these senescent stem cells likely adversely affect neurogenesis from their non-senescent neighbors.

"When we improve the neighborhood by getting rid of deleterious cells in the stem cell niche, we begin to mobilize and wake up the dormant stem cells, enabling them to generate new neurons for spatial learning and memory," Kaplan says. "We think that it is the senescent stem cells we removed that were responsible for improving the function of the

normal non-senescent stem cells in the niche."

While the findings implicate the senescence of stem cells in age-related decline, the stem cells are clearly not the only important cellular substrates for senescence in the nervous system. A potential role for cellular senescence in the brain has been most widely studied within the context of neurodegenerative disorders. In particular, senescent microglia, astrocytes, and oligodendrocyte progenitor cells accumulate in the aged degenerating human brain, and clearance of these senescent cells in mouse models can ameliorate some of the adverse consequences of neurodegeneration and obesity. But these studies focused on senescent microglia and glial cells in neuropathological conditions rather than normal aging.

"In addition, most studies on waking up dormant stem cells have focused on mobilizing the cells themselves," Kaplan says. "A key question when we age, however, is whether it is something intrinsic in stem cells that causes them to become dormant or if it is the environment that they reside in that elicits this dormant state. It is well known that the stem cell niche, or neighborhood, deteriorates with age. Waking up dormant stem cells themselves may not be useful if, when they do so, their neighborhood does not allow them to function optimally."

According to the authors, one study limitation was the use of middle-aged mice and not older mice that might have more relevance to potential therapeutic strategies for the loss of cognitive abilities in older adults. Nonetheless, the findings may have implications for the treatment of age-related conditions.

"A remaining question is whether reducing the number of senescent stem cells alone will improve normal stem cell function and cognition or if removing other senescent cell types is also important," Kaplan says. "While our conditions are more specific for removing senescent stem

cells, it is likely that treatments that reduce the amounts of all deleterious senescent cells in the brain will produce the best outcomes."

More information: David R. Kaplan, Restoration of hippocampal neural precursor function by ablation of senescent cells in the aging stem cell niche, *Stem Cell Reports* (2022). DOI: 10.1016/j.stemcr.2021.12.010 . www.cell.com/stem-cell-reports … 2213-6711(21)00649-4

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