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PRESS RELEASE (2025/07/28)

Understanding the Epigenetic Mechanisms Behind Premature Aging of the Brain

Researchers identify the role of the Setd8 gene associated with the age-related decline in neural stem cell activity and proliferation

Ikoma, Japan—Age often brings a gradual decline in the ability to learn new things and retain memories. This phenomenon, often associated with the elderly, is linked to the brain's deteriorating capacity to generate new neurons—a process that primarily occurs in the hippocampus —as neural stem cells (NSCs) divide and mature. Recent research suggests this decline begins much earlier in life than previously thought, potentially starting in early adulthood.

While it is established that overall decline in brain function is associated with dwindling NSCs, the precise underlying molecular changes and their timelines remain unclear. Epigenetic changes—modifications that affect gene expression without altering the DNA sequence—play crucial roles in cellular aging, but their impact on NSCs remains unknown.

In this vein, a research team comprising Shuzo Matsubara, Kanae Matsuda-Ito, Haruka Sekiryu, Hiroyoshi Doi, Takumi Nakagawa, and Kinichi Nakashima from Kyushu University, Naoya Murao from the University of Miyazaki, and Hisanobu Oda from Saiseikai Kumamoto Hospital, and led by Associate Professor Taito Matsuda from the Laboratory of Neural Regeneration and Brain Repair at the Nara Institute of Science and Technology (NAIST), Japan, set out to uncover the early aging processes in NSCs. Their study was made available online on June 3, 2025 and published on July 01, 2025, in Volume 44, Issue 13 of *The EMBO Journal*.

The researchers used single-cell sequencing techniques to analyze gene expression in NSCs and newly generated neurons across different life stages in mice. This enabled them to map the key molecular changes that NSCs undergo from birth through early adulthood, along with the corresponding alterations in their ability to produce new neurons.

A key discovery was linked to a gene called *Setd8*, which controls the addition of a chemical tag (molecule) on DNA-packaging proteins called histones. The researchers found that *Setd8* showed a marked decrease in expression as the brain aged. In turn, this reduction in *Setd8* levels was directly linked to impaired NSC activity and proliferation, as well as noticeable problems in memory in mice. The team also demonstrated that artificially lowering *Setd8* levels mimicked various molecular signatures of aging NSCs, suggesting it could be a critical biomarker of early aging.

Overall, the results highlight the unknown role of *Setd8* in NSC aging, which has strong implications from a biomedical standpoint. "Understanding how Setd8 affects neural stem cell aging opens the possibility of developing new therapies to slow down or reverse early brain aging. This could help preserve memory and learning ability, and may lead to future treatments

for age-related conditions like Alzheimer's disease," remarks Dr. Matsuda. "This aligns with our laboratory's research on cellular reprogramming technologies, which we hypothesized could make it possible to 'rejuvenate' aged, functionally declined cells."

While further efforts will be needed to translate these findings into therapeutic solutions and clinical practice, Dr. Matsuda looks forward to continuing this exciting line of research. "I am deeply honored to be able to advance reprogramming research at the NAIST, where Professor Shinya Yamanaka initiated his groundbreaking work on induced pluripotent stem cells," he concludes.

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For more information about this research, see " Epigenetic regulation of neural stem cell aging in the mouse hippocampus by Setd8 downregulation," Shuzo Matsubara, Kanae Matsuda-Ito, Haruka Sekiryu, Hiroyoshi Doi, Takumi Nakagawa, Naoya Murao, Hisanobu Oda, Kinichi Nakashima, and Taito Matsuda *The EMBO Journal* https://doi.org/10.1038/s44318-025-00455-8

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia. Through its VISION 2030, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

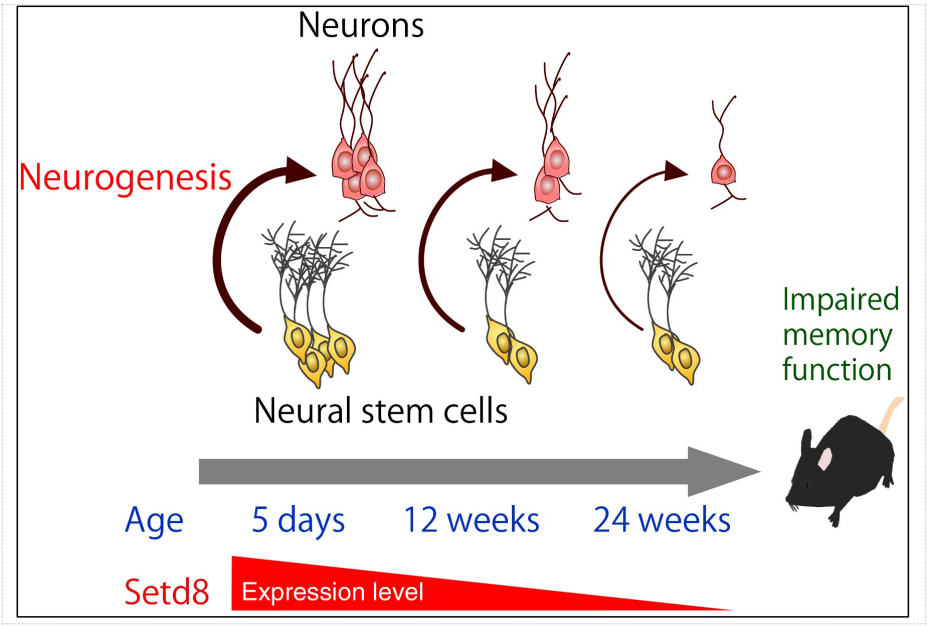

Fig. 1. A decline in the expression of the epigenetic regulator Setd8 in neural stem cells (NSCs) during early adulthood leads to chromatin condensation and reduced gene expression, suppressing NSC proliferation and contributing to premature brain aging. This illustration depicts the transition of NSCs from an active to aged state, revealing the key mechanism underlying the onset of cognitive decline. (Dr. Taito Matsuda from Nara Institute of Science and Technology, Japan)

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