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New research shows key molecules within nerve cells persist throughout life

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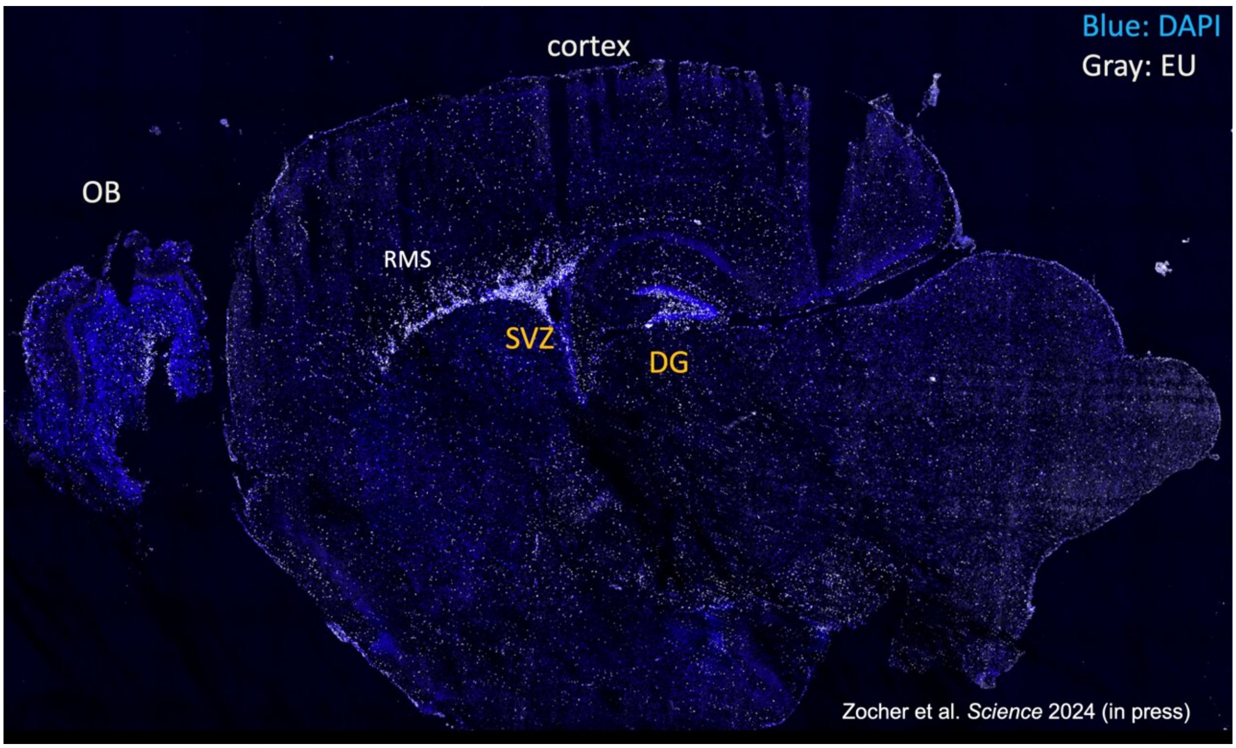

RNA and DNA are indicated with gray (EU; 5-ethynyluridine) and blue (DAPI) staining, respectively. Visible brain regions include the olfactory bulb (OB), rostral migratory stream (RMS), subventricular zone (SVZ), and the dentate gyrus (DG). Credit: Zocher et al./*Science*

After two decades in the United States, Martin Hetzer returned home to Austria in 2023 to become the 2nd President of the Institute of Science and Technology Austria (ISTA). A year into his new role, the molecular biologist remains engaged in the realm of aging research.

Hetzer is fascinated by the biological puzzles surrounding the aging processes in organs like the brain, heart, and pancreas. Most cells comprising these organs are not renewed throughout a human's entire life span. Nerve cells (neurons) in the human brain, for instance, can be as old as the organism, even up to more than a century, and must function for a lifetime.

This remarkable age of neurons might be a major risk factor for neurodegenerative disorders such as Alzheimer's disease. Crucial to comprehending these kinds of ailments is a deeper understanding of how nerve cells function over time and maintain control. This potentially opens doors to therapeutically counteract the aging processes of these specific cells.

The latest collaborative publication by Hetzer, Tomohisa Toda from the Friedrich-Alexander University Erlangen-Nürnberg (FAU), who is also associated with the Max Planck Center for Physics and Medicine, Erlangen, and colleagues, gives new insights into this underexplored field of intricate mechanisms.

For the first time in mammals, the study shows that RNA—an essential group of molecules important for various biological processes inside the cell—can persist throughout life. The scientists identified specific RNAs with genome-protecting functions in the nuclei of nerve cells of mice that remain stable for two years, covering their entire lives. The findings, published in the journal *Science*, underpin the importance of long-lived key molecules for maintaining a cell's function.

Longevity of key molecules

The inside of cells is a very dynamic place. Some components are constantly renewed and updated; others stay the same their whole lives. It is like a city in which the old buildings blend in with the new ones. DNA found in the nucleus—the city's heart—for instance, is as old as the organism. "DNA in our nerve cells is identical to DNA within the developing nerve cells in our mother's womb," explains Hetzer.

Unlike stable DNA, which is constantly being repaired, RNA, especially messenger RNA (mRNA), which forms proteins upon DNA's information, is characterized by its transient nature. The cellular scope, however, extends beyond mRNA to a group of so-called non-coding RNAs. They do not turn into proteins; instead, they have specific duties to contribute to the overall organization and function of the cell. Intriguingly, their lifespan remained a mystery. Until now.

RNAs that last the whole life

Hetzer and Co. set out to decipher that secret. Therefore, RNAs were labeled, i.e. "marked," in the brains of newborn mice. "For this labeling, we used RNA analogs—structurally similar molecules—with little chemical hooks that click fluorescent molecules on the actual RNAs," explains Hetzer. This assured efficient tracking of the molecules and powerful microscopic snapshots at any given time point in the mice's lives.

"Surprisingly, our initial images revealed the presence of long-lived RNAs, in various cell types within the brain. We had to further dissect the data to identify the ones in the nerve cells," Hetzer explains. "Fruitful collaboration with Toda's lab enabled us to make sense of that chaos during brain mapping."

Collaboratively, the researchers were able to focus solely on long-lived RNAs in neurons. They quantified the molecules' concentration throughout a mouse's life, examined their composition and analyzed their positions.

While humans have an average life expectancy of around 70 years, the typical lifespan of a mouse is 2.5 years. After one year, the concentration of long-lived RNAs was slightly reduced compared to newborns. However, even after two years, they remained detectable indicating a lifelong persistence of these molecules.

RNAs help protect the genome

Additionally, the scientists proved long-lived RNAs' prominent role in cellular longevity. They found out that long-lived RNAs in neurons consist of mRNAs and non-coding RNAs and accumulate near the heterochromatin—the densely packed region of the genome, typically homing inactive genes. Next they further investigated the function of these long-lived RNAs.

In molecular biology, the most effective approach to achieve this is by reducing the molecule of interest and observing its subsequent effects.

"As their name and our previous experiments suggest, these long-lived RNAs are extremely stable," says Hetzer. The scientists, therefore, employed an in vitro (outside a living organism) approach, using neuronal progenitor cells—stem cells with the capacity to give rise to neural cells, including neurons.

The model system allowed them to effectively intervene with these long-lived RNAs. A lower amount of long-lived RNAs caused problems in the heterochromatin architecture and stability of genetic material, eventually affecting the cells' viability. Thus, the important role of long-lived RNAs' in cellular longevity was clarified.

The study highlights that long-lived RNAs may function in the lasting regulation of genome stability.

"Lifelong cellular maintenance during aging involves an extended life span of key molecules like the long-lived RNAs, we just identified," Hetzer adds. The precise mechanism, however, remains unclear. "Together with unidentified proteins, long-lived RNAs likely form a stable structure that somehow interacts with the heterochromatin."

Upcoming research projects in Hetzer's lab are set on finding these missing links and understanding the biological characteristics of these long-lived RNAs.

More information: S. Zocher, Lifelong persistence of nuclear RNAs in the mouse brain, *Science* (2024). DOI: 10.1126/science.adf3481

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