RNA that doesn't age: Neuroscientists discover building blocks in nerve cells that last a life time

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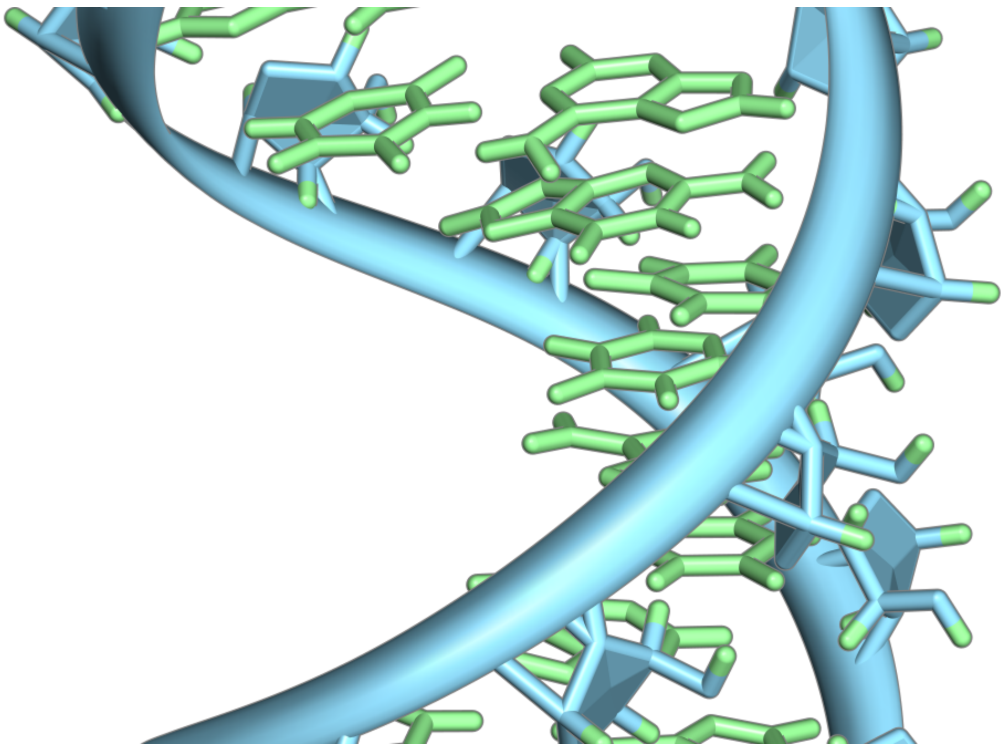

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Certain RNA molecules in the nerve cells in the brain last a life time without being renewed. Neuroscientists from Friedrich-Alexander-

Universität Erlangen-Nürnberg (FAU) have now demonstrated that this is the case together with researchers from Germany, Austria and the U.S.

RNAs are generally short-lived molecules that are constantly reconstructed to adjust to environmental conditions. With their findings that have been published in the journal *Science*, the research group hopes to decipher the complex aging process of the brain and gain a better understanding of related degenerative diseases.

Most cells in the human body are regularly renewed, thereby retaining their vitality. However, there are exceptions: the heart, the pancreas and the brain consist of cells that do not renew throughout the whole lifespan, and yet still have to remain in full working order.

"Aging neurons are an important risk factor for neurodegenerative illnesses such as Alzheimer's," says Prof. Dr. Tomohisa Toda, Professor of Neural Epigenomics at FAU and at the Max Planck Center for Physics and Medicine in Erlangen. "A basic understanding of the aging process and which key components are involved in maintaining cell function is crucial for effective treatment concepts:"

In a joint study conducted together with neuroscientists from Dresden, La Jolla (U.S.) and Klosterneuburg (Austria), the working group led by Toda has now identified a key component of brain aging: the researchers were able to demonstrate for the first time that certain types of ribonucleic acid (RNA) that protect genetic material exist just as long as the neurons themselves.

"This is surprising, as unlike DNA, which as a rule never changes, most RNA molecules are extremely short-lived and are constantly being exchanged," Toda explains.

In order to determine the life span of the RNA molecules, the Toda group worked together with the team from Prof. Dr. Martin Hetzer, a cell biologist at the Institute of Science and Technology Austria (ISTA).

"We succeeded in marking the RNAs with fluorescent molecules and tracking their lifespan in mice brain cells," explains Toda, who has unique expertise in epigenetics and neurobiology and who was awarded an ERC Consolidator Grant for his research in 2023. "We were even able to identify the marked long-lived RNAs in two-year-old animals, and not just in their neurons, but also in somatic adult neural stem cells in the brain."

In addition, the researchers discovered that the long-lived RNAs, which they referred to as LL-RNA for short, tend to be located in the cells' nuclei, closely connected to chromatin, a complex of DNA and proteins that forms chromosomes.

This indicates that LL-RNA play a key role in regulating chromatin. In order to confirm this hypothesis, the team reduced the concentration of LL-RNA in an in-vitro experiment with adult neural stem cell models, with the result that the integrity of the chromatin was strongly impaired.

"We are convinced that LL-RNAs play an important role in the long-term regulation of genome stability and therefore in the life-long conservation of nerve cells," explains Toda.

"Future research projects should give a deeper insight into the biophysical mechanisms behind the long-term conservation of LL-RNAs. We want to find out more about their biological function in chromatin regulation and what effect aging has on all these mechanisms."

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

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