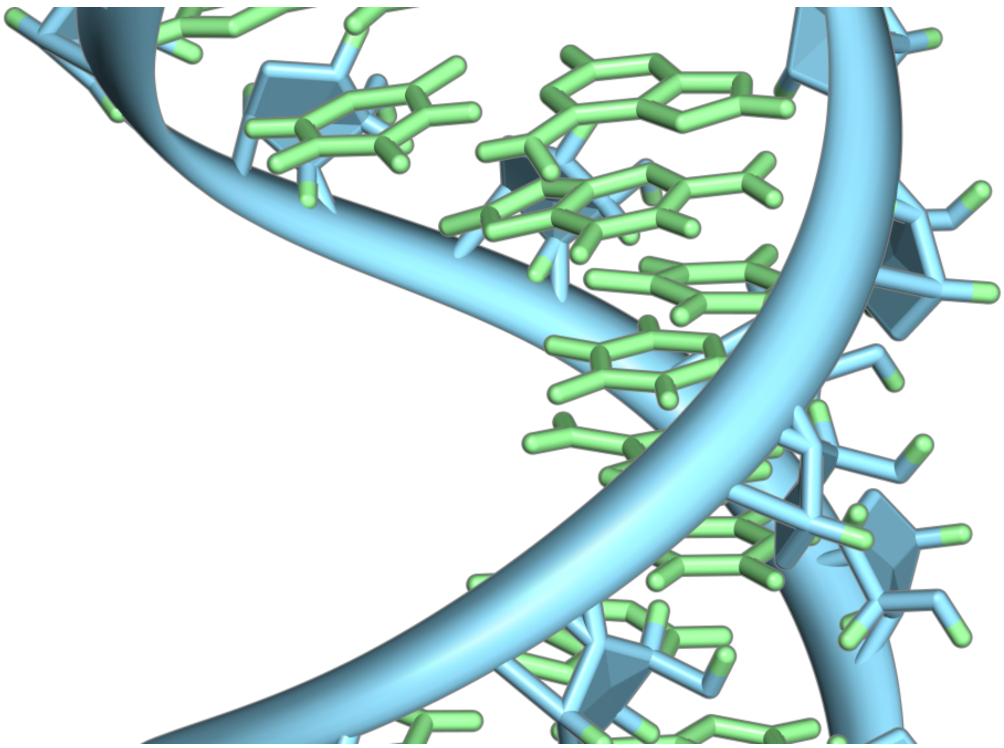
Changes to RNA aid the process of learning and memory

October 31 2018



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

RNA carries pieces of instructions encoded in DNA to coordinate the production of proteins that will carry out the work to be done in a cell. But the process isn't always straightforward. Chemical modifications to

DNA or RNA can alter the way genes are expressed without changing the actual genetic sequences. These epigenetic or epitranscriptome changes can affect many biological processes such as immune system response, nervous system development, various human cancers and even obesity.

Most of these changes happen through methylation, a process in which chemical molecules called methyl groups are added to a DNA or RNA molecule. Proteins that add a methyl group are known as "writers," and proteins that can remove the methyl groups are "erasers." For the methylation to have a biological effect, there must be "reader" proteins that can identify the change and bind to it.

The most common modification on messenger RNA in mammals is called N6-methyladenosine (m6A). It is widespread in the nervous system. It helps coordinate several neural functions, working through reader proteins in the YTH family of proteins.

In a new study published in *Nature*, scientists from the University of Chicago show how Ythdf1, a member of the YTH family that specifically recognizes m6A, plays an important role in the process of learning and memory formation. Using CRISPR/Cas9 gene editing tools to knock out Ythdf1in mice, they demonstrated how it promotes translation of m6A-modified messenger RNA (mRNA) in response to learning activities and direct nerve cell stimulus.

"This study opens the door to our future understanding of learning and memory," said Chuan He, Ph.D., the John T. Wilson Distinguished Service Professor of Chemistry, Biochemistry and Molecular Biology at UChicago and one of the senior authors of the study. "We saw differences in long-term memory and learning between the normal and knockout mice, demonstrating that the m6A methylation plays a critical role through Ythdf1."

In 2015, He published a study in *Cell* showing how Ythdf1 recognizes m6A-modified mRNAs and promotes their translation to proteins. The new study further demonstrates how this translation increases specifically in response to nervous system stimulation.

Hailing Shi, a graduate student in He's lab, led the new study, working with colleagues from Shanghai Tech University in China and the University of Pennsylvania. Mice express more Ythdf1 mRNAs in the hippocampus, part of the brain crucial to spatial learning and memory. So, the researchers conducted several experiments with both normal mice and mice without Ythdf1 to test the effects on their ability to learn from experiences.

In one scenario called the Morris water maze to test spatial memory, they used a water tank with a submerged platform a mouse could stand on to avoid swimming. Mice got several tries to learn where the platforms were located based on visual cues in a testing room. Then the platform was removed. The normal mice did a better job remembering where the platform used to be than the knockout mice.

The researchers also tested contextual and auditory fear memory in the different groups of mice by administering electrical shocks in combination with certain sounds in specific settings. Again, the normal mice demonstrated better contextual memory than knockout mice. They showed a fear response after being placed in the same setting again without the associated sounds, but not after hearing the sounds in a different setting.

The memory and learning deficits were reversible, however. When the researchers injected knockout mice with a virus carrying Ythdf1, their performance on memory and learning tasks improved dramatically.

The researchers also tested the response of cultured mouse neurons directly in the lab. When the normal cells were stimulated, they increased new protein production, compared to much less activity in Ythdf1 knockout cells.

"It's really an exciting finding to show how the protein can respond to a neuronal stimulus which could contribute to controlled translation," Shi said.

"It's a stimulation-dependent upregulation of translation," He added. "It makes sense because you don't want to fire up your neurons constantly, only when you have a stimulation."

While the current study identifies one important function for YTHDF1, there may be many other functions involved with other biological processes.

"This is not just limited to learning and memory. This stimulation induced translation should apply to many other systems," He said. "The same m6A modification is known to play a role in the immune system when there is an infection, or when a cell moves to a different part of the body. So, I think this is a general concept."

More information: Hailing Shi et al, m6A facilitates hippocampus-dependent learning and memory through YTHDF1, *Nature* (2018). DOI: 10.1038/s41586-018-0666-1

Provided by University of Chicago Medical Center