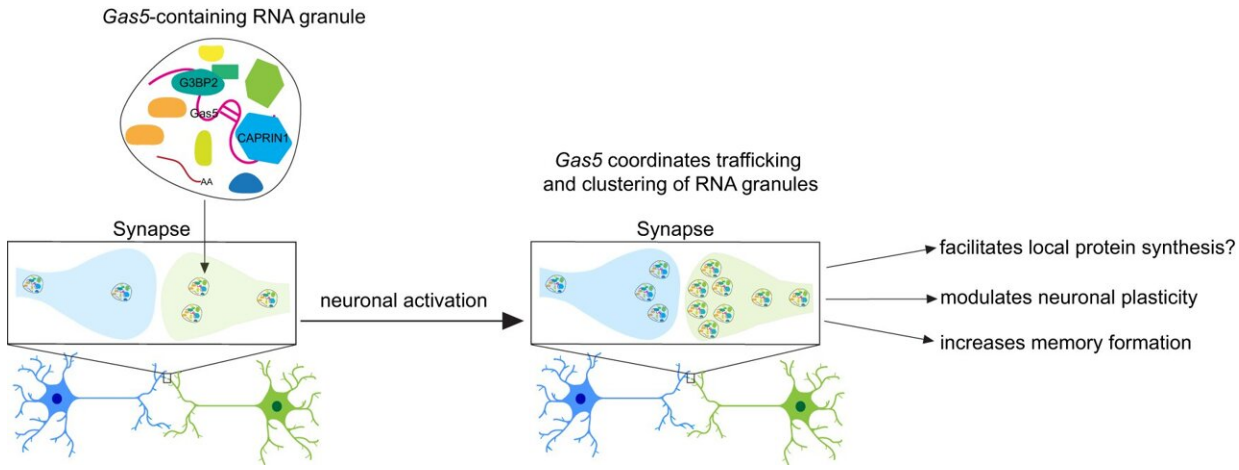
New classes of RNA for learning and memory found

November 30 2023



Model of the proposed mechanism by which Gas5 influences synaptic activity and the formation of fear extinction memory. Extinction learning leads to the accumulation of the Gas5 variant in the synaptic compartment, which then sequesters CAPRIN1 and G3BP2 containing RNA granules away from clustering, leading to an increase in local protein synthesis and tighter control over synaptic plasticity. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-43535-1

Researchers from The University of Queensland (UQ) have discovered a new way a ribonucleic acid (RNA) impacts fear-related learning and memory.

Professor Timothy Bredy at UQ's Queensland Brain Institute said this is

an exciting example of RNA's role in fine-tuning the cellular functions in the brain.

In a paper published in *Nature Communications*, the researchers demonstrated that a non-coding RNA known as Gas5 coordinates the trafficking and clustering of RNA molecules inside the long processes of neurons, and orchestrates neuronal excitability in real time that contributes to learning and memory.

"Understanding the complex world of RNA is a rapidly emerging area of neuroscience research, where we are constantly learning more about how different classes of RNA control the communication between and within brain cells," Bredy said.

"In this study, we found learning related RNAs at the synapse, and one in particular called Gas5, seem to be uniquely required for fear extinction memory.

"There's a lot more happening with these kinds of RNA molecules than we first thought, and that they influence cellular function on a millisecond timeframe, which mirrors the real-time changes in synaptic function that happen in the brain during learning, is extraordinary.

"Non-coding RNA may be the missing link to understanding how the brain processes critically important inputs that lead to the formation of memory."

This study builds on earlier findings from the Bredy lab that identified a separate population of learning-related RNAs that accumulate near the synapse—the junction between neurons that allow them to communicate.

In that paper, published in the *Journal of Neuroscience*, the team shared the discovery of several new synapse-specific RNA harboring a specific

chemical tag called N^6-methyladenosine (m^6A).

Lead author Dr. Sachithrani Madugalle said the findings highlighted the importance of m^6A-modified RNAs in regulating synaptic plasticity.

"Readers are proteins that bind to the chemical tag and direct it to locations and functions," Dr. Madugalle said.

"The readers allowed us to determine the functional role of m^6A-modified RNA molecules in the formation of new memories.

"By examining one such RNA, Malat1, we discovered the key proteins that interact with this RNA and support processes related to an important type of memory called fear extinction.

"Fear extinction impairment is associated with post-traumatic stress disorder (PTSD).

"When Malat1 is chemically decorated with m^6A, this allows it to interact with different proteins in the synaptic compartment, which can then alter the mechanisms involved in the formation of fear extinction memory.

"This new information may inform the development of future RNA therapies to address PTSD.

"By understanding where, when, and how an RNA molecule is activated and having a precise marker will help us identify the target for therapies."

In both studies, the team employed an innovative new tool that allowed them to manipulate the functional state of an RNA molecule, together with Professor Bryan Dickinson and Dr. Simone Rauch at the University

of Chicago.

"We are now looking for ways to harness RNA to control the aspects of synaptic function underlying memory formation and to potentially develop an RNA therapeutic for the treatment of PTSD and phobia," Professor Bredy said.

More information: Wei-Siang Liau et al, Fear extinction is regulated by the activity of long noncoding RNAs at the synapse, *Nature Communications* (2023). DOI: 10.1038/s41467-023-43535-1

Sachithrani U. Madugalle et al, Synapse-Enriched m6A-Modified Malat1 Interacts with the Novel m6A Reader, DPYSL2, and Is Required for Fear-Extinction Memory, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.0943-23.2023

Provided by University of Queensland