Research sheds light on mysterious messenger RNA modifications

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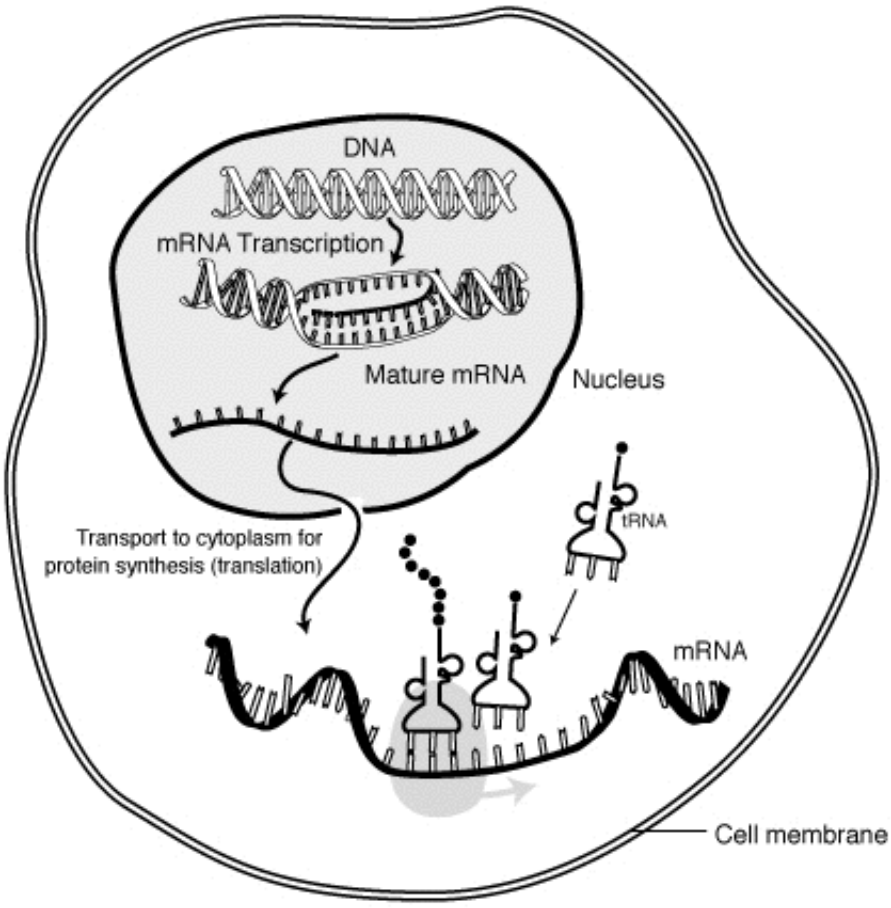

The "life cycle" of an mRNA in a eukaryotic cell. RNA is transcribed in the nucleus; processing, it is transported to the cytoplasm and translated by the ribosome. Finally, the mRNA is degraded. Credit: Public Domain

A team led by scientists at the University of Birmingham has come a step closer to uncovering the purpose of a distinctive set of modifications found at the beginning of messenger RNA which have long remained a fundamental mystery in molecular biology.

Messenger RNAs (mRNAs) are vital for protein production. Their specific structure at the beginning of the chain, called a cap, has two main functions. It protects the mRNA from breaking down, but also it plays a key role in the way the messenger RNA produces proteins.

In addition to the cap structure, the first few nucleotides of an mRNA can carry small decorations called methylation. These occur in animals as well as in some of their parasites like SARS viruses and trypanosomes, but their purpose has remained enigmatic.

Although scientists have known about these mRNA modification for more than 45 years, its effect on the function of mRNA has not been well understood. This is because scientists have not been able to show what happens when this methylation in mRNA is 'knocked out', or removed from animal model organisms.

In a new study, published in *Nature Communications,* researchers from the Universities of Birmingham, Oxford, Nottingham and Warwick succeeded in creating a knockout model using fruit flies (Drosophila) by removing two key genes. That means they were able to show what happens when the flies don't have the two enzymes used in the methylation process.

They found that, although the modified flies did still live, the two enzymes played an important role in the animals' reward learning process. These flies showed a defect in their ability to learn the association of a specific odor with a sugar reward.

Lead author Dr. Matthias Soller from the School of Biosciences at the University of Birmingham says: "The study shows us that mRNA modifications have important functions in the brain. Even though these flies are alive, they are not very capable of learning essential survival skills."

The research builds on work previously done by one of the paper's co-authors, Professor Rupert Fray at the University of Nottingham, who found that cap modifications are highly dynamic in mice.

The team discovered that these modifications played a role in transporting the mRNAs to synapses—the site of communication between neurons.

Professor Scott Waddell from the Centre for Neural Circuits and Behaviour at Oxford University said: "This learning phenotype opens many new questions. Although we do not yet know the detailed nature of the underlying neuronal dysfunction, it is reminiscent of the genetic disease associated with Fragile X Mental Retardation Protein FMRP, which also involves RNA biology and is known to produce defects in synapse development and plasticity."

Dr. Irmgard Haussmann from Birmingham City University adds: "Analyzing the cap modifications is very challenging and further technical hurdles need to be taken to look at modifications in specific mRNAs."

"This is highly relevant as SARS and other viruses that have their own cap methylation enzyme, but it is not really understood what role this plays in virus-host interactions," adds Dr. Nathan Archer from the University of Nottingham School of Veterinary Medicine and Sciences.

The next step for the team will be to investigate in more detail the

mechanism by which the modified mRNA is able to influence protein expression relevant to reward learning and virus propagation.

More information: Irmgard U. Haussmann et al, CMTr cap-adjacent 2′-O-ribose mRNA methyltransferases are required for reward learning and mRNA localization to synapses, *Nature Communications* (2022). DOI: 10.1038/s41467-022-28549-5