Study finds RNA modification is responsible for disruption of mitochondrial protein synthesis in Alzheimer's disease

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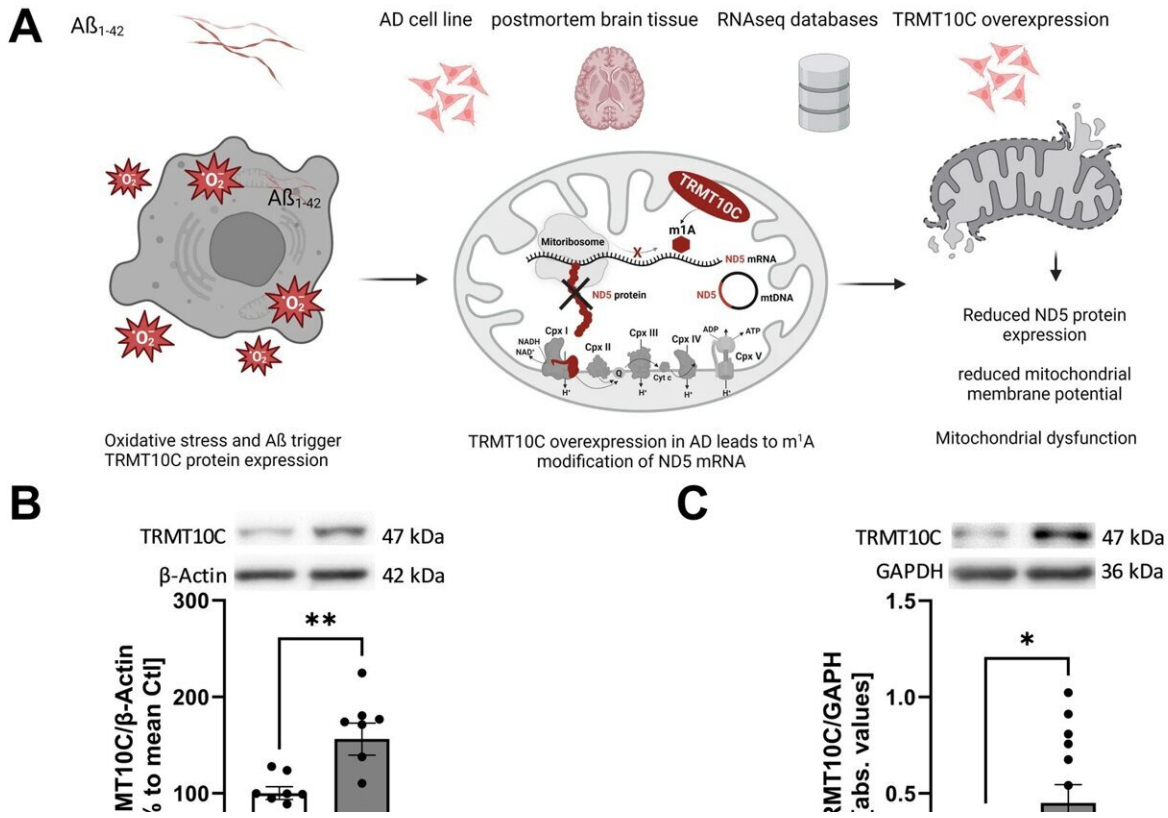

TRMT10C protein and mRNA levels are increased in AD cell and animal models and cortex samples of AD patients. Credit: *Molecular Psychiatry* (2024). DOI: 10.1038/s41380-024-02421-y

A team of researchers at Johannes Gutenberg University Mainz (JGU) has identified a mechanism that causes mitochondrial dysfunction in Alzheimer's patients resulting in a reduction of the supply of energy to the brain.

"This effect is attributable to an RNA modification that has not previously been reported," said Professor Kristina Friedland of the Institute of Pharmaceutical and Biomedical Sciences at JGU. She supervised the related study in collaboration with her colleague Professor Mark Helm.

Their results contribute to a better understanding of the pathophysiology of Alzheimer's disease. Also involved in the research were groups at the Mainz University Medical Center, the Institute of Molecular Biology (IMB), Université de Lorraine, and the Medical University of Vienna. The corresponding paper has been published in *Molecular Psychiatry*.

Mitochondria affected by functional disorder

Mitochondria are organelles inside cells that are in charge of the provision of energy throughout the body, particularly in the brain. For 95% of its energy, the brain is reliant on the metabolism of glucose in the mitochondria. It has long been known that impairment of glucose metabolism occurs in the early stages of Alzheimer's disease. This impairment is due to dysfunction of the mitochondria induced by the aging process and the build-up of amyloid-beta.

A source of energy in the form of adenosine triphosphate (ATP) is formed in the inner mitochondrial membrane by means of a sequence of reactions known as the respiratory chain. Involved in this process are more than one thousand proteins that are transported from the cellular nuclei to the mitochondria.

"But there are also proteins that are synthesized by the mitochondria themselves. One of these is ND5, a subunit of complex I of the respiratory chain," explained Professor Kristina Friedland. A substance called NADH gives electrons to complex I, which transfers these to ubiquinone, resulting in ubiquinol.

During this process, four proteins are pumped from the matrix into the intermembrane space. ND5 plays an important role in this connection, and any mutations of the mitochondrial encoded gene of this subunit can result in serious mitochondrial disorders, such as Leigh syndrome.

It has already been demonstrated that the mRNA that provides the instructions for the synthesis of this protein can undergo methylation. In body cells, mRNA carries the genetic information and—together with tRNA—is responsible for its translation into proteins. Methylation of mRNA leads to a change to its chemical structure so that it can no longer correctly interact with tRNA.

"The synthesis process is undermined, and fewer proteins of the subunit ND5, which is of central relevance to complex I, are formed because the whole process commences with the respiratory chain," added Friedland.

TRMT10C enzyme causes methylation and thus inhibition of the synthesis of ND5

The teams of Friedland and Helm at the Institute of Pharmaceutical and Biomedical Sciences at Mainz University were able to show that it is an enzyme called TRMT10C that induces this methylation and, thus, the subsequent repression of ND5. The researchers observed suppression of the biosynthesis of proteins of the ND5 subunit in a suitable cell model as well as in the brains of Alzheimer's patients.

The authors stated, "As a consequence, here demonstrated for the first time, TRMT10C induced m^1A methylation of ND5 mRNA leads to mitochondrial dysfunction. Our findings suggest that this newly identified mechanism might be involved in Aβ-induced mitochondrial dysfunction."

More information: Marko Jörg et al, N1-methylation of adenosine (m1A) in ND5 mRNA leads to complex I dysfunction in Alzheimer's disease, *Molecular Psychiatry* (2024). DOI: 10.1038/s41380-024-02421-y

Provided by Johannes Gutenberg University Mainz