Modifying messenger RNA may provide a new target for Alzheimer's disease

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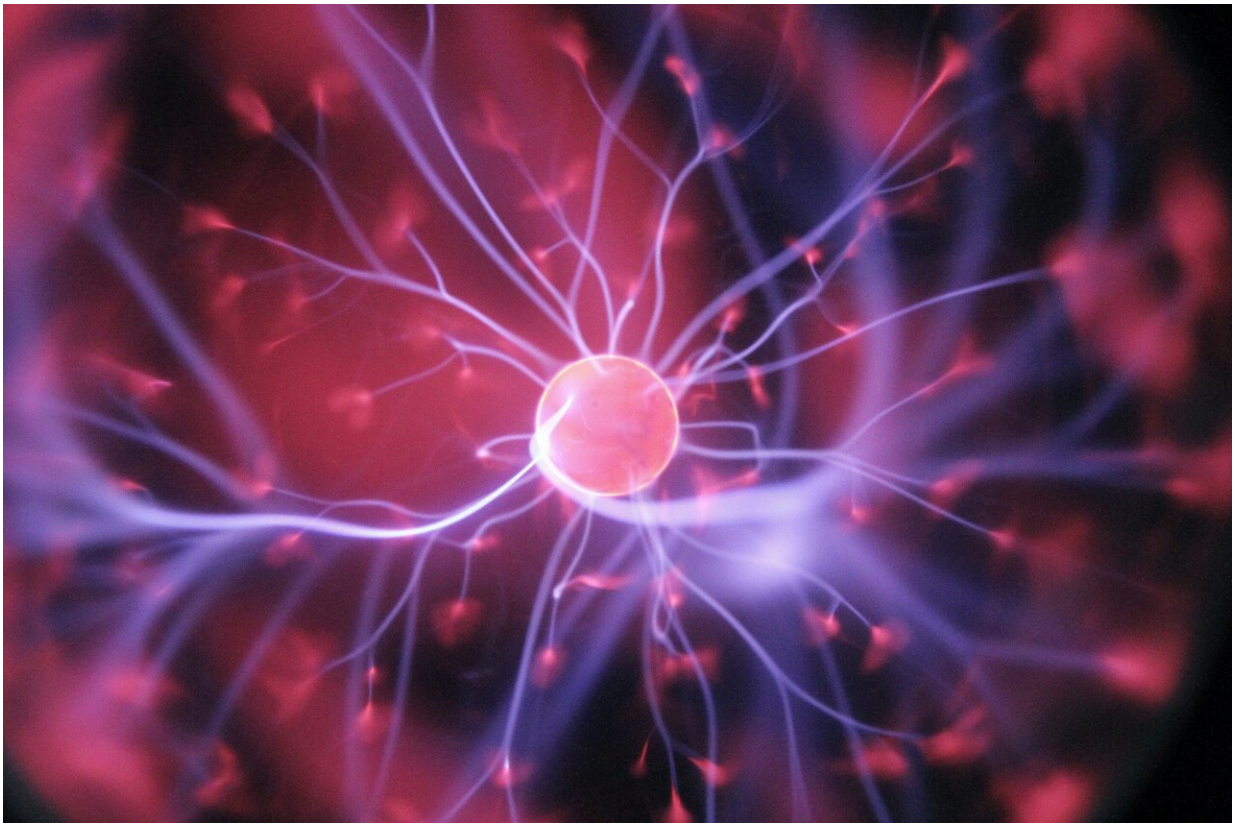

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Reducing the methylation of a key messenger RNA can promote migration of macrophages into the brain and ameliorate symptoms of Alzheimer's disease in a mouse model, according to a new study

publishing March 7 in the open access journal *PLOS Biology* by Rui Zhang of Air Force Medical University in Xian, Shaanxi, China. The results illuminate one pathway for entrance of peripheral immune cells into the brain, and may provide a new target for treatment of Alzheimer's disease.

A presumed trigger for the development of Alzheimer's disease is the accumulation of proteinaceous, extracellular amyloid-beta plaques in the brain. High levels of amyloid-beta in mice leads to neurodegeneration and cognitive symptoms reminiscent of human Alzheimer's disease, and reduction of amyloid-beta is a major goal in development of new treatments.

One potential pathway for getting rid of amyloid-beta is the migration of blood-derived myeloid cells into the brain, and their maturation into macrophages, which, along with resident microglia, can consume amyloid-beta. That migration is a complex phenomenon controlled by multiple interacting players, but a potentially important one is the methylation of messenger RNA within the myeloid cells.

The most common type of mRNA methylation, called m6A, is carried out by the enzyme METTL3, so the authors first asked whether deficiency of METTL3 in myeloid cells had any effect on cognition in the Alzheimer's disease mouse model. They found that it did—treated mice performed better on various cognitive tests, an effect that could be inhibited when they blocked the migration of myeloid cells into the brain.

How did decreased mRNA methylation promote myeloid cell migration? The authors elucidated a complex mechanism. Through analysis of mRNA expression patterns and other techniques, they showed that depletion of METTL3 reduced the activity of a key m6A reader protein, which recognizes m6A-modified mRNAs and promotes their translation

into protein. That led to a decline in another protein, and that inhibited the production of yet another protein, called ATAT1. Loss of ATAT1 reduced the attachment of acetyl groups to microtubules, and that reduction in turn promoted migration of the myeloid cells into the brain, followed by maturation into macrophages, increased clearance of amyloid-beta, and improved cognition in mice.

"Our results suggest that m6A modifications are potential targets for the treatment of Alzheimer's disease," the authors concluded, while noting that much about this pathway in Alzheimer's disease remains to be explored. Because mRNA methylation has a fundamental effect on a wide variety of downstream targets, effective drug development within this pathway may require moving further downstream to avoid unwanted effects.

More information: Loss of the m6A methyltransferase METTL3 in monocyte-derived macrophages ameliorates Alzheimer's disease pathology in mice, *PLOS Biology* (2023). DOI: 10.1371/journal.pbio.3002017

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