Rapamycin increases Alzheimer's-associated plaques in mice, study finds

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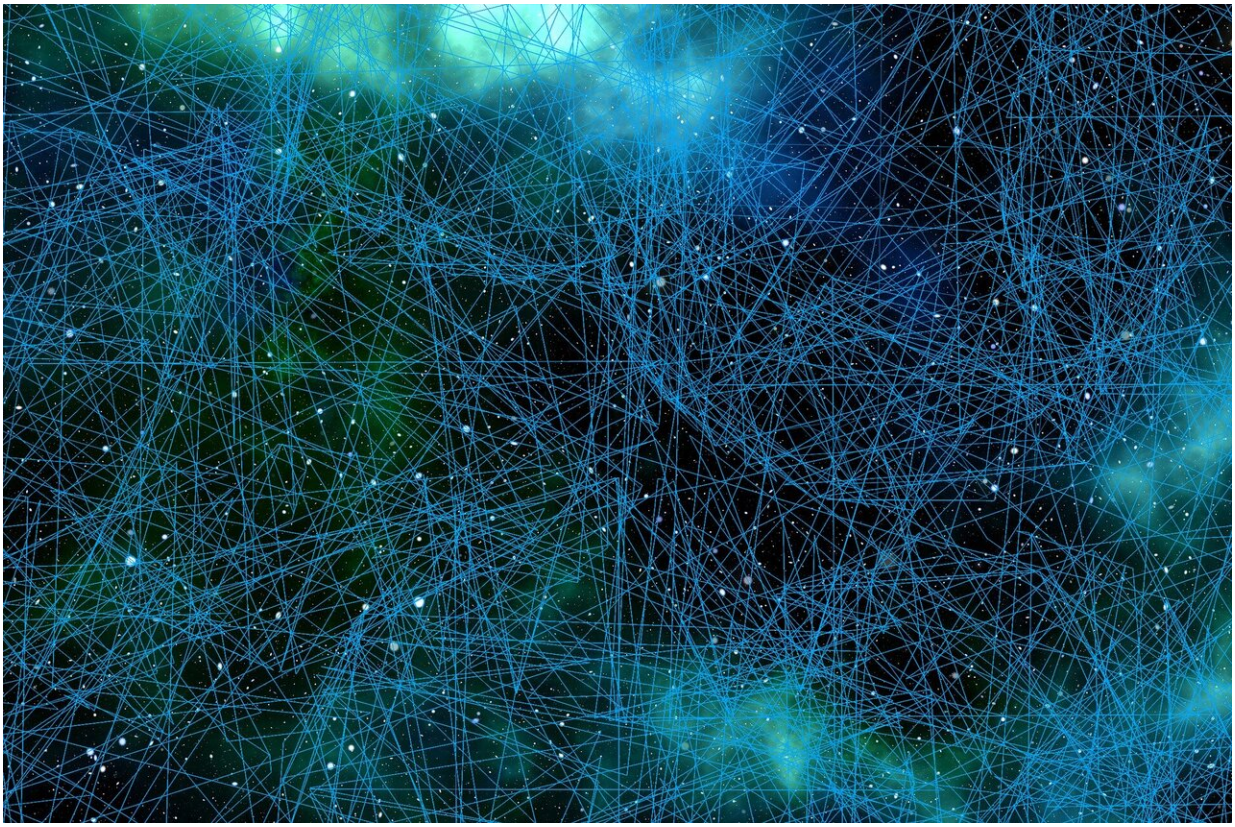

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Researchers from The University of Texas Health Science Center at San Antonio (UT Health San Antonio) have found that oral administration of rapamycin to an Alzheimer's disease mouse model causes an increase in

beta (β)-amyloid protein plaques. β-amyloid buildup is a hallmark of Alzheimer's disease.

Rapamycin is approved to treat transplant and cancer patients. Publicly available data suggest that the drug might also improve learning and memory in aged mice. However, the UT Health San Antonio researchers observed that after rapamycin treatment, a protein called Trem2 (triggering receptor expressed on myeloid cells 2) is dramatically diminished. Trem2 is present in microglia, which are immune cells in the brain and spinal cord.

"Trem2 is a receptor located on the surface of the microglia, and it enables these cells to engulf and degrade β-amyloid," said study senior author Manzoor Bhat, Ph.D.. "Loss of Trem2 in microglia impairs the vital function of amyloid degradation, which in turn causes a buildup of β-amyloid plaques." Dr. Bhat is professor and chairman of the Department of Cellular and Integrative Physiology at UT Health San Antonio and vice dean for research in the university's Joe R. and Teresa Lozano Long School of Medicine.

Drug target

Importantly, the study, published June 7 in the *Journal of Neuroscience*, also featured a novel way to increase Trem2 in microglia. When the study lead author, Qian Shi, Ph.D., assistant professor in the Department of Cellular and Integrative Physiology, deleted a gene called Tsc1 from the microglia, there was a marked increase in Trem2 levels and a decrease in β-amyloid plaques.

Previous research has shown that loss of Tsc1 leads to activation of the mTOR (mammalian target of rapamycin) signaling pathway. Rapamycin, in contrast, blocks this pathway. "We expected that selective loss of Tsc1, only in microglia and not in neurons or other cells, would have

negative consequences because inhibiting mTOR with rapamycin has known therapeutic uses in some disease models," Dr. Shi said. "But the opposite was occurring." Thus, repressing Tsc1 solely in microglia to enhance β-amyloid uptake could be a potential drug target, Dr. Shi said.

The experiments were conducted in a specific mouse strain called the 5XFAD, which is used as a model for human Alzheimer's disease. The study is relevant to β-amyloid-associated Alzheimer's and is not generalizable to other Alzheimer's pathologies, Dr. Bhat said.

More investigation warranted

Findings from this study may give the medical world a reason to pause testing rapamycin on anyone at risk of Alzheimer's disease. "Rapamycin may have benefits in terms of suppressing the immune system and as a tumor suppressor," Dr. Bhat said. "But in a situation where it negatively impacts the expression of Trem2 or other critical proteins, it may have a detrimental effect. We caution that rapamycin's benefits in β-amyloid-associated Alzheimer's must be studied more carefully."

The Bhat laboratory specializes in creating and analyzing genetic models of human diseases. The lab's investigators have uncovered a number of novel pathways that involve axonal myelination and demyelination and how mTOR signaling in glial cells, such as microglia, could be exploited for therapeutic benefits in human diseases including Alzheimer's disease.

More information: Microglial mTOR Activation Upregulates Trem2 and Enhances β-Amyloid Plaque Clearance in the 5XFAD Alzheimer's Disease Model, *JNeurosci* (2022). DOI: 10.1523/JNEUROSCI.2427-21.2022