Medical Xpress

Memory deficits resulting from epigenetic changes in Alzheimer's disease can be reversed

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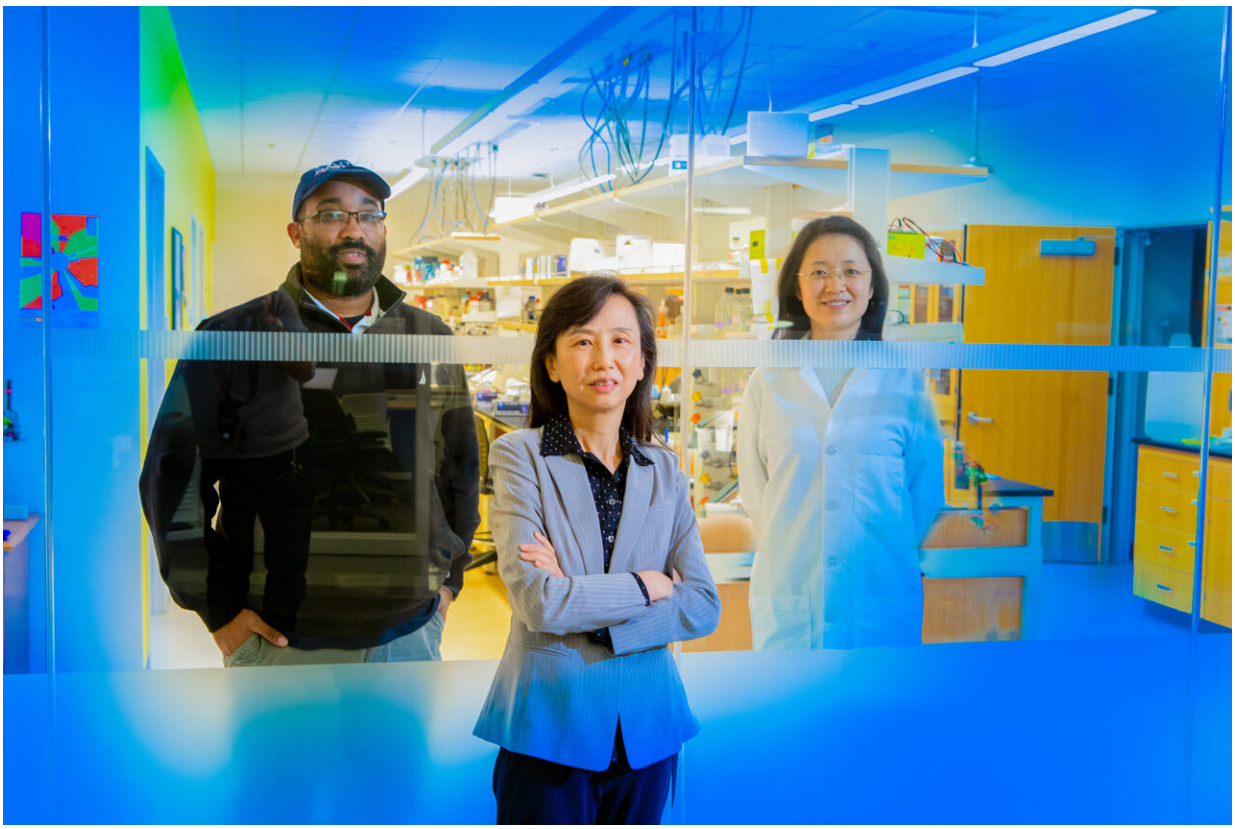

Photo illustration: UB co-authors of the Science Advances paper are L to R: Jamal Williams, doctoral candidate; Zhen Yan, PhD, SUNY Distinguished Professor and senior author and Qing Cao, PhD, postdoctoral fellow and first author. (Individuals were photographed separately.) Credit: Douglas Levere/University at Buffalo

Memory loss associated with Alzheimer's disease (AD) may be able to be restored by inhibiting certain enzymes involved in abnormal gene transcription, according to a preclinical study by researchers at the University at Buffalo. The findings could pave the way toward new treatments for Alzheimer's disease.

The paper will be published on Dec. 9 in *Science Advances*.

"By treating AD mouse models with a compound to inhibit these enzymes, we were able to normalize gene expression, restore neuronal function, and ameliorate cognitive impairment," said Zhen Yan, Ph.D., senior author and SUNY Distinguished Professor in the Department of Physiology and Biophysics in the Jacobs School of Medicine and Biomedical Sciences at UB.

Alzheimer's disease alters the expression of genes in the prefrontal cortex, a key region of the brain controlling cognitive processes and executive functions.

By focusing on gene changes caused by epigenetic processes (those that are not related to changes in DNA sequences) such as aging, the UB researchers were able to reverse elevated levels of harmful genes that cause memory deficits in AD.

The current research extends the work the UB team reported in 2019 in the journal *Brain*, in which they were able to reverse the loss or downregulation of genes beneficial to cognitive function in AD.

In this new paper, the UB team reports that it has reversed the upregulation of genes involved in impairing cognitive function.

Packaging the DNA

Yan explained that transcription of genes is regulated by an important process called histone modification, where histones, the proteins that help package DNA into chromosomes, are modified to make that packaging looser or tighter. The nature of the packaging, in turn, controls how genetic material gains access to a cell's transcriptional machinery, which can result in the activation or suppression of certain genes.

Yan said they found that H3K4me3, a histone modification called histone trimethylation at the amino acid lysine 4, which is linked to the activation of gene transcription, is significantly elevated in the prefrontal cortex of people with AD and mouse models of the disease.

That epigenetic change, she said, is linked to the abnormally high level of histone-modifying enzymes that catalyze the modification known as H3K4me3.

The UB researchers found that when the AD mouse models were treated with a compound that inhibits those enzymes, they exhibited significantly improved cognitive function.

"This finding points to the potential of histone modifying enzyme-targeted drugs for AD treatment, which may have broad and powerful impact," said Yan.

New target genes

In making that discovery, the UB team also identified a number of new target genes, including Sgk1 as a top-ranking target gene of the epigenetic alteration in AD. Sgk1 transcription is significantly elevated in the prefrontal cortex of people with AD and in animal models with the disorder.

Yan said they found that abnormal histone methylation at Sgk1 contributes to its elevated expression in AD. "Interestingly, the upregulation of Sgk1 is also strongly correlated with the occurrence of cell death in other neurodegenerative diseases, including Parkinson's disease and amyotrophic lateral sclerosis," she said.

Sgk1 encodes an enzyme activated by cell stress, which plays a key role in numerous processes, such as regulating ion channels, enzyme activity, gene transcription, hormone release, neuroexcitability and cell death. The researchers found that it is highly connected to other altered genes in AD, suggesting it may function as a kind of hub that interacts with many molecular components to control disease progress.

"In this study, we have found that administration of a specific Sgk1 inhibitor significantly reduces the dysregulated form of tau protein that is a pathological hallmark of AD, restores prefrontal cortical synaptic function, and mitigates memory deficits in an AD model," she said. "These results have identified Sgk1 as a potential key target for therapeutic intervention of AD, which may have specific and precise effects."

More information: "Targeting histone K4 trimethylation for treatment of cognitive and synaptic deficits in mouse models of Alzheimer's disease" *Science Advances* (2020). advances.sciencemag.org/lookup … .1126/sciadv.abc8096

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