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Researchers identify proteins that might contribute to memory loss and Alzheimer's disease

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A scientific group led by the Translational Genomics Research Institute (TGen) have identified three kinases, or proteins, that dismantle connections within brain cells, which may lead to memory loss associated with Alzheimer's disease.

These findings, the results of a multi-year TGen study, are published in this month's edition of BMC Genomics in a paper titled: High-content siRNA screening of the kinome identifies kinases involved in Alzheimer's disease-related tau hyperphosphorylation.

The three kinases were found to cause a malfunction in tau, a protein critical to the formation of the microtubule bridges within brain cells, or neurons. These bridges support the synaptic connections that, like computer circuits, allow neurons to communicate with each other.

"The ultimate result of tau dysfunction is that neurons lose their connections to other neurons, and when neurons are no longer communicating, that has profound effects on cognition — the ability to think and reason," said Dr. Travis Dunckley, an Associate Investigator in TGen's Neurodegenerative Research Unit and the scientific paper's senior author.

Tau performs a critical role in the brain by helping bind together microtubules, which are sub-cellular structures that create scaffolding in

the neurons, allowing them to stretch out along bridges called axons. The axons support the synaptic, or chemical, connections with other neurons.

Under normal circumstances, kinases regulate tau by adding phosphates. This process, called tau phosphorylation, enables the microtubules to unbind and then bind again, allowing brain cells to connect and reconnect with other brain cells.

"That facilitates synaptic plasticity. It facilitates the ability of people to form new memories — to form new connections between different neurons — and maintain those memories. So, it's an essential function," Dr. Dunckley said.

However, sometimes the tau protein becomes hyperphosphorylated, a condition in which the tau creates neurofibrillary tangles, one of the signature indicators of Alzheimer's.

"When tau protein is hyperphosphorylated, the microtubule comes apart — basically destroying that bridge — and the neurons can no longer communicate with each other," Dr. Dunckley said.

TGen investigators created sophisticated tests to look at all 572 known and theoretical kinases within human cells. They identified 26 associated with the phosphorylation of tau. Of these 26, three of them — EIF2AK2, DYRK1A and AKAP13 — were found to cause hyperphosphorylation of tau, permanently dismantling the microtubule bridges.

"This paper shows, for the first time, these three kinases affect Alzheimer's disease-relevant tau hyperphosphorylation, in which most of the tau protein is now driven into a permanently phosphorylated form," Dr. Dunckley said.

Dr. Eric Reiman, clinical director of TGen's Neurogenomics Division and executive director of the Banner Alzheimer's Institute, explained that tau holds together the skeleton inside neurons. When phosphate molecules stick to tau proteins, the skeleton falls apart and the neurons begin to retract their synaptic branches and die, leading to memory loss and thinking problems.

In this study, researchers used a molecular tool called siRNA to screen the entire human genome, said Dr. Reiman, a co-author of the scientific paper. This tool enabled the TGen-led team to discover which proteins, when genetically turned off, prevent phosphate molecules from sticking to tau. The three kinases, or proteins, that appear to contribute to the formation of brain tangles, can now be targeted by protein-inhibitor drugs.

"This study used a powerful tool to discover three proteins that may be involved in tangle formation. If safe and well-tolerated tangle-busting medications can be developed, they offer great promise in the treatment of Alzheimer's disease," said Dr. Reiman, who also is Director of the Arizona Alzheimer's Consortium.

The next step will be to identify drug compounds that can negate the effects of the three kinases linked to tau hyperphosphorylation.

"The reason that we did this study was to identify therapeutic targets for Alzheimer's disease, whereby we could modify the progression of tau pathology," Dr. Dunckley said. "This was a screen to identify what the relevant targets are. Now, we want to match those targets to treatments."

Provided by Translational Genomics Research Institute

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