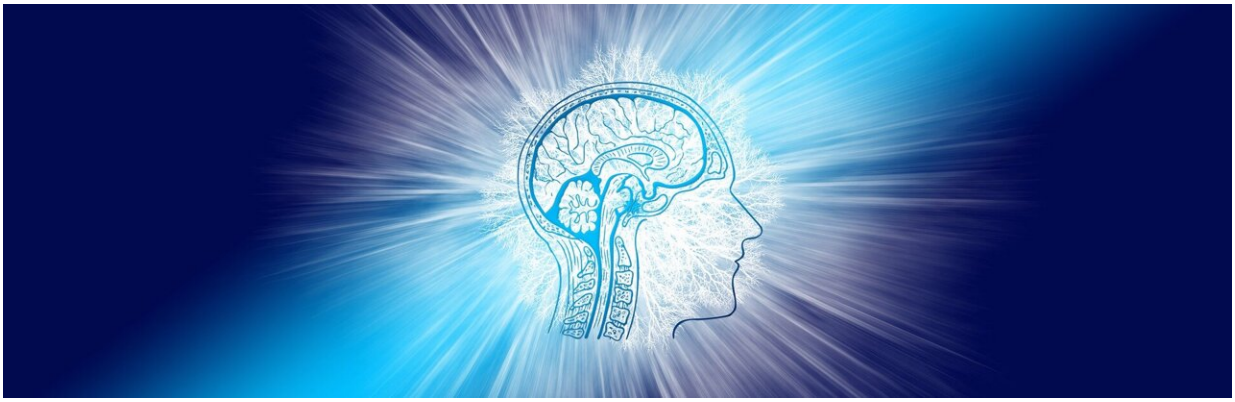
New tau regulators and therapeutic targets for neurodegenerative disorders discovered

January 6 2023, by Graciela Gutierrez



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Neurodegenerative diseases affect millions of people worldwide and as our life expectancy increases, more individuals are expected to be affected in the coming decades. Tauopathies such as Alzheimer's disease are a class of neurodegenerative disorders involving an accumulation of tau proteins, which eventually results in massive loss of brain cells. There is little consensus about the underlying causes and no effective treatments are available currently for these disorders.

In a current study published in *Neuron* the goal of researchers at Baylor College of Medicine and Texas Children's Hospital was to conduct an unbiased screen to find genes whose inhibition can reduce the levels of

tau protein. They identified new tau regulators that can serve as viable and effective therapeutic targets for Alzheimer's disease and other tauopathies.

This study was led by Dr. Huda Zoghbi, professor of molecular and human genetics and neuroscience at Baylor and founding director of the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's. The study involved multidisciplinary collaborations with other Duncan NRI faculty, Drs. Juan Botas and Zhandong Liu.

A cross-species screen reveals three new tau regulators

First, the Liu lab performed computational modeling and prediction analysis of the known 17,000 human genes and generated a compendium of 6,600 genes that were deemed to be "druggable," meaning the proteins produced by these genes can be modified by chemical compounds.

"Next, we used a cross-species approach involving mammalian cells and fruit flies to comb through this large collection to find genes that impact tau levels both in mammals and fruit flies," said Dr. Jiyoen Kim, assistant professor of neuroscience in the Zoghbi lab and lead author of the study.

In both screens, the activity of the genes was reduced using RNA interference technology, with a small subset of genes targeted by CRISPR technology in the cell-based screen.

"Our strategy of performing parallel screens in mammalian cells and fruit flies allowed us to select targets that showed up as top hits in both species," said co-author Dr. Ismael Al-Ramahi, assistant professor of

molecular and human genetics at Baylor and a member of the Duncan NRI.

This approach led them to 11 new validated tau regulators. Of these, three—USP 7, RNF130 and RN149—converged on the ubiquitin protein degradation pathway. The team further investigated these proteins looking to understanding how their regulating of the ubiquitin pathway will likely reveal mechanistic insights into tau degradation.

USP7, RNF130 and RNF149 regulate tau levels via the CHIP system

The team discovered that USP7 stabilizes tau by protecting it from CHIP-mediated degradation. They also found that RNF130 and RNF149 decrease the levels of the tau degrader (CHIP). To test if these target genes can regulate CHIP and tau levels in the brain, the team turned off their expression in adult mice that overexpress mutant tau.

"Turning off the expression of USP7, RNF130 or RNF149 in adult mice with tauopathy increased CHIP level and reduced tau proteins," Kim said. "We also saw a decrease in other tell-tale signs of tau-mediated damage and neuro-inflammation. Most excitingly, these mice performed as well as age-matched normal mice in tasks that required learning and memory—a strong indicator that increasing CHIP levels in addition to a concomitant reduction in tau levels can improve neuronal and overall brain function in these mice."

Although these three proteins have never been linked with each other before, it is notable that their functions converged on CHIP, which highlights its central role in maintaining tau levels in check.

"We rationalized that identifying tau regulators that can be inhibited by

small-molecule drugs will be worthwhile given the likelihood that treatments to prevent dementia are best initiated in the pre-symptomatic phase and are likely to go on for decades," Zoghbi said. "We are excited to have found three targets that reduce tau level and show marked improvements in disease characteristics and learning and memory in animal models. This discovery opens the exciting possibility of leveraging small-molecule inhibitors to lower tau levels and hopefully, prevent memory deficits in those at risk for Alzheimer's disease and other tauopathies."

More information: Jiyoen Kim et al, Evolutionarily conserved regulators of tau identify targets for new therapies, *Neuron* (2023). DOI: 10.1016/j.neuron.2022.12.012

Provided by Baylor College of Medicine