Research provides new understanding of Parkinson's and Alzheimer's disease and opens path to treatment

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A team of scientists at Baylor College of Medicine and Texas Children's Hospital has discovered that in three separate laboratory models, the protein TRIM28 can promote the accumulation of two key proteins that drive the development of Parkinson's, Alzheimer's and related diseases. The discovery, which appears in eLife, offers a new understanding of these diseases and possible opportunities for drug development.

"TRIM28 is a protein that plays an essential role during embryonic development," said senior author Dr. Huda Zoghbi, professor of molecular and human genetics and of pediatrics - neurology and developmental neuroscience at Baylor and director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital. "Here we have discovered that it can also regulate proteins that contribute to the development of Alzheimer's and Parkinson's disease."

Neurodegenerative diseases such as Alzheimer's and Parkinson's disease are driven by the accumulation of proteins to levels that are toxic to the brain. Two of these proteins are alpha-synuclein, which accumulates in Parkinson's disease, and tau, which drives Alzheimer's disease.

"A number of patients with Parkinson's disease also present with symptoms of dementia. In these cases the brains show accumulation of both alpha-synuclein and tau," said first author Dr. Maxime Rousseaux, postdoctoral associate in the Zoghbi lab. "And there is a subset of

patients with dementias that are driven by tau, but where you also find alpha-synuclein accumulation."

This medical evidence inspired the researchers to investigate why of all the proteins that accumulate in the brain in these diseases, tau and alpha-synuclein are the two that often are found together in Parkinson's and Alzheimer's.

To study this, the scientists carried out two sets of screening experiments. They carried out screening and validation in human cells in the Zoghbi lab, and in fruit flies in the laboratory of Dr. Juan Botas, professor of molecular and human genetics and of molecular and cellular biology at Baylor. In one set of experiments they screened for genes that alter the levels of alpha-synuclein and in another they screened for genes that alter the levels of tau. They found a number of genes that can regulate either tau or alpha-synuclein, but only one strong regulator of both, TRIM28.

"When we reduced the activity of TRIM28 by 50 percent, the levels of tau and alpha-synuclein decreased and the damage to the cells was markedly reduced," said Zoghbi, who also is an investigator at the Howard Hughes Medical Institute.

To find clues about the mechanism by which TRIM28 brings tau and alpha-synuclein together, the scientists asked what would happen to these molecules if they increased the amount of TRIM28 in the cells.

"We worked with two mouse models – one of alpha-synuclein accumulation and one of tau accumulation – and overexpressed TRIM28 before the animals showed further accumulation of either protein or symptoms of disease," said Rousseaux. "We observed that overexpressing TRIM28 accelerated the accumulation of the proteins in the respective animal models."

Further experiments showed that tau and alpha-synuclein form complexes with TRIM28 and that these complexes stabilize the proteins. Using brain cells grown in the lab, the scientists revealed that the complexes accumulate preferentially in the nucleus of the cells and are toxic.

Collaborating with a team at Johns Hopkins University School of Medicine, they also discovered that TRIM28 was linked to the accumulation of tau and alpha-synuclein in the nucleus in postmortem brain tissue from individuals who suffered from Parkinson's disease and related disorders.

"Our work shows that by reducing the activity of TRIM28 we can clearly reduce the accumulation of tau and alpha-synuclein in fruit flies and mouse models of the disease," said Zoghbi. "These results encourage us to consider the possibility of developing drugs that could reduce the levels of TRIM28 to help prevent the development of Alzheimer's, Parkinson's and related diseases."

Provided by Baylor College of Medicine

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