Acetylation may contribute to dementia and Alzheimer's disease

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A new study uncovers a protein modification that may contribute to the formation of neuron-damaging neurofibrillary tangles in the human brain. The research, published by Cell Press in the September 23 issue of the journal *Neuron,* may lead to new strategies for treatment of neurodegenerative diseases that result from pathological aggregation of tau protein.

Tau protein is common in the central nervous system where it helps to stabilize microtubules that form the neuronal cytoskeleton. Tau mutations have been linked with dementia and Alzheimer's disease (AD), and accumulation of phosphorylated tau protein (p-tau) has been implicated in neurodegeneration. However, the molecular mechanisms that underlie abnormal tau aggregation have not been elucidated.

"We know that an enzyme called SIRT1 is reduced in the AD brain and that this reduction correlates with the accumulation of p-tau. Further, overexpression of SIRT1 protects against neuronal loss in a mouse model of AD," explains senior study author, Dr. Li Gan from the Gladstone Institute of Neurological Disease in San Francisco, California. "However, how SIRT1 protects against tau-mediated neurodegeneration is not clear."

SIRT1 is a deacetylase, an enzyme that removes acetyl groups from proteins. Like phosphorylation, acetylation regulates many different cellular functions, including cytoskeleton dynamics. "To determine whether tau is acetylated and whether tau acetylation contributes to tau

accumulation, we investigated tau acetylation in neurons, mouse models of tauopathy, and AD brains," says Dr. Gan.

Dr. Gan's group found that tau acetylation prevents degradation of p-tau, and patients at early and moderate stages of tauopathy exhibited elevated tau acetylation. The researchers went on to show that inhibiting SIRT1 increased levels of acetylated and pathogenic tau while a small molecule inhibitor of p300, an enzyme known to attach acetyl groups to proteins, promoted tau deacetylation and eliminated p-tau associated with pathological conditions.

While the link between tau acetylation and tau phosphorylation is not known, the results provide new insight into tau-mediated neuropathology. "Our findings support the model that the abnormally elevated acetylation at an early stage of the disease could block clearance of p-tau from neurons, leading to its accumulation," concludes Dr. Gan. "Our observation that p300 diminished tau acetylation and effectively eliminated p-tau supports the idea that interfering with tau acetylation may be a new approach for reducing tau-related pathology."

Provided by Cell Press