Pin1 is beneficial in Alzheimer's disease, detrimental to some forms of dementia

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The most common form of dementia, Alzheimer's disease, and a relatively rare hereditary form of dementia, frontotemporal dementia with parkinsonism-17, share a common pathology: Both are the result of an overaccumulation of tau proteins, which form tangled lesions in the brain's neurons and eventually lead to the collapse of the brain cells responsible for memory. And, although mutations in the gene encoding tau have not been found in individuals with Alzheimer's disease, they have been identified in individual with frontotemporal dementia, and are often used as models for studying Alzheimer's disease.

A new study finds that the Pin1 enzyme, previously shown to be of benefit in "detangling" tau in Alzheimer's disease, actually has the contradictory effect in cases in which the tau has certain mutations. Consequently, while increasing Pin1 in neurons effectively suppresses the disease development in cases of Alzheimer's, it actually accelerates disease progression in the case of frontotemporal dementia.

Led by researchers at Beth Israel Deaconess Medical Center (BIDMC) and reported in the April 22 advance on-line issue of *The Journal of Clinical Investigation*, these new findings offer novel ideas for the development of therapies for Alzheimer's disease and other dementias, and also point to the importance of using appropriate animal models for studying distinct tau-related neurodegenerative disorders and screening for therapeutic drugs.

"We were completely surprised to discover these diametrically opposed

outcomes," explains senior author Kun Ping Lu, MD, PhD, a scientist in the Division of Hematology/Oncology at BIDMC and Professor of Medicine at Harvard Medical School. "It appears that while boosting Pin1 activity is beneficial in cases of Alzheimer's disease, inhibition of Pin1 is helpful for dementias that carry the P301L tau mutation [as is the case with frontotemporal dementia]."

Pin1 (prolyl isomerase) was first discovered by Lu and Salk Institute investigator Tony Hunter in 1995. In 2003, Lu and colleagues demonstrated that Pin1 promotes the removal of phosphates from tau, thereby "detangling" the protein which, in cases of Alzheimer's disease, had become knotted and overburdened with excess phosphate molecules. Three years later, in 2006, the Lu team discovered that Pin1 also inhibits the production of toxic amyloid Abeta peptides, the central component of senile plaques and the second neuropathological hallmark in brains of Alzheimer's patients. They further confirmed that when Pin1 was missing, neurons in regions of the brain responsible for memory would collapse under the weight of the tau protein tangles and toxic amyloid peptides, ultimately leading to age-dependent neurodegeneration. Together with other findings that Pin1 activity is inhibited in Alzheimer's brains by many conditions, such as stresses, these results indicate that loss of Pin1 activity is a major contributing factor in the development of Alzheimer's disease.

In this latest study, Lu and his coauthors set out to learn if by boosting levels of the Pin1 enzyme, the onset of Alzheimer's could be prevented.

As predicted, the investigators found in both human cell lines and in mice that when Pin1 was normally present, the tau proteins readily degraded; when the enzyme was removed, the tau proteins stabilized and failed to break down. Subsequent mouse experiments in which Pin1 was moderately overexpressed in brain cells 10 days after birth again found that the tau protein degraded much more quickly than it did in normal

control mice.

But, when the scientists next went on to cross two separate mouse models – those that overexpressed the Pin1 enzyme and mouse models of Alzheimer's disease – they made a surprising discovery: Not only did the exact same Pin1 overexpression not suppress tau stability, it actually exacerbated the tau pathology and neurodegeneration among mice overexpressing P301L tau mutant.

"Transgenic mice overexpressing human wild-type tau or tau mutants have been typically used as Alzheimer's models," explains Lu, adding that the P301L-tau-mutant- mice are widely preferred due to their robust tau pathology and neurodegeneration. However, since no tau mutations are found in cases of Alzheimer's disease, it remains unclear as to how appropriate tau mutant mice actually are as an Alzheimer's model.

"The significance of our findings are two-fold," he notes. "First, we have established a proof of concept that boosting Pin1 activity may offer a new idea for preventing or even treating the tau pathology and neurodegeneration in Alzheimer's disease.

"And, second, given that no tau mutation is found in Alzheimer's patients, this research suggests that it would be prudent to not use P301L tau as an Alzheimer's disease model, especially when screening and testing drugs, as it may produce diametrically opposite effects. Therefore, it is critical to use appropriate animal models for studying distinct tau-related neurodegenerative disorders and to develop disease-specific therapies for these devastating diseases."

Source: Beth Israel Deaconess Medical Center