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Gene therapy bolsters enzyme activity to combat Alzheimer's disease in mice

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St. Jude Children's Research Hospital scientists have identified an enzyme that can halt or possibly even reverse the build-up of toxic protein fragments known as plaques in the brains of mice with Alzheimer's disease. The research appeared in a recent edition of the scientific journal *Nature Communications*.

Plaques decreased substantially in mice treated with gene therapy to increase activity of the enzyme neuraminidase 1 (NEU1) in a region of the brain involved in learning and memory. Plaques accumulate between neurons in the brains of Alzheimer's patients and are a hallmark of the disease.

The results raise hopes the enzyme could lead to new methods of diagnosing and treating Alzheimer's disease, a neurodegenerative disorder that causes problems with memory, thinking and behavior. More than 5 million Americans are currently living with the problem. The number is expected to rise as the population ages.

"The findings suggest that down-regulation of NEU1 and a reduced supply of the enzyme may contribute to the development of Alzheimer's disease or similar neurodegenerative disorders in some patients," said the study's corresponding author Alessandra d'Azzo, Ph.D., a member in the St. Jude Department of Genetics. "Among the questions we are asking is whether a therapeutic window exists when the enzyme could be used to halt or even reverse the disease."

NEU1 belongs to a family of enzymes in cells whose job is to dismantle and recycle unneeded proteins and other components. The work is done inside cell structures called lysosomes.

The enzyme is missing or reduced in a rare inherited disorder called sialidosis that can affect children and adolescents. This is the first report linking NEU1 to age-related neurodegenerative disorders like Alzheimer's. In collaboration with the University of California, Davis, D'Azzo and her colleagues have begun checking NEU1 levels in brain tissue of Alzheimer's patients at different stages of the disease.

D'Azzo's long-standing interest in sialidosis and related disorders known as lysosomal storage diseases led to the discovery. The findings include evidence of how the protein fragments that make up the Alzheimer's plaque are deposited outside neurons and how loss of NEU1 possibly contributes to disease progression and spread.

The work was done in a mouse developed in d'Azzo's laboratory that lacked the NEU1 gene. These studies revealed that loss of NEU1 activity was associated with a build-up in lysosomes of the amyloid precursor protein (APP), which they identified as a natural target of the enzyme. Improperly processed, APP is broken into the toxic peptides that form Alzheimer's plaques. Those fragments include amyloid beta peptide 42 (Aβ-42), which researchers suspect play a major role in the Alzheimer's disease process.

Not only did APP accumulate in lysosomes of mice lacking NEU1 but researchers found evidence that the build-up promoted the production of Aβ-42 and other toxic peptides tied to Alzheimer's disease. Aβ-42 was detected in the spinal fluid and hippocampus of mice that lacked NEU1, but not in mice with a functional NEU1 gene. The hippocampus plays a critical role in learning and memory and is the brain region that is often an early casualty of Alzheimer's disease.

Previously, d'Azzo's laboratory discovered that NEU1 directs a process called lysosomal exocytosis. Cells use this process to repair the outer membrane of cells and to selectively expel material in lysosomes. Working with nerve cells growing in culture, investigators reported that the absence of NEU1 was accompanied by an increase in a protein named LAMP1. The protein is a key regulator of lysosomal exocytosis. Increased LAMP1 levels were followed by excessive lysosomal exocytosis in nerve cells, resulting in increased release of Alzheimer-linked peptides from neurons.

Loss of NEU1 also accelerated the disease process in mice bred to mimic early-onset Alzheimer's in humans. Without the enzyme, both APP and the protein fragments that make up plaques accumulated faster in these mice.

But within weeks of using gene therapy to bolster NEU1 activity, d'Azzo's group reported that plaques declined dramatically in the hippocampus of treated mice. Scientists used an altered cold virus as the vector to deliver both the NEU1 and PPCA genes to mouse brain cells. The PPCA protein is required for NEU1 to function properly. The gene therapy vector was developed at St. Jude.

"These results suggest that not only is NEU1 deficiency a risk factor for developing Alzheimer's disease, but that this enzyme could be used to slow or even reverse the disease process," d'Azzo said.

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