

Collagen VI may help protect the brain against Alzheimer's disease

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Scientists from the Gladstone Institute of Neurological Disease (GIND), UCSF, and Stanford have discovered that a certain type of collagen, collagen VI, protects brain cells against amyloid-beta ($A\beta$) proteins, which are widely thought to cause Alzheimer's disease (AD). While the functions of collagens in cartilage and muscle are well established, before this study it was unknown that collagen VI is made by neurons in the brain and that it can fulfill important neuroprotective functions.

The team of investigators led by GIND director Lennart Mucke, MD, reported in the current edition of the journal *Nature Neuroscience*, that collagen VI is increased in brain tissues of Alzheimer's patients.

"We first noticed the increase in collagen VI in the brain of AD mouse models, which inspired us to look for it in the human condition and to define its role in the disease," said Dr. Mucke.

The Gladstone team had profiled changes in gene expression using DNA microarrays, which provides an unbiased method for identifying key biological pathways. By comparing all of the genes that are active in disease and normal tissue, one can get valuable information on new pathways and potential therapeutic targets.

The researchers looked at the dentate gyrus, a specific area of the brain that is critical to memory and particularly vulnerable in AD, and compared the genes that were turned on and off in normal mice and a mouse model of AD. This analysis revealed the striking increase in

collagen VI in the brains of mice that model AD.

Building on this initial finding, the team examined brain tissue from AD patients and normal non-demented humans and found that collagen VI expression was also higher in the AD patients. They further discovered that the cellular source of the collagen VI in the brain was neurons, the very cells that the disease attacks and that we all need to think and remember.

"These findings were really surprising and exciting to us because nobody knew anything about collagen VI in the brain," said Jason Cheng, MD, co-lead author of the study. "We were particularly curious whether collagen VI contributed to neuronal damage in AD or was produced as a defense mechanism against it," added Dena Dubal, MD, PhD, co-lead author of the study.

To answer this and other questions, the scientists carried out a series of informative cell culture experiments. These experiments revealed found that A β added to neurons grown in culture increased the expression of collagen VI and that this process involved the immune regulatory cytokine TGF β . What is more, the team discovered that increasing the amount of collagen VI in the cultures effectively protected the neurons against A β toxicity.

"This striking protective effect suggests that increased neuronal production of collagen VI is an important component of the brain's defense against A β ," said Dr. Mucke. "It made us really curious about the underlying mechanisms."

To clinch these mechanisms, Dr. Mucke's team examined the direct interactions of collagen VI with A β . They looked at how A β attacks individual neurons in cell culture. Small poisonous A β assemblies, called oligomers, bind strongly to vulnerable neurons in the brain, but in the

presence of collagen VI, this binding was blocked. Using immunohistochemistry and atomic force microscopy, they showed that collagen VI and A β form large aggregates with each other that may sequester the smaller, more toxic A β complexes away from neurons.

"We are eager to explore how this kind of process might be enhanced therapeutically and how we can best leverage it for the development of more effective treatments for this devastating condition," said Dr. Dubal.

Source: Gladstone Institutes

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