Alzheimer's precursor protein controls its own fate, study finds

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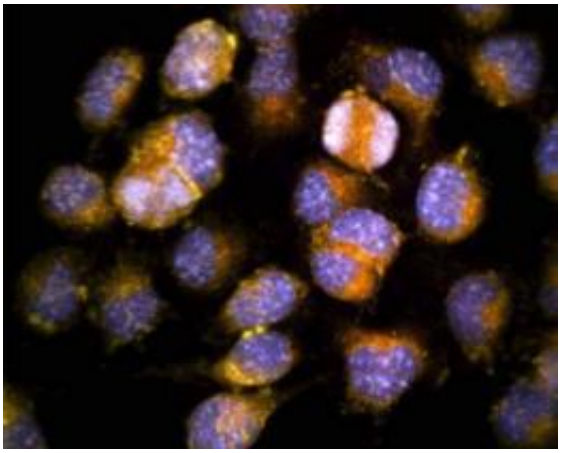

This is a microscopic image showing co-localization of a fragment of the amyloid precursor protein, known as sAPP-α, with BACE1, an enzyme involved in the development of characteristic Alzheimer's amyloid deposits. This merging suggests sAPP-α may serve as a mechanism to inhibit BACE1 activity and thus lower production of toxic amyloid beta associated with Alzheimer's disease. Credit: © University of South Florida

A research team led by the University of South Florida Department of Psychiatry & Behavioral Neurosciences has found that a fragment of the amyloid precursor protein (APP) -- known as sAPP-α and associated with Alzheimer's disease -- appears to regulate its own production. The finding may lead to ways to prevent or treat Alzheimer's disease by controlling the regulation of APP.

Their study is published online today in Nature Communications.

"The purpose of this study was to help better understand why, in most cases of Alzheimer's disease, the processing of APP becomes deregulated, which leads to the formation of protein deposits and neuron loss," said study senior author Dr. Jun Tan, professor of psychiatry and the Robert A. Silver Chair, Rashid Laboratory for Developmental Neurobiology at the USF Silver Child Development Center. "The many risk factors for Alzheimer's disease can change the way APP is processed, and these changes appear to promote plaque formation and neuron loss."

An estimated 30 million people worldwide and 5 million in the U.S. have Alzheimer's. With the aging of the "Baby Boom" generation, the prevalence of the debilitating disease is expected to increase dramatically in the U.S. in the coming years. Currently, there are no disease-modifying treatments to prevent, reverse or halt the progression of Alzheimer's disease, only medications that may improve symptoms for a short time.

"For the first time, we have direct evidence that a secreted portion of APP itself, so called 'sAPP-α,' acts as an essential stop-gap mechanism," said the study's lead author Dr. Demian Obregon, a resident specializing in research in the Department of Psychiatry & Behavioral Neurosciences at USF Health. "Risk factors associated with Alzheimer's disease lead to a decline in sAPP-α levels, which results in excessive activity of a key enzyme in Aβ formation,"

In initial studies using cells, and in follow-up studies using mice genetically engineered to mimic Alzheimer's disease, the investigators found that the neutralization of sAPP-α leads to enhanced Aβ formation. This activity depended on sAPP-α's ability to associate with the APP-converting enzyme, BACE1. When this interaction was blocked, Aβ

formation was restored.

The authors suggest that through monitoring and correcting low sAPP-α levels, or through enhancing its association with BACE, Alzheimer's disease may be prevented or treated.

Provided by University of South Florida