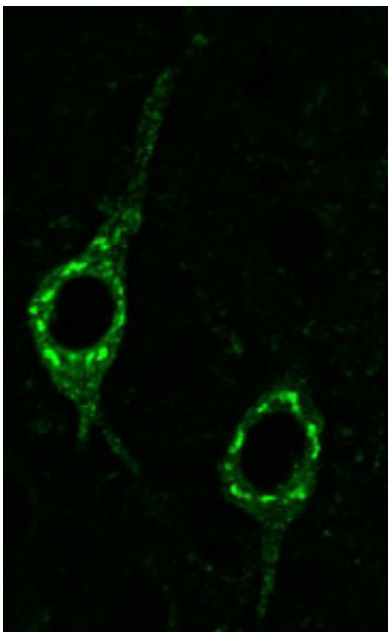
# Case of mistaken identity: Study questions role of A-beta molecules in Alzheimer's disease pathology

June 28 2011



Confocal microscope image of neurons in the 3xTgAD mice stained for the amyloid-ß (Aß) precursor protein (APP) showing APP (green) within these nerve cells which were not labeled by antibodies that detect free Aß, the peptide cleavage product of APP that, when released from APP by proteases will be secreted and for Alzheimer plaques outside nerved cells in the brain of these mice similar to Alzheimer patients. Credit: Edward B. Lee, Perelman School of Medicine at the University of Pennsylvania

Increasingly, researchers are suggesting that amyloid plaques and

neurofibrillary tangles may be relatively late manifestations in the course of Alzheimer's disease (AD) pathology. Identifying earlier events in the development of AD remains a challenge. The laboratory of Virginia M.-Y. Lee, PhD, director of the Center for Neurodegenerative Disease Research, Perelman School of Medicine at the University of Pennsylvania, was the first, in 1993, to demonstrate unequivocally the presence of A-beta peptides -- a hallmark of AD -- inside neurons. But their role in Alzheimer's disease remained unclear.

"It was exciting when a 'triple transgenic' mouse model of AD was reported in 2003 to show robust staining of cells interpreted as A-beta peptides inside neurons," says Edward Lee, MD, PhD, assistant professor of Pathology and Laboratory Medicine, co-author on a study just out in the Journal of Neuroscience that questions the role of A-beta peptides in AD pathology.

The triple transgenic mouse has since become a popular model in AD studies, says Edward Lee. In these mice, A-beta molecules were detected before amyloid-plaque and neurofibrillary-tangle pathology showed up, suggesting that intraneuronal A-beta peptides lead to amyloid plaques, which then lead to neurofibrillary tangles inside neurons.

The Penn researchers examined the trajectory of neuronal inclusions over time using rigorous biochemical and genetic methods. Virginia Lee's group discovered a case of mistaken identity: The intraneuronal molecules appear not to be A-beta peptides themselves, but rather the A-beta amino acid sequence nested within its parent protein, the A-beta precursor protein. What's more, blocking A-beta peptides from forming in the triple transgenic mice had no effect on the formation of neurofibrillary tangles.

According to Virginia Lee, this finding is significant for Alzheimer drug development because it underlines the need for tau-focused drug

discovery for AD since the idea that intracellular A-beta drives tangle formation was not substantiated. Therapies aimed at blocking A-beta production may not have any effect on tangle formation, which is consistent with human clinical trial data to date.

The role of intraneuronal A-beta in AD is still unclear, but these results have profound implications for studies of mechanisms of AD and for AD drug discovery since mouse models of presumptive intracellular A-beta are widely used, state the authors.

Please take a look at the Alzforum webinar about the debate on intraneuronal A-beta as a potential instigator of Alzheimer's disease: www.alzforum.org/res/for/journ … etail.asp?liveID=193

**More information:** Paper: www.jneurosci.org/content/31/21/7691.abstract

Provided by University of Pennsylvania School of Medicine