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Mouse Model Confirms Role Of Amyloid In Alzheimer's Disease

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A new study provides strong support for the current hypothesis about how Alzheimer's disease develops in the brain, and important clues to how brain proteins interact in the condition.

The findings, based on a mouse model of the disease, also suggest that any therapy for Alzheimer's disease must be given early on if it is to be most effective.

When examined after death, the brains of people who had Alzheimer's disease show two hallmark lesions: plaques of amyloid-beta (Ab) peptides and neurofibrillary tangles of tau protein. According to the amyloid cascade hypothesis, the aberrant accumulation of Ab peptide, with consequent buildup of neurofibrillary tangles, is the trigger for all cases of Alzheimer's disease.

Frank LaFerla, associate professor in the department of neurobiology and behavior at the University of California at Irvine, told *BioWorld Today*: "Not everyone working in this field supports this hypothesis, but our work on a mouse model provides the most compelling evidence to date in support of it. This hypothesis suggests that if you remove Ab, you should affect the downstream consequences of Ab, namely neurofibrillary tangles – and this is exactly what we have now shown."

The finding is crucial for those seeking to find a treatment for Alzheimer's disease, because there is no point in developing a therapy targeted at removing plaques if that has no effect on the tangles.

LaFerla and his team report their findings in the Aug. 4, 2004, issue of *Neuron* in a paper titled "A-beta Immunotherapy Leads to Clearance of Early, but not Late, Hyperphosphorylated Tau Aggregates via the Proteasome."

The paper also reports that early stage deposits of tau protein can be cleared from the brains of mice treated with a therapy that removes Ab peptides, but that later-stage deposits are much more resistant to treatment.

Working out the relationship between plaques and tangles in humans virtually is impossible because only post-mortem material is available for study. No mouse model for Alzheimer's disease featuring both plaques and tangles was available, either – until recently when LaFerla's group developed one.

"This meant we were uniquely positioned to address the question of what happens to neurofibrillary tangles after you remove the Ab from the brain," LaFerla said.

They began to investigate. First, they injected antibodies into the hippocampus of the animals' brains, but only on one side; the other side provided a control. The antibodies specifically target the Ab protein for destruction by the immune system.

Later histological examination showed that plaques cleared from the site of the injection, but not on the non-injected side. Injecting an antibody targeting the tau protein had no effect on either the number of plaques or the number of tangles.

"We were fascinated to see," LaFerla added, "that injecting antibodies against Ab not only cleared the plaques, but also cleared the tangles. The plaques were removed pretty rapidly, by three days after the injection, but the tangles were not cleared until about seven days after the injection."

When the researchers examined which type of pathology returned first, they found that plaques were first to reappear.

"This suggests that Ab needs to accumulate to a certain level to facilitate the aggregation of the tau protein," LaFerla said. "By 45 days post-injection, the pathology is comparable on both sides of the brain, which provides very strong in vivo evidence that Ab and tau interact."

One striking finding that has important clinical implications, he added, was that once late-stage neurofibrillary tangles had appeared, injecting antibodies to Ab could no longer clear them. "This suggests that the sooner

you begin treatment of an Alzheimer's disease patient, the better the chances of success – and this applies, in theory, whatever the treatment," LaFerla said.

Further experiments by the team addressed the mechanism by which removal of Ab protein could clear away the intracellular deposits of tau protein. The group hypothesized that perhaps Ab interferes with the proteasome, an intracellular organelle responsible for degraded, misfolded proteins.

They, therefore, injected a proteasome inhibitor at the same time as the antibody against Ab, forecasting that should have no effect on the clearance of Ab, but that it should halt the removal of tau. That was, indeed, what they found.

They were also able to show that tau could not be removed following injection of Ab antibodies if the tau was hyperphosphorylated, a characteristic of late-stage neurofibrillary tangles.

Because only one side of those animals' brains was injected, LaFerla and his colleagues were unable to evaluate if behavioral and cognitive signs were altered by the treatment. That work is the subject of a separate study, which is expected to be published soon.

The group also would like to investigate whether advanced tau lesions can be removed with other treatments. ■