New method to stimulate immune system may be effective at reducing amyloid burden in Alzheimer's

February 11 2009

Researchers at NYU Langone Medical Center have discovered a novel way to stimulate the innate immune system of mice with Alzheimer's disease (AD) - leading to reduced amyloid deposits and the prevention of Alzheimer's disease related pathology - without causing toxic side effects. The study entitled "Induction of Toll-like Receptor 9 Signaling as a Method for Ameliorating Alzheimer's Disease Related Pathology" was published in *The Journal of Neuroscience*.

NYU Langone researchers stimulated the innate immune system via the Toll-like 9 receptor (TLR9) via treatment with cytosine-guanosine containing DNA oligodeoxynucleotides (CpG ODNs) in Tg2576 AD model transgenic mice. This treatment produced a 66% and 80% reduction in the cortical and vascular amyloid burden, when compared with non-treated AD mice. Also, vaccinated Tg2576 mice performed similarly to non-treated mice on a radial arm maze used in the study, showing improvements in behavior and reduced amyloid burden.

"Our results indicate that stimulation of the innate immune system through TLR9 with CpG ODNs is an effective and apparently non-toxic method to reduce the amyloid burden in the brain," said Thomas Wisniewski, MD, professor of neurology, pathology and psychiatry at NYU Langone Medical Center. "Furthermore we found that amyloid reduction was associated with significant cognitive benefits in an AD mouse model. This approach has significant implications for future

human immunomodulatory approaches to prevent AD in humans."

The deposition of amyloid β (Aβ) in the central nervous system in the form of amyloid plaques is a hallmark of Alzheimer's disease. Aβ accumulation destroys neurons in the brain, leading to deficits in cognitive abilities. Immunomodulation or vaccination for AD is emerging as an effective means of shifting the equilibrium from Aβ accumulation to clearance; however, excessive cell mediated inflammation and cerebral microhemorrhages - two forms of toxicity- were shown to occur in previous vaccination studies targeting the adaptive immune system.

"This innate immune approach did not have any of the problems previously reported with immunomodulation targeting the adaptive immune system, such as encephalitis, hemorrhages or lack of an effect on vascular amyloid, suggesting that this method has significant advantages," said Dr. Wisniewski "The treatment with CpG ODNs has already been tested in normal human volunteers and found to be safe- in studies where CpG ODNs was to be used to treat chronic infections; hence this AD treatment has the potential to be brought to clinical trial relatively quickly."

With injection of CpG ODNs used as a treatment to stimulate the innate immune system in Tg2576 AD model mice, the animals were closely monitored for signs of toxicity during behavioral testing and later for any signs of pathology through dissection. No toxicity was evident in the CpG ODN treated group. During behavioral testing in a maze the mice differed significantly between Tg2576 AD group and the CgP ODN treated group that better navigated the maze. The mice were dissected at 17 months of age after behavioral testing and the brains were processed for analysis. CpG ODN treated mice had fewer plaques compared to Tg2576 AD mice.

In addition to the analysis of Aβ burden, researchers evaluated the treatment effect of CpG ODNs on microglial (cells that act as the first form of active immune defense in the central nervous system) in Tg2576 AD mice. CpG ODNs treatment resulted in overall cortical and hippocampal brain reduction in immunoreactivity at 17 months.

"In evaluating the efficiency of CpG ODN treatment in the AD mice model, we found that simulation of TLR9 signaling led to a remarkable reduction of amyloid burden which was paralleled by a reduction in the numbers of activated defensive immune responses in the central nervous system (CNS)," said Dr. Wisniewski. "Thus the effect of CpG ODNs on immune cells may induce heightened levels of surveillance and activity by these cells and thus increased influx into the brain and clearance of Aβ. Activation of immune cells may elicit entrance of other cells into the CNS and induce either Aβ clearance or induce CNS cell signaling leading to recruitment of cells capable of clearing Aβ."

Researchers noted that the findings show administration of CpG ODNs clearly was beneficial, leading to reductions in both amyloid deposition and cognitive decline. This shows that modulation of the immune system may be beneficial for human AD patients but the methods used must be modified to prevent toxicity.

Link to Full Article: www.jneurosci.org/cgi/content/ … e&resourcetype=HWCIT

Source: NYU Langone Medical Center / New York University School of Medicine