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Targeted immune booster removes toxic proteins in mouse model of Alzheimer's disease

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Alzheimer's disease experts at NYU Langone Medical Center and elsewhere are reporting success in specifically harnessing a mouse's immune system to attack and remove the buildup of toxic proteins in the brain that are markers of the deadly neurodegenerative disease.

Reporting on their experiments in the journal *Acta Neuropathologica Communications* online Sept. 3, the researchers say the work advances the development of more effective clinical treatments for Alzheimer's because their immune booster reduced both amyloid beta plaques and tau tangles. Previous immunomodulatory efforts, they say, were singularly successful in decreasing amyloid beta deposits but made limited progress in reducing the buildup of tau proteins that are also a key disease characteristic linked to progressive brain damage.

"Our study results confirm that precisely boosting the immune system in mice can work effectively against Alzheimer's disease, a treatment model that could very well be applied in humans," says senior study investigator and neurologist Thomas Wisniewski, MD, a professor at NYU Langone.

If further animal testing proves successful, human clinical trials could begin within a year, says Wisniewski, who also serves as director of NYU Langone's Center for Cognitive Neurology and co-director of its Alzheimer's Disease Center.

In their written report, the research team calls their findings the first positive results for targeted stimulation of the natural, or innate immune system to both prevent the onset of Alzheimer's disease in animals bred to develop dementia, and to reverse its symptoms after the disease has already set in.

Using the dementia-prone mice, the team gave monthly injections of an immune system booster known as a type B, CpG, oligodeoxynucleotide that specifically binds to Toll-like receptor 9, or TLR9 for short. Activation of TLR9 triggers an immune response. Tests in mice that received the immune system booster injections showed that amyloid plaque formation was 50 percent to 70 percent less than in mice that received no therapy. Reductions in amyloid beta were almost the same for mice treated early on, at age 7 months, and before disease onset, compared to mice treated at age 11 months, which already had mild dementia. Immunostaining tests on brain tissue in treated mice showed one to two times fewer damaged neurons containing disease-related tau aggregates than in untreated mice.

Further cognitive, behavioral testing showed that treated mice made roughly half the number of mistakes in finding their way in water-reward mazes than untreated mice. Dementia-associated brain inflammation was also halved in treated mice, the researchers report, with "classic signs of a traditional immune response against both amyloid beta and tau proteins," as demonstrated by the presence of immune system cytokines and T-helper cells.

According to researchers, treated mice behaved "almost like normal" mice that never develop Alzheimer's-like symptoms.

Wisniewski says that unlike vaccines, which try to trigger an antibody-mediated stimulation of the body's immune system, his team's new approach attempts to "jump start and rejuvenate" the brain's natural

microglial cell repair function. The breakdown of microglial repair—possibly from aging—has been linked for decades to the formation and removal of amyloid plaques and tau tangles in Alzheimer's disease.

Researchers say they selected TLR9 as the immune booster because it was a known stimulant for removing germs. A bacterial cytosine-guanosine sequence, or CpG, such as type B, CpG, oligodeoxynucleotide, was chosen to help activate TLR9 on brain cells because previous testing had shown it to be effective at triggering an immune response in both mice and humans, with very few side effects.

According to study lead investigator Henrieta Scholtzova, MD, PhD, a clinical fellow at NYU Langone, the latest series of experiments build on the team's original observations in 2009, also in mice, that CpG immune boosting was possible, and could reduce amyloid plaque formation.

"Now that we have shown that we can influence microglial function in Alzheimer's disease, to both prevent and repair tau-damaged brain tissue, then it is highly plausible that our treatment approach could also be applied to other neurodegenerative diseases tied to aging," says Scholtzova.

Alzheimer's disease remains the leading cause of dementia worldwide. The disease, which has no effective treatment, afflicts some 5.2 million Americans, mostly women, killing up to a half-million each year.

More information: www.actaneurocomms.org/content/2/1/101

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