Medical Xpress

Rheumatoid arthritis signaling protein reverses Alzheimer's disease in mouse model

August 23 2010

Huntington Potter, professor at the USF Health Byrd Alzheimer's Institute, University of South Florida, was principal investigator for the study. Credit: © University of South Florida

A signaling protein released during rheumatoid arthritis dramatically reduced Alzheimer's disease pathology and reversed the memory impairment of mice bred to develop symptoms of the neurodegenerative disease, a new study by the University of South Florida reports. Researchers found that the protein, GM-CSF, likely stimulates the body's natural scavenger cells to attack and remove Alzheimer's amyloid deposits in the brain.

The study appears online today in the *Journal of* Alzheimer's Disease.

People with rheumatoid arthritis, a chronic disease leading to

inflammation of joints and surrounding tissue, are less likely than those without arthritis to develop Alzheimer's. While it was commonly assumed that non-steroidal anti-inflammatory drugs may help prevent onset and progression of Alzheimer's disease, recent NSAID clinical trials proved unsuccessful for patients with Alzheimer's.

The USF researchers are among the first to look at what effect innate immunity gone awry in rheumatoid arthritis may play in protecting against Alzheimer's disease.

"Our findings provide a compelling explanation for why rheumatoid arthritis is a negative risk factor for Alzheimer's disease," said principal investigator Huntington Potter, PhD, professor of molecular medicine at the USF Health Byrd Alzheimer's Institute and director of the Florida Alzheimer's Disease Research Center.

"Moreover, the recombinant human form of GM-CSF (Leukine®) is already approved by the FDA and has been used for years to treat certain cancer patients who need to generate more immune cells," Dr. Potter said. "Our study, along with the drug's track record for safety, suggests Leukine should be tested in humans as a potential treatment for Alzheimer's disease."

The researchers analyzed three rheumatoid arthritis growth factors in mouse models and identified the signaling protein GM-CSF as the most promising for potential protective benefit against Alzheimer's disease. Then, they peripherally injected GM-CSF into two groups of mice - those genetically altered to develop memory problems mimicking Alzheimer's disease and normal, aged mice. Behavioral tests confirmed the Alzheimer's mice were exhibiting signs of memory impairment at age 12 months. Another two control groups of mice - the Alzheimer's mice and normal mice - were administered saline (placebo).

After the 10th day of injections, all the mice began a series of behavioral testing. At the end of the 20-day study, the cognitively impaired mice treated with GM-CSF performed substantially better on tests measuring their working memory and learning. In fact, their memories were similar to normal aged mice without dementia. Even the normal mice treated with GM-CSF performed slightly better than their untreated peers. The Alzheimer's mice administered saline continued to do poorly on the tests.

"We were pretty amazed that the treatment completely reversed cognitive impairment in 20 days," said Tim Boyd, PhD, who, together with Steven Bennett, PhD, is a study lead author.

In addition, the brains of GM-CSF-treated Alzheimer's mice showed more than a 50-percent decrease in beta amyloid, a substance forming the sticky clumps of plaques that are a hallmark of Alzheimer's disease. This reduction in Alzheimer's plaques and associated restoration of memory was accompanied by more immune cells known as microglia in the brain. Microglia are like the body's natural garbage collection cells that rush to damaged or inflamed areas to get rid of toxic substances.

The researchers suggest that GM-CSF boosted during the immune system overdrive of rheumatoid arthritis helps harness the beneficial properties of inflammation in the brain. The protein may do this by recruiting more microglia from the peripheral blood into the brain to remove Alzheimer's plaques, Dr. Potter said. An apparent increase in neural cell connections in the brains of the GM-CSF-treated mice may also help explain GM-CSF's association with improving memory decline in Alzheimer's disease, the researchers said.

The USF Health Byrd Alzheimer's Institute plans to begin a pilot clinical trial later this year investigating GM-CSF (Leukine) in patients with mild or moderate Alzheimer's disease.

More information: "GM-CSF up-regulated in Rheumatoid Arthritis reverses cognitive impairment and amyloidosis in Alzheimer mice;" Tim D. Boyd, PhD; Steven P. Bennett, PhD; Takashi Mori, DVM, PhD; Nikolas Governatori, BS; Melissa Runfeldt, BS; Michelle Norden; Jaya Padmanabhan, PhD; Peter Neame, PhD; Inge Wefes, PhD; Juan Sanchez-Ramos, PhD, MD; Gary W. Arendash, PhD, Huntington Potter, PhD; *Journal of Alzheimer's Disease*; Vol. 21:2 (August 23, 2010).

Provided by University of South Florida