Enriched blood cells preserve cognition in mice with features of Alzheimer's disease

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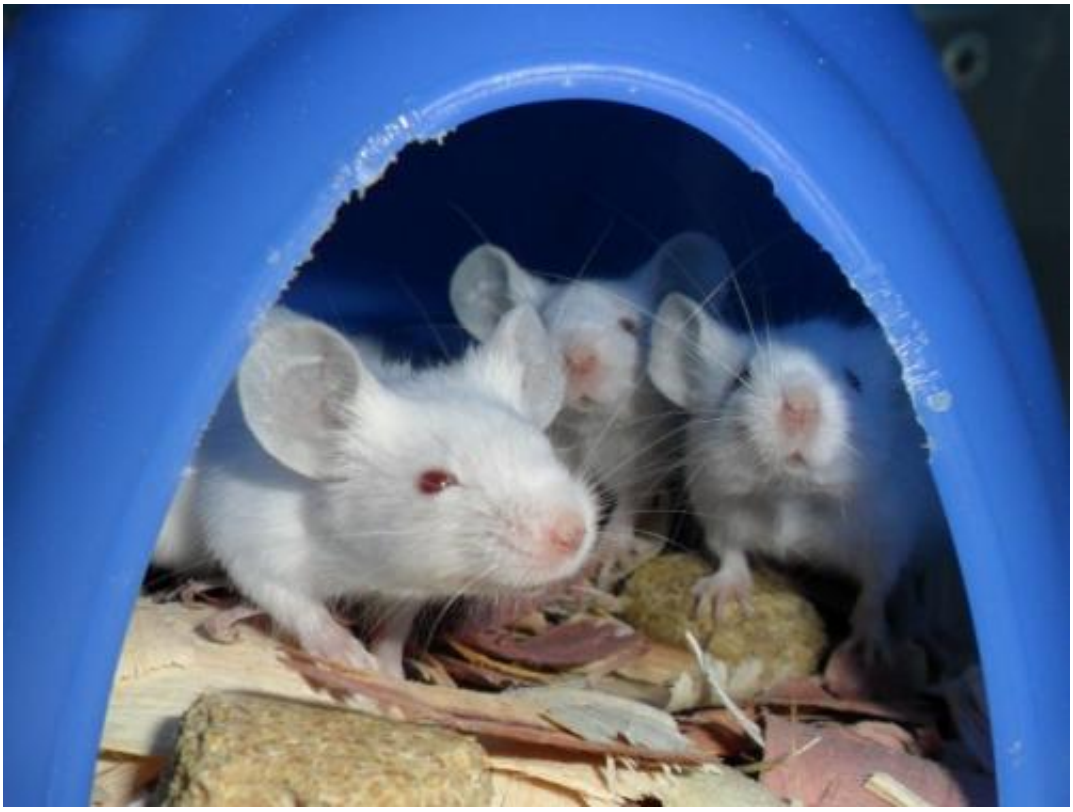

Credit: Martha Sexton/public domain

Cedars-Sinai researchers have successfully tested two new methods for preserving cognition in laboratory mice that exhibit features of Alzheimer's disease by using white blood cells from bone marrow and a drug for multiple sclerosis to control immune response in the brain.

Under the two approaches, immune cells from outside the brain were found to travel in greater numbers through the blood into the brain. The study showed measurable benefits in mice, an encouraging step toward further testing of these potentially powerful strategies in human trials.

Researchers point out that the brain's own immune cells are critical for its healthy function. During the progression of Alzheimer's disease, these cells are found to be defective. In this study, the researchers discovered that immune cells infiltrating the brain from the blood effectively resisted various abnormalities associated with the condition.

"These cells appear to work in the brain in several ways to counter the negative effects associated with Alzheimer's disease," said Maya Koronyo-Hamaoui, PhD, assistant professor of neurosurgery and biomedical sciences at Cedars-Sinai, and the senior author of the article published in *Brain*, a journal of Oxford University Press.

"The increasing incidence of Alzheimer's disease and the lack of any effective therapy make it imperative to explore new strategies, especially those that can target multiple abnormalities in such a complicated disease," Koronyo-Hamaoui added.

In Alzheimer's disease, a protein fragment known as amyloid-beta builds up at the synapses of neurons - the point where neuron-to-neuron communication occurs. As a result, synapses are lost and cognitive function becomes severely impaired.

Immune cells in the brain that are exposed to increasing concentrations of the toxic protein fragment deteriorate and lose their ability to attack and clear away the buildup. Over time, these cells themselves go awry, contributing to harmful inflammation and becoming toxic to the neurons.

During the course of the disease, cells that support the brain's structure and function also fail at the cellular and molecular levels, steadily impairing memory and learning functions.

In efforts to boost an effective immune response, the Cedars-Sinai scientists have devised ways to "recruit" white blood cells known as monocytes from bone marrow to attack the protein fragments and preserve the synapses.

The researchers evaluated two such methods and their therapeutic potential. In one, they extracted a specific type of monocytes from the bone marrow of healthy young mice and injected the cells into the tail veins of sick mice once a month. A second group of sick mice received weekly under-the-skin injections of glatiramer acetate, an FDA-approved drug used for the treatment of multiple sclerosis; the drug has been shown to foster the migration of white blood cells from the bloodstream to the brain. A third group received both treatments.

All three groups experienced a substantial decrease in Alzheimer's-like pathology and symptoms.

The varied approaches were effective in "recruiting" protective monocytes to "lesion sites" in the brain, removing protein fragments and reducing harmful inflammation through the secretion of chemicals that regulate immunity at the molecular level, said Koronyo-Hamaoui, the head of Cedars-Sinai's neuroimmunology laboratory at the Maxine Dunitz Neurosurgical Institute and a faculty member in the Department of Neurosurgery and Department of Biomedical Sciences.

In this study, glatiramer acetate was further found to profoundly affect monocytes' function, she added.

"This study provides the evidence that a subgroup of unmodified

monocytes, extracted from the bone marrow of healthy mouse donors and grafted into the bloodstream, can migrate into the brains of sick mice, directly clear abnormal protein accumulation and preserve cognitive function," said Yosef Koronyo, the article's first author and a research associate in the Department of Neurosurgery.

Koronyo added that the study gives unprecedented details about monocyte numbers migrating into brain lesion sites and the compounds they secrete, and shows that the body's natural monocytes can have direct effects on the integrity of synapses.

More information: *Brain*, "Therapeutic effects of glatiramer acetate and grafted CD115+ monocytes in a mouse model of Alzheimer's disease," published online June 6, 2015. DOI: dx.doi.org/10.1093/brain/awv150

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