Popular Alzheimer's theory may be false trail

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The idea that anti-inflammatory drugs might protect people struggling with dementia from Alzheimer's disease has received a blow with the online release of a study of human brain tissue in *Acta Neuropathologica*.

Researchers with the McKnight Brain Institute of the University of Florida, in collaboration with scientists at the University of Frankfurt, Germany, discovered that inflammation of microglia — an abundant cell type that plays an important supporting role in the brain — does not appear to be associated with dementia in Alzheimer's disease.

The finding supports recent clinical trial results that indicate anti-inflammatory drugs are not effective at fighting dementia in patients with Alzheimer's disease, which affects about 5.3 million Americans.

"For almost 20 years now, it's been claimed that brain inflammation contributes to the development of Alzheimer's disease dementia, and based on that claim, numerous clinical trials with anti-inflammatory drugs have been conducted. They have been unsuccessful," said Wolfgang Streit, Ph.D., a professor of neuroscience at the College of Medicine. "In the current paper we have shown that the brain's immune system, made up of microglia, is not activated in the brains of Alzheimer's patients, as would be the case if there were inflammation. Instead, microglia are degenerating. We claim that a loss of microglial cells contributes to the loss of neurons, and thus to the development of dementia."

Microglial cells are a subset of a very large population of brain cells

known as glial cells. Neurons are the workhorse cells of the brain, enabling thought and movement, but glia are their faithful sidekicks, providing physical and nutritional support.

Glial cells, which outnumber neurons 10-to-1, are at the heart of a popular explanation for Alzheimer's disease that suggests protein fragments called beta amyloid — Abeta for short — clump together in the spaces between brain cells, causing memory loss and dementia. Inflammation theories suggest that microglia become "activated" and mount an immune response to these protein clumps, and instead of being helpful, a toxic release of chemicals occurs, worsening the disease effects.

However, Streit's high-resolution observations did not find evidence that Abeta activates, or inflames, human microglia cells. Nor did researchers find evidence that inflammation is to blame for brain cell death.

"This paper potentially represents a paradigm shift in the way we look at Alzheimer's disease," said Mark A. Smith, Ph.D., a professor of pathology at Case Western Reserve University and editor-in-chief of the Journal of Alzheimer's Disease. "The study goes against the very popular idea of neuro-inflammation; instead, the idea that microglia are senescent is consistent with a number of features of the disease.

"The research makes a very good case that these cells are subject to aging," said Smith, who did not participate in the study. "These cells were thought to be activated (against Alzheimer's), but this paper makes a strong case that they are not. The study has taken a novel approach that has led to a novel insight."

Using a commercially available antibody, Streit for the first time created a marker for microglial cells in human brain specimens that had been in chemical storage. The specimens were from 19 people with varying

degrees of Alzheimer's, ranging from severe to none at all. Two of the samples were from Down syndrome patients, who are known to develop Alzheimer's pathology in middle age.

When researchers examined these cells alongside neurons under a high-resolution microscope, they found that — unless an infection had occurred elsewhere in the body — microglial cells from Alzheimer's patients were not distinctly larger or unusually shaped, which would have been the case had they been inflamed.

"What I expected to see is activated microglia right next to dying neurons," Streit said. "That is what I did not find. What I propose is glia are dying, and the neurons lose support. We now need to find out what caused glia to degenerate. Rather than trying to find ways to inhibit microglia with anti-inflammatory drugs, we need to find ways to keep them alive and strong. It's a whole new field."

The microglial cells had a tangled, fragmented appearance, similar to neurons in the throes of Alzheimer's disease or — old age.

"These cells are breaking into pieces," said Streit, who collaborated with Alzheimer's researcher Heiko Braak, M.D, of the Institute for Clinical Neuroanatomy in Frankfurt. "They are on their way out. For the first time, we are proving that microglial cells are subject to aging and may undergo degeneration, and that the loss of these cells precedes the loss of neurons. Research has been so focused on finding activated microglia, no one considered that these cells were degenerating and neurons lost support."

Source: University of Florida (news : web)