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Researchers find mechanisms that may unlock answers to Alzheimer's disease

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Four million people in the United States and 15 to 20 million people worldwide are affected by Alzheimer's disease. These numbers are likely to triple by 2050 due to the fact that 24 percent of the population will be more than 65 years old. In their attempt to combat the disease, two University of Missouri-Columbia professors have identified new mechanisms that could have major implications in the development of treatments for the disease. The National Institutes of Health recently awarded a $6 million grant to the Mizzou researchers to continue their study.

Grace Sun and Gary Weisman, professors of biochemistry in the School of Medicine and the College of Agriculture, Food and Natural Resources, are entering the second phase of an $11 million project aimed at identifying the causes of Alzheimer's disease. Previous studies have indicated toxic effects of a protein, the amyloid-beta peptide or "A-beta," which accumulates in amyloid plaques in the brain of Alzheimer's patients. Despite unknown mechanisms, increased production of this peptide may cause impairments of brain functions.

"When the A-beta protein comes together inside the plaque, it will fold into an abnormal shape that is toxic to cells," Sun said. "While we know this has some effect on brain function, we don't know how toxic it is or at what stage the toxicity begins. In the past five years, we have started to understand how this disease works. With the new grant, we will be able to go forward and see if there are treatments that can modify the cellular response in the brain."

The abnormal A-beta impairs the synapse connections that occur among neurons. These synapses control the communication among the brain cells, including how memory is processed. Besides neurons, A-beta also attacks astrocytes and microglial cells. Astrocytes are an important cell type that provides nutrients to neurons. Microglia cells are immune cells activated for defense related functions. Effects of A-beta on astrocytes and microglia may create abnormal inflammatory responses that can harm neurons and other brain cells.

The next phase of the study includes three projects. Sun will study mechanisms whereby A-beta affects phospholipases, a group of enzymes that, when activated, will destroy membranes in brain cells. Current evidence suggests that A-beta activates some of these enzymes.

In the second project, Weisman will study mechanisms of inflammation in the brain and A-beta's role in creating the inflammatory response. Weisman will explore the role of a group of receptors that control both the function of the enzyme that produces A-beta in brain cells and regulates inflammation. By suppressing this receptor's function, Weisman hopes to identify new treatments that minimize A-beta production and inflammation.

Gibson Wood, professor of pharmacology at the University of Minnesota, will lead the third project, which will study the role of cholesterol in the brain. Wood's study will evaluate the effects of statin drugs, typically used to treat high cholesterol. Wood's previous research showed that statins have other beneficial effects in addition to lowering cholesterol. His study will test if the drugs also combat the ill effects of A-beta and limit the progression of Alzheimer's disease.

Findings from the research program have been published in the Journal of Neuroinflammation, the Journal of Neuroscience and the Journal of Biological Chemistry. Funding for the study has come from the National

Institute of Aging, part of the National Institutes of Health, and the University of Missouri-Columbia.

“Without matching funds from MU and interdisciplinary collaboration, we would not be able to conduct this research,” Sun said.

According to the National Institutes of Health, Alzheimer’s disease is the most common form of dementia among older adults and affects areas of the brain that control memory, judgment, behavior and intelligence. The disease was first discovered more than 100 years ago by a German physician, Dr. Alois Alzheimer, when he diagnosed a patient who died of a dementia-type illness at age 55.

Source: University of Missouri-Columbia