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GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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GLADSTONE RESEARCHERS IDENTIFY NEW DRUG TARGET FOR ALZHEIMER'S DISEASE

Researchers at the Gladstone Institute of Neurological Disease have identified a potential new way to stop brain cell death related to Alzheimer's disease.

Working with cell cultures, the scientists investigated how amyloid beta ($A\beta$) proteins, which build up in the brain tissue of people with Alzheimer's disease, kill neurons. The cell cultures were established from brain tissue of laboratory rats. Study findings showed that $A\beta$ could be prevented from causing neuronal cell death with a compound called resveratrol, which is also found as a natural ingredient in red wine.

"Our study suggests that resveratrol and related compounds may protect against neuronal loss associated with Alzheimer's disease," explains senior author Li Gan, PhD, a staff research investigator at the Gladstone Institute of Neurological Disease and an assistant professor of neurology at UC San Francisco. "This could certainly open up new avenues for drug development."

The research results are reported in the December 2 issue of the *Journal of Biological Chemistry*.

According to the research team, it was particularly interesting that the beneficial effect of resveratrol was not due to a direct effect on $A\beta$ or on neurons but on other types of brain cells, called microglia.

Microglia are the immune cells of the brain. They can protect or hurt neurons, depending on which of their powerful defense or attack pathways are activated. The investigators found that $A\beta$ triggers a pathway in microglia that makes them attack neurons with poisonous chemicals.

A key mediator in this pathway is a protein called $NF_{\kappa}B$, which resveratrol happens to block. Without resveratrol, $A\beta$ activates $NF_{\kappa}B$ in microglia, turning them into powerful neuron killing machines. Researchers found that, in the presence of resveratrol or of other molecules that blocked $NF_{\kappa}B$, microglia were well behaved, and $A\beta$ was unable to harm the neurons.

The study thus pinpoints $NF_{\kappa}B$ as an important contributor to the destructive power of $A\beta$, making it a key drug target, and it singles out resveratrol as holding the most promise for therapeutic intervention.

Research co-authors are Jennifer Chen, Sarah Mueller-Steiner, and Lennart Mucke of the Gladstone Institute of Neurological Disease and the UCSF Department of Neurology; Yungui Zhou and Sali Yi of the Gladstone Institute of Neurological Disease; and Lin-Feng Chen and Hakju Kwon of the Gladstone Institute of Virology and Immunology.

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The Gladstone Institute of Neurological Disease is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution. It is affiliated with UCSF, a leading university that consistently defines health care worldwide by conducting advanced biomedical research, educating graduate students in the life sciences, and providing complex patient care. For further information, visit www.gladstone.ucsf.edu and www.ucsf.edu.

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