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New research brings initial find of Alois Alzheimer to fore once again

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The two dominant proteins that determine how much blood flows through the body's arteries have been implicated in Alzheimer's disease, in a new study in the Jan. 16 issue of the *Proceedings of the National Academy of Sciences*. They offer new, surprising targets against Alzheimer's disease just as scientists are getting back in touch with the vascular roots of the disease that were first recognized early last century.

The research, putting proteins often linked to heart disease front and center in a brain disease whose causes remain a mystery, hark back to what German physician Alois Alzheimer noted when he first recognized the disease 100 years ago. Though Alzheimer noted changes in both the brain's cells and in the small arteries and capillaries that supply and drain blood to and from the brain, over the decades doctors separated the two concepts and have come to focus mainly on the toxic effects of the disease on cells. The changes to blood vessels have been pushed to the background.

The latest findings from the University of Rochester Medical Center mesh not only with Dr. Azheimer's initial observations but also with new findings from today's best imaging technologies. While the first visible symptom of Alzheimer's may be a person forgetting names or faces, the very first physical change is actually a decline in the amount of blood that flows in the brain. Doctors have found that not only is blood flow within the brain reduced, but that the body's capacity to allocate blood to different areas of the brain on demand is blunted in people with the disease.

"A reduction in blood flow precedes the decline in cognitive function in Alzheimer's patients," said Berislav Zlokovic, M.D., Ph.D., professor in the Department of Neurological Surgery and a neurovascular expert whose research is causing scientists to consider the role of reduced blood flow in Alzheimer's disease.

"People used to say, well, the brain is atrophying because of the disease, so not as much blood as usual is needed. But perhaps it's the opposite, that the brain is dying because of the reduced blood flow," he added.

The new findings are the product of a five-year collaboration between two types of scientists that traditionally don't work closely together: neuroscientists who focus on the brain, and cardiovascular experts who put most of their focus on the heart.

The first step in the study came when Zlokovic's team compared the activity of genes in the brain from several people with Alzheimer's who had died, to that of several people without the disease who had died. It's a type of study widely done now by scientists looking at a host of diseases, using vast gene arrays that can tell how active thousands of genes are in a part of the body.

As Zlokovic perused the list of genes whose activity differed depending on whether the person had Alzheimer's or not, he recognized that several play a role in constricting the arteries. He asked colleague Joseph Miano, Ph.D., a cardiovascular researcher and expert on the smooth muscle that makes up part of the arteries, to take a look.

Miano recognized the group as genes that are all controlled by one of two master regulators of gene activity in smooth muscle cells. Those proteins, myocardin and SRF (serum response factor), are well known for the control they exert on blood vessel walls. Working together, the two are the chief players that regulate how much the smooth muscle cells

inside the arteries contract. The more the cells contract, the narrower the artery becomes, and the less blood that flows.

In a series of experiments carried out together by Miano's and Zlokovic's students and colleagues, the teams demonstrated the power of the genes in the brain.

First they confirmed that both genes are more active in the brains of Alzheimer's patients than they are in the brains of people without the disease. They also found that when SRF or myocardin are more active than usual in human smooth muscle tissue from the brain, the muscle contracts more than usual.

In mice they found that when the genes were more active than usual, blood flow in the brain was reduced, much like it is in Alzheimer's disease in people. And finally, the scientists found that when they silenced SRF, the phenomenon was reversed, and blood flowed more freely.

While the two genes are widely known to cardiovascular researchers like Miano, they're not studied much in the Alzheimer's community. One study by Columbia University researchers last year did find that SRF seems to play a role in learning and memory, but its role in Alzheimer's has not been explored.

"This is fresh and exciting work," said Miano, an expert on smooth muscle and associate professor of Medicine in the Cardiovascular Research Institute. "For many vascular biologists, blood flow in the brain is an afterthought, if that."

All this activity takes place in the smooth muscle that lines most of the 60,000 miles of blood vessels that wind their way through our bodies. SRF and myocardin control dozens of proteins that, when overactive,

pull the muscle tightly, constricting arteries and reducing the amount of blood that can flow through them. A similar type of muscle also lines our airways. When smooth muscle there stays constricted too long, the result can be asthma, since not enough air is getting to the lungs.

Now the group is looking for ways to stop the two proteins from working together to constrict the blood vessels, so that blood flow in the brains of people with Alzheimer's disease would return to normal, much as the team achieved in mice.

"More and more, people are paying attention to the role of the vascular system in Alzheimer's disease," said Zlokovic, director of the Frank P. Smith Laboratories for Neurosurgical Research, who has made several findings that implicate blood flow and the blood-brain barrier transport mechanism as key components of the Alzheimer's disease process.

The technology has been licensed to Socratech, a Rochester biotech company created by Zlokovic to search for new treatments for Alzheimer's and stroke. Miano has served as a consultant to Socratech and is now leading a research effort there looking for compounds to inhibit SRF and myocardin.

Source: University of Rochester