Two cardiovascular proteins pose a double whammy in Alzheimer's

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Researchers have found that two proteins which work in tandem in the brain's blood vessels present a double whammy in Alzheimer's disease. Not only do the proteins lessen blood flow in the brain, but they also reduce the rate at which the brain is able to remove amyloid beta, the protein that builds up in toxic quantities in the brains of patients with the disease.

The work, described in a paper published online Dec. 21 in the journal *Nature Cell Biology*, provides hard evidence directly linking two processes thought to be at play in Alzheimer's disease: reduction in blood flow and the buildup of toxic amyloid beta. The research makes the interaction between the two proteins a seductive target for researchers seeking to address both issues.

Scientists were surprised at the finding, which puts two proteins known for their role in the cardiovascular system front and center in the development of Alzheimer's disease.

"This is quite unexpected," said Berislav Zlokovic, M.D., Ph.D., a neuroscientist and a senior author of the study. "On the other hand, both of these processes are mediated by the smooth muscle cells along blood vessel walls, and we know that those are seriously compromised in patients with Alzheimer's disease, so perhaps we shouldn't be completely surprised."

The new findings are the result of a seven-year collaboration between

two laboratories. Zlokovic heads the Center for Neurodegenerative and Vascular Brain Disorders, looking at molecular roots of diseases like Alzheimer's. Several years ago, after he found that several genes well known to cardiovascular researchers seemed to be especially affected in Alzheimer's patients, he turned to Joseph Miano, Ph.D. to help analyze the findings. Miano is interim director of Aab Cardiovascular Research Institute and associate professor of Medicine, and he is senior co-author of the new study.

"To some, it might seem odd that a cardiovascular group would intersect with a neuroscience group to study Alzheimer's disease," Miano said. "But there's a great deal of evidence to suggest that Alzheimer's disease is a problem having much to do with the vascular plumbing. And Rochester is the type of institution where partnerships like these are easy to strike up."

For 15 years Zlokovic's laboratory has focused on the molecular mechanisms regulating blood supply and the role of the blood-brain barrier in the development of Alzheimer's disease. It's not simply that reduced blood supply hurts brain cells by causing a shortage of oxygen and other nutrients. Rather, deterioration of blood flow seems to gum up the brain's ability to remove toxic amyloid beta.

Normally, amyloid is picked up efficiently by blood vessels that then whisk the toxic trash away. But in Alzheimer's disease, the system no longer is able to keep up with the body's production of the substance. The molecular trash accumulates, and Zlokovic and others believe the buildup kills brain cells.

The current work focuses on two proteins well known to cardiovascular researchers, SRF (serum response factor) and myocardin. The two work together within smooth muscle cells that line blood vessels to activate genes that are necessary for smooth muscle to function properly. SRF

binds to certain snippets of DNA called CArG boxes and serves as an anchor, while myocardin piggybacks along and turns on the genes to which SRF sticks. Together they act as a master switch that determines whether smooth muscle cells contract – one of many ways the body controls just how much blood is flowing in the body.

Two years ago, Zlokovic and Miano published a study showing that the two proteins are much more active in the blood vessels of brains of people with Alzheimer's disease than in people who do not have the disease. They showed that when they reduced the activity of the proteins, blood flow in the brain increased, and when the genes were more active, blood flow decreased.

The latest report goes further, implicating the molecular duo in the slowed removal of amyloid beta. The team found that SRF and myocardin working together turn on a molecule known as SREBP2. That protein inhibits a molecule known as LRP-1, which helps the body remove amyloid beta. In other words, when SRF and myocardin are active, toxic amyloid beta accumulates.

The findings came primarily from the team's studies of brain cells taken from people who had Alzheimer's disease and comparing them to cells from healthy elderly people.

Compared to the smooth muscle cells from healthy adults, the cells from patients with Alzheimer's disease had about five times as much myocardin and four times as much SRF, about five times as much SREBP2, and about 60 percent less LRP-1. That translated into a reduced ability to remove amyloid beta: Cells taken from patients with the disease had only about 30 percent of the ability to remove the substance as cells taken from their healthy counterparts.

When the team lowered levels of SRF to the same level that exists in

healthy cells, the cells from Alzheimer's patients improved in their ability to remove amyloid beta, doing it just as well as cells from healthy individuals. Conversely, when the team boosted levels of SRF and myocardin in the healthy cells, the changes lowered by about 65 percent those cells' ability to remove amyloid beta.

In mice, the team found parallel results. When the team boosted SRF or myocardin in healthy mice, those mice had about twice as much SREBP2 in their smooth muscle cells in the brain's blood vessels. They also had 90 percent less LRP-1, three times as much amyloid beta in their arteries, and 70 percent more amyloid beta in their brain tissue.

When the team reduced SRF and myocardin in mice prone to developing Alzheimer's disease, those mice had 60 percent less SREBP2, about four times as much LRP-1, and a 50-percent reduction in amyloid beta in their blood vessels.

The first author of the study is Robert Bell, a graduate student in Zlokovic's laboratory who is in Department of Pathology and Laboratory Medicine's graduate program. He had searched for months, without success, for evidence of a direct effect on LRP-1 by SRF/myocardin. A subsequent literature search turned up findings that the molecules might affect SREBP2. With that finding, the team was able to move forward and put the whole picture together.

Now the team has turned its attention to studying the role of hypoxia, which seems to play a role in turning on myocardin, as well as searching for molecules that block the hookup between SRF and myocardin.

Source: University of Rochester