The pericyte becomes a player in Alzheimer's, other diseases

November 17 2010

Cells in the brain called pericytes that have not been high on the list of targets for treating diseases like Alzheimer's may play a more crucial role in the development of neurodegenerative diseases than has been realized.

The findings, published Nov. 4 in *Neuron*, cast the pericyte in a surprising new role as a key player shaping blood flow in the brain and protecting sensitive brain tissue from harmful substances. By manipulating pericyte levels, scientists were able to re-create in the brains of mice an array of abnormalities that mirror in striking fashion the brain difficulties that occur in many people as they age.

"For 150 years these cells have been known to exist in the brain, but we haven't known exactly what they are doing in adults," said Berislav Zlokovic, M.D., Ph.D., the neuroscientist who led the research at the University of Rochester Medical Center. "It turns out that pericytes are very important for helping maintain a brain environment crucial to the health of neurons. The pericyte offers us an exciting new target for new treatments for neurodegenerative diseases."

While damage to neurons oftentimes causes the symptoms that patients experience – dementia in Alzheimer's, and movement difficulties in Parkinson's disease, for instance – neuroscientists know that neurons depend on a broad variety of factors coming together to create just the right environment to thrive. Zlokovic himself has pioneered the concept that impaired blood flow and flaws in the blood-brain barrier may play a

huge role in the development of diseases like Alzheimer's through their impact on neurons.

In the most recent findings from Zlokovic's laboratory, the two first authors who contributed equally to the research, graduate student Robert Bell and M.D./Ph.D. student Ethan Winkler, teased out the role of the pericyte in the process. Pericytes ensheath the smallest blood vessels in the brain, wrapping around capillaries like ivy wrapping around a pipe and helping to maintain the structural integrity of the vessels.

It turns out that pericytes do much more. The team found that the cells are central to determining the amount of blood flowing in the brain and play an instrumental role in maintaining the barrier that stops toxic substances from leaking out of the capillaries and into brain tissue. When the team reduced the number of working pericytes in the brains of mice, the effects included reduced blood flow, greater exposure of brain tissue to toxic substances, impaired learning and memory, and damage to the neurons – all phenomena that are more likely to happen to people as they age.

"This work shows that other cells in the brain have a tremendous effect on the neurons, even driving the neurodegenerative process," said Winkler. "This is very exciting."

To make the finding, the team studied mice in which the normal number of pericytes is reduced dramatically. Scientists studied young mice (about one month old), middle-aged mice (about six to eight months old), and older mice (14 to 16 months old).

The amount of damage that occurred depended on age, with the worst damage occurring consistently in the oldest mice – a finding that parallels what happens with people, whose brains are much more likely to suffer neurodegenerative conditions like Alzheimer's or Parkinson's

disease as they age. The mice experienced an array of problems that match up pretty closely with the brain abnormalities that people with neurodegenerative conditions like Alzheimer's experience.

Among the findings in mice with reduced levels of pericytes:

Cerebral blood flow was reduced, and the problem worsened as the mice got older. Older mice had 50 percent less blood flow than mice of similar age with a normal number of pericytes. Younger and middle-age mice had 23 percent less and 33 to 37 percent less blood flow, respectively.

Serum proteins and toxic molecules were much more likely to gain entry to the brain, thanks to a breakdown of the blood-brain barrier. For instance, molecules such as hemosiderin, fibrin, thrombin and plasmin are toxic in the brain and are normally not found in brain tissue. The older mice had 20 to 25 times as much accumulation of these toxins in their brain tissue as their normal counterparts; the younger and middle-age mice had three times as much and 8 to 10 times as much, respectively.

The breakdown in the blood-brain barrier was especially evident in blood vessel structures known as tight junctions, which play an important role in stopping harmful substances from reaching brain tissue. Their activity in the older mice was down 40 to 60 percent in older and middle-age mice compared to their normal counterparts.

Compared to normal mice, the mice with fewer pericytes had structural damage to their neurons, including loss of dendritic length and spine density. Again, the amount of damage correlated to the age of the mice, with older mice showing more damage. The team also documented impaired learning and memory in the middle-age and the older mice, but not the youngest mice.

"Our findings show that chronic vascular damage due to pericyte loss results in neurodegeneration," said Zlokovic, who is Dean's Professor in the Departments of Neurosurgery and Neurology and director of the Center for Neurodegenerative and Vascular Brain Disorders. "It may be that a vascular insult is common to many different types of neurodegenerative processes and may be significant in causing the symptoms seen in diseases such as Alzheimer's and amyotrophic lateral sclerosis."

The findings could cause neuroscientists to change their views of the origins of many neurodegenerative disorders, said Bell, who notes that a recently developed tool to track pericyte activity in the brain helped the team tackle the role of the pericyte.

"If all your tools are designed to study neurons, you'll learn a lot about neurons," Bell said. "We haven't known much about pericytes simply because we haven't had good tools to watch them. If you can't see the cells, you can't study them."

Provided by University of Rochester Medical Center