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## "Bad" Enzymes May Wear White Hats After Stroke

Enzymes that can harm the brain immediately after a stroke may actually be beneficial days later, according to new research. Insights from the study could change the way stroke is treated, extending the window for effective treatment from a couple of hours to a couple of weeks. The results may suggest new ideas for drug development.

Working with rats, a team from the Harvard Medical School Departments of Radiology and Neurology found that the enzyme matrix metalloproteinase-9 (MMP-9) may help remodel brain tissue seven to 14 days after a stroke. Their findings are published in the April 2006 issue of *Nature Medicine*, and were made available in an advance online publication on March 26, 2006.

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Matrix metalloproteinases are a large group of enzymes that help break down the extracellular matrix, a complex structure that surrounds and supports cells. Newer research is showing that MMPs may also contribute to blood vessel growth, as well as the death, proliferation, differentiation, and movement of cells.

Sophia Wang, who was a Howard Hughes Medical Institute (HHMI) medical student fellow at Harvard Medical School, is second author of the article. She was deeply involved with the study's data analysis, and established a way to quantify the response of proteins involved in the cell growth and blood vessel remodeling that occurs after stroke. She also assisted with behavioral studies of rats that had received MMPs to see how well they recovered after a stroke.

HHMI medical student fellows are medical students who are interested in biomedical research. The fellowships support a year of research, usually between the second and third years of medical school. The program is designed to encourage medical students to become physician-scientists.

Just after a stroke—a temporary loss of blood to the brain caused by a clot or burst blood vessel—MMPs chew up damaged brain tissue. This increases the risk of swelling and hemorrhage in the brain. Some current stroke treatment

research seeks ways to inhibit MMPs to minimize their danger—but this new study shows that a different approach may be required in the long run.

"We have mostly thought of MMPs as being 'bad,'" said senior author Eng H. Lo of the Neuroprotection Research Laboratory at Massachusetts General Hospital, Wang's mentor. "Our data strongly suggest that they play a totally different role during stroke recovery."

To understand the action of MMPs, the team induced stroke in rats and injected some with an MMP inhibitor at different times after the stroke. When the injection was given immediately following the stroke, rats showed smaller areas of brain damage. Injections given at three days had no effect, but those given at seven days or 14 days led to more extensive brain damage, compared with rats that did not receive an inhibitor.

The team also looked for MMPs within the brains of rats following stroke. They found the enzymes in the damaged areas at one and three days after the stroke. However, seven to 14 days after the stroke, high levels of MMPs were found instead in what's known as the peri-infarct cortex—an area close to the damaged tissue that is involved in stroke recovery.

"The peri-infarct zone is very dynamic and potentially very malleable for long periods of time after stroke," said Lo. "I think that makes a big difference in how we think about treatment.

"One of the biggest problems facing stroke patients is that it's a neurodegenerative disorder, but also a medical emergency," he explained. "With other neurological disorders, such as Alzheimer's disease, the disease process is much slower. This study suggests that with stroke, we may now be able to think beyond acute treatment times of just a few hours, and find ways of manipulating peri-infarct recovery over several weeks."

Currently, the only FDA-approved drug for treating stroke—tissue plasminogen activator, or tPA—must be given within three hours after a stroke occurs. Otherwise, said Lo, the drug can amplify the "bad" effects of MMPs, increasing the risk of swelling and bleeding.

To further establish MMPs' role in healing stroke damage, first author Bing-Qiao Zhao used two naturally occurring proteins as markers for neurovascular remodeling. He had the group look for Egr1 and RECA-1, both of which indicate neuron and blood vessel regrowth. Rats that received an MMP inhibitor seven days after stroke had much lower levels of these proteins, indicating impaired healing. These rats also had more problems completing a behavioral task than rats that did not receive an MMP inhibitor.

While current efforts to design MMP-targeted drugs aim to inhibit the enzymes completely after a stroke, the researchers caution that, based on their findings, it may be necessary to regulate the activity of MMPs much more precisely to enable the patient's optimal recovery.

During nine months in Lo's lab, Wang also conducted research involving MMPs, statins, and Alzheimer's disease. Statins are a class of drugs that reduce serum cholesterol levels.

"I did some work suggesting that statins might counteract the hemorrhagic effect of tPA and might someday be used as an adjuvant therapy with tPA," she said. "I also did some work with beta amyloid, the protein implicated in Alzheimer's disease. It seems that beta amyloid might increase levels of MMP-9 where MMPs would harm rather than help, and statins might help counteract that. So statins could play a role in treating Alzheimer's disease."

Wang learned of Lo's research during her undergraduate years at Harvard, where she earned a degree in biochemistry. Before choosing him as her mentor for the HHMI fellowship, she worked in his laboratory for a summer before matriculating at Mt. Sinai School of Medicine in New York. She's scheduled to receive her M.D. in 2007.

"I was very fortunate to work on all these projects," Wang said. "I had a great time, and a wonderful mentor."

The first author on the *Nature Medicine* paper is Bing-Qiao Zhao, of the Neuroprotection Research Laboratory and Program in Neuroscience at Harvard. Authors Hahn-Young Kim, Hannah Storrie, Bruce R. Rosen, David J. Mooney, and Xiaoying Wang are also affiliated with Harvard.