Naturally occurring enzyme can break down key part of Alzheimer's plaques

October 24 2006

Scientists have identified a naturally occurring enzyme that can break down a key component of the brain plaques characteristic of Alzheimer's disease. The finding may provide researchers with new opportunities to understand what goes wrong in the brains of Alzheimer's patients and could one day help them seek new therapies.

Researchers at Washington University School of Medicine in St. Louis showed earlier this summer that the enzyme, matrix metalloproteinase 9 (MMP-9), degrades abnormally aggregated proteins known as amyloid fibrils, a main ingredient of brain plaques. In the brain, MMP-9 is made by support cells known as astrocytes.

MMP-9 is already well-known because of its links to cancer metastases, vascular disease, arthritis and other pathologies. Scientists called the new link to Alzheimer's encouraging, noting that previously identified enzymes only degrade a smaller, nonaggregated component of Alzheimer's plaques.

"We already knew of three enzymes that break down amyloid beta (Abeta), a protein fragment that clumps together with itself to form the fibrils," says Jin-Moo Lee, M.D., Ph.D., assistant professor of neurology. "But the thinking up until now had been that Abeta might be clumping together so tightly that the fibrils were indestructible."

In a new study, appearing October 25 in The *Journal of Neuroscience*, Lee's group found that disabling the mouse gene for MMP-9 increased

levels of Abeta in the spaces between brain cells. The finding proves that MMP-9 contributes to clearance of Abeta from extracellular spaces and suggests its dysfunction could potentially contribute to the development of Alzheimer's.

"MMP-9 and other enzymes like it are secreted from brain support cells and active in the spaces outside of cells, and that's where we saw an increase in Abeta levels in the mice that lacked the gene for MMP-9," Lee notes. "That's relevant to Alzheimer's because all the amyloid plaques are extracellular, and the formation of the plaques seems to be related to an elevated level of Abeta that accumulates over time in those spaces."

In earlier studies, Lee's lab analyzed the production of MMP-9 in astrocytes. They found astrocytes close to amyloid plaques increased their MMP-9 production. Imaging studies also showed that MMP-9 levels increased around blood vessels laden with amyloid.

"Astrocytes become activated around plaques as they develop, and then eventually form a wall surrounding the plaques," he says.

Lee's results have led him to formulate a provocative but as yet unproven theory about an old mystery of Alzheimer's disease: why plaques continue to increase in number over time but only grow to a certain size.

"Even though everything we know about the fibrils suggests they should constantly grow, plaques reach a mature size and stop growing," Lee says. "It's possible that production of MMP-9 and other similar substances by support cells in the brain is establishing a balance that prevents the plaques from growing beyond a certain size."

To follow up, Lee plans to crossbreed mice lacking MMP-9 with a line of mice genetically modified to develop an Alzheimer's-like condition.

Scientists want to see if removing MMP-9 causes the mice to develop Alzheimer's more quickly.

In a parallel project that will test MMP-9's potential as a therapeutic, Lee and his collaborators will use viruses to alter production of MMP-9 in the mouse model. Researchers want to learn if increasing levels of the enzyme present in the brain can delay onset of Alzheimer's.

Source: Washington University School of Medicine, By Michael Purdy