Scientists find a key culprit in stroke brain cell damage

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Researchers have identified a key player in the killing of brain cells after a stroke or a seizure. The protein asparagine endopeptidase (AEP) unleashes enzymes that break down brain cells' DNA, scientists at Emory University School of Medicine have found. The results are published in the March 28 issue of the journal *Molecular Cell*.

Finding drugs that block AEP may help doctors limit permanent brain damage following strokes or seizures, says senior author Keqiang Ye, PhD, associate professor of pathology and laboratory medicine at Emory.

When a stroke obstructs blood flow to part of the brain, the lack of oxygen causes a buildup of lactic acid, the same chemical that appears in the muscles during intense exercise. In addition, a flood of chemicals that brain cells usually use to communicate with each other over-excites the cells. Epileptic seizures can have similar effects.

While some brain cells die directly because of lack of oxygen, others undergo programmed cell death, a normal developmental process where cells actively destroy their own DNA.

"The mystery was: how do the acidic conditions trigger DNA damage?" Ye says. "This was a very surprising result because previously we had no idea that AEP was involved in this process."

AEP is a protease, a class of enzymes that cuts other proteins. AEP is also called legumain because of its relatives in plants, and is found at its highest levels in the kidney, says Ye.

He and his co-workers had suspected that another class of proteases called caspases, involved in programmed cell death, controlled DNA damage after a stroke.

At first, he and postdoctoral fellow Zhixue Liu, PhD, thought the results of a critical experiment that led them to AEP were an aberration because the experiment was performed under overly acidic conditions.

"But if you can repeat the mistake, it's not a mistake," Dr. Ye says, adding that follow-up work allowed them to set aside caspases as suspects and focus on AEP.

The researchers began by looking for proteins that stick to another protein called PIKE-L, which they previously had studied because of its ability to interfere with programmed cell death in brain cells.

They discovered that PIKE-L sticks to SET, a protein that other scientists had found regulates DNA-eating enzymes involved in programmed cell death. In addition, PIKE-L appears to protect SET from attack by AEP.

Liu and Ye found that a drug scientists use to mimic the acidic overload induced by stroke activates AEP, driving it to break down DNA in brain cells. In mice genetically engineered to lack AEP, both the drug and an artificial stroke resulted in reduced DNA damage and less brain cell death than in regular mice.

This outcome suggests "that AEP might be the major proteinase mediating this devastating process," the authors wrote.

Source: Emory University