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Microbiologists describe new insights into human neurodegenerative disease

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Microbiology researchers at the University of Georgia studying a soil bacterium have identified a potential mechanism for neurodegenerative diseases.

A role for the protein HSD10 had been suspected in patients with Alzheimer's disease and Parkinson's disease, but no direct connection had previously been established. This new breakthrough suggests that HSD10 reduces oxidative stress, promotes cell repair and prevents cellular death.

The authors first discovered that an enzyme related to HSD10, CsgA, produces energy during sporulation in the bacterium *Myxococcus xanthus*. Spores enable cells to survive under nutrient-limiting conditions and can be thought of as the bacterial version of plant seeds. CsgA was found to degrade the phospholipid cardiolipin into fragments that were used as energy sources during sporulation much the same way humans produce and burn fat. Though normally a component of the lipid layer surrounding the cells, cardiolipin becomes dispensable as cells shrink to become spores.

The study was published Sept. 3 in the early online edition of *Genes & Development*.

In humans, this mechanism of cardiolipin degradation seems to have been appropriated for a different purpose. Cardiolipin is also found in mitochondria, where it surrounds and protects the energy-making

machinery from oxidative stress.

HSD10 is a versatile protein with many known functions but its role in oxidative stress has remained a mystery. The authors showed that HSD10 preferentially degrades highly toxic cardiolipin peroxides, free radical produced during oxidative stress that would normally initiate apoptosis, or cell death.

HSD10 activity is strongly inhibited when bound to the amyloid beta peptide so prevalent in Alzheimer's disease.

"Normally, apoptosis is beneficial for regulating multi-cellular systems," said the study's lead author Tye Boynton, a postdoctoral research associate in the Franklin College of Arts and Sciences. "But with rampant oxidative stress leading to uncontrolled cellular death, you end up with diseases such as Alzheimer's and Parkinson's. HSD10 potentially prevents this by removing these damaged lipids before they have a chance to act."

When cardiolipin becomes damaged by oxidative stress, the newly formed cardiolipin peroxides induce apoptosis instead of energy production. The UGA research team, led by microbiology professor Lawrence Shimkets, showed for the first time that HSD10 can mitigate oxidative damage.

"This research suggests that HSD10 prevents neurodegeneration by destroying cardiolipin peroxides and provides a fresh perspective on the etiology of Alzheimer's disease that could inform novel drug strategies," Shimkets said.

More information: The study, "Myxococcus CsgA, Drosophila Sniffer and human HSD17B10 are cardiolipin phospholipases," is available at www.genesdev.org/cgi/doi/10.1101/gad.268482.115