Targeting Astrocytes Slows Disease Progression in ALS

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In what the researchers say could be promising news in the quest to find a therapy to slow the progression of amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, scientists at the University of California, San Diego (UCSD) School of Medicine have shown that targeting neuronal support cells called astrocytes sharply slows disease progression in mice.

The study, conducted in the laboratory of Don Cleveland, Ph.D., UCSD Professor of Medicine, Neurosciences and Cellular and Molecular Medicine and member of the Ludwig Institute for Cancer Research, will appear in the advance online publication on *Nature Neuroscience*'s website on February 3.

"Mutant genes that cause ALS are expressed widely, not just in the motor neurons," Cleveland explained. "Targeting the partner cells like astrocytes, which live in a synergistic environment with the neuron cells, helps stop the 'cascade of damage.' Therapeutically, this is the big news."

ALS is a progressive disease that attacks the motor neurons, long and complex nerve cells that reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body, which act to control voluntary movement. Degeneration of the motor neurons in ALS leads to progressive loss of muscle control, paralysis and untimely death. Estimated to affect some 30,000 Americans, most people are diagnosed with ALS between the ages of 45 and 65. Typically, ALS patients live only one to five years after initial diagnosis.

In findings published in *Science* in June 2006, Cleveland and his colleagues showed that in early stages of inherited ALS, small immune cells called microglia are damaged by mutations in the SOD1 protein, and that these immune cells then act to significantly accelerate the degeneration of the motor neurons. The new study demonstrates that much the same thing happens to astrocytes, support cells that are essential to neuronal function, and whose dysfunction is implicated in many diseases. The researchers speculate that the non-neuronal cells play a vital role in nourishing the motor neurons and in scavenging toxins from the cellular environment. As with microglia, the helper role of astrocytes is altered due to mutations in the SOD1 protein.

"We tested what would happen if we removed the mutant gene from astrocytes in mouse models," said Cleveland. "What happened was it doubled the lifespan of the mouse after the

onset of ALS."

Astrocytes are key components in balancing the neurotransmitter signals that neurons use to communicate. To examine whether mutant SOD1 damage to the astrocytes contributes to disease progression in ALS, researchers in the Cleveland lab used a genetic trick to excise the mutant SOD1 gene, but only in astrocytes. Reduction of the disease-causing mutant SOD1 in astrocytes did not slow disease onset or early disease; however, the late stage of the disease was extended, nearly doubling the normal life expectancy of a mouse with ALS.

"Silencing the mutant gene in the astrocytes not only helps protect the motor neuron, but delays activation of mutant microglia that act to accelerate the progression of ALS," said Cleveland.

The findings show that mutant astrocytes are likely to be viable targets to slow the rate of disease spread and extend the life of patients with ALS. Cleveland added that this may prove especially important news to researchers in California and elsewhere working with stem cells. "This gives scientists a good idea of what cells should be replaced using stem cell therapy. Astrocytes are very likely much easier to replace than the slow-growing motor neuron."

Additional contributors to the study include Koji Yamanaka, Seung Joo Chun and Severine Boillee, Ludwig Institute for Cancer Research and UCSD Department of Medicine and Neuroscience; Noriko Fujimore-Tonou and Hirofumi Yamashita, Yamanaka Research Unit, RIKEN Brain Science Institute, Saitama, Japan; David H. Gutmann, Department of Neurology, Washington University, St. Louis; Ryosuke Takahashi, Department of Neurology, Kyoto University, Japan; and Hidemi Misawa, Department of Pharmacology, Kyoritsu University of Pharmacy, Tokyo.

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