Damaged Motor Neurons in ALS Contribute to Their Own Death

April 23, 2007 |

Researchers from The Ludwig Institute and the University of California, San Diego (UCSD) School of Medicine have discovered that when motor neurons damaged by amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, inappropriately send the wrong signal, immune cells react by killing the messenger. Their surprising finding provides new direction for therapies to treat ALS.

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 be published online April 27 in advance of publication in the journal *Proceedings of the National Academy of Sciences.*

Working in mouse models with an inheritable form of ALS, the researchers found that motor neurons – whose normal role is to trigger muscles to contract – were behaving inappropriately.

"What was very surprising is that the motor neurons themselves are acting partly like immune cells and, as they get damaged, respond by expressing signaling proteins, which are normally components of the immune system," said Christian Lobsiger, Ph.D., of the Cleveland lab. The researchers theorize that, somehow sensing that something is wrong with the signaling neuron, the immune cells respond to these signals by accelerating the death of the motor neuron. "The immune cells of the nervous system, called microglia – which are themselves impaired in patients with ALS – rush in to clean up damage. But instead of helping the damaged motor neurons, they just make things worse," he said.

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, the 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 suggests a way that the motor neurons respond to ALS damage within them by signaling to the immune system, which could then lead to amplification of the initial damage.

"We now know that the motor neurons not only fail to regenerate properly, but, in fact, hasten their own degeneration by sending the wrong signal to immune cells," said Cleveland.

While work is currently being done to develop therapies for ALS targeted at the damaged immune cells and the signaling from motor neurons to those immune cells, this study suggests that therapies could also be developed to target the motor neurons themselves.

"If we can either suppress the motor neuron from expressing these immune-system related signals, or somehow 'protect' the neuron from attack by immune cells, this could offer a therapeutic approach for ALS to be used alone or in combination with therapies directed at the immune cells," said Lobsiger.

Sevérine Boilée of the Cleveland lab also contributed to the study, which was funded by a grant from the National Institutes of Health and the Packard Center for ALS Research at Johns Hopkins University.

# # #

Media Contact: Debra Kain, 619-543-6163, ddkain@ucsd.edu

Lou Gehrig's Disease (ALS)

Share This Article

Related News

UC San Diego Health Begins Treating Multiple Myeloma with CAR T-cell Therapy
6/3/2021

Social Justice as Part of the Remedy for What Ails Us
6/3/2021

Diet Plays Critical Role in NASH Progressing to Liver Cancer in

Mouse Model
6/1/2021

Noted Researcher and Scientific Leader Jack E. Dixon Retires
5/27/2021

View All News >

Follow Us

Follow @ucsdhealth