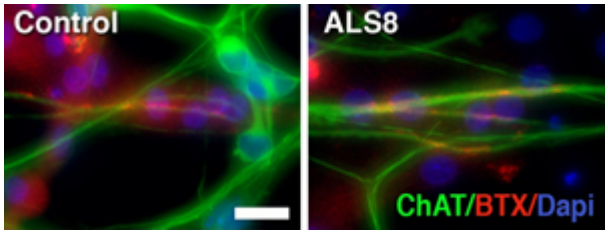
Stem Cell Model Offers Clues To Cause of Inherited ALS

June 28, 2011 |

An international team of scientists led by researchers at the University of California, San Diego School of Medicine have used induced pluripotent stem cells (iPSCs) derived from patients with amyotrophic lateral sclerosis (ALS) to reveal for the first time how reduced levels of a specific protein may play a central role in causing at least one inherited form of the disease.

The work, published in the June 2011 online issue of the journal *Human Molecular Genetics*, could help scientists overcome a major hurdle in the study and treatment of ALS, an incurable neuromuscular disorder also known as Lou Gehrig's disease. ALS is universally fatal, with a median age of onset of 55 years and survival of two to five years after symptoms appear. Past research efforts have long been stymied by difficulties in translating successful drug tests in animal models of ALS to humans.

"There is an urgent need for ALS human models that can be translated into clinical trials to verify therapeutic targets in the human genetic background," said Alysson R. Muotri, PhD, assistant professor in the UCSD Departments of Pediatrics and Cellular and Molecular Medicine, and one of the study's senior authors. "Rodents have been used in the past and still have a critical impact in unveiling the complexity of ALS, but the vast majority of drugs that have demonstrated efficacy in rodent models have not done the same in preclinical and clinical human trials."



motor neurons (green) derived from ALS induced pluripotent stem cells forming neuromuscular junctions (red). *Image courtesy of Alysson Muotri, UCSD.*

In the new work, Muotri and colleagues turned to iPSCs derived from the skin cells of patients with a familial form of ALS called ALS8 to create motor neurons that provided a novel in vitro model of the disease. iPSCs from ALS patients have been described before, but finding cellular

and molecular phenotypes has proved to be a continuing challenge. The use of a familial form of ALS offered an advantage once (since?) the mutated gene could be tracked during motor neuron differentiation.

"We don't know what causes most cases of ALS, but for roughly 10 percent of patients with ALS, the disease is the result of inherited genetic mutations," Muotri said. "One of these familial forms is ALS8, which results from mutations in the VAPB gene. Using iPSCs from several patients from two independent families, we found that VAPB protein levels are reduced in ALS8-derived motor neurons compared to similar cells from non-carrier siblings of ALS8 patients."

Muotri said the finding suggests reduced VAPB protein levels may be a key to the development of ALS8 and perhaps other forms of the disease as well, including sporadic or non-hereditary ALS, where reduced VAPB protein levels have also been documented.

"The VAPB protein is involved in many cellular processes, so it seems likely it contributes to the pathogenesis of other forms of ALS," Muotri said. "We don't yet know how the loss of VAPB is involved in causing familial or sporadic ALS, but the new ability to study this disease in human cells provides an unprecedented opportunity to answer that question, to develop new early diagnostic tools and to identify new targets for future drugs and therapies."

Co-authors of the study are Miguel Mitne-Neto, UCSD Department of Pediatrics/Rady Children's Hospital-San Diego, UCSD Department of Cellular and Molecular Medicine and Human Genome Research Center, University of Sao Paulo; Marcela Machado-Costa, Helga A.C. Silva and Acary S.B. Oliveira, Federal University of Sao Paulo, Paulista School of Medicine; Maria C.N. Marchetto, Salk Institute for Biological Studies; Mario H. Bengtson and Claudio A. Joazeiro, Department of Cell Biology, The Scripps Research Institute; Hiroshi Tsuda and Hugo J. Bellen, Department of Molecular and Human Genetics, Baylor College of Medicine; Monize Lazar and Mayana Zatz, Human Genome Research Center, Department of Genetic and Evolutive Biology, University of Sao Paulo

Funding for this research came from the Muscular Dystrophy Association.

About ALS

Amyotrophic lateral sclerosis is a rapidly progressive, invariably fatal neurological disease that attacks the neurons responsible for controlling voluntary muscle movement. It does not generally impair cognitive function. An estimated 20,000 to 30,000 Americans have ALS, with 5,000 new cases diagnosed each year. ALS strikes most commonly between the ages of 40 and 60, affecting men more often than women, but with no distinction of race or ethnic background. In 90 percent of all ALS cases, the disease appears to occur randomly without clearly associated risk factors. Ten percent of cases are inherited, due to gene mutations.

# # #

Media Contact: Scott LaFee, 619-543-6163, slafee@ucsd.edu

Related Specialties

ALS Center
Neuroscience

Share This Article

Related News

Massive Study Links Nearly 600 Genomic Regions to Self-Regulating Behaviors
8/26/2021

Brain Organoids Mimic Head Size Changes Associated with Type of Autism
8/25/2021

State Stem Cell Agency Funds Three New UC San Diego Projects
8/25/2021

Two Studies Seek to Go Beyond the GIST of Intestinal Tract Cancer
8/24/2021

View All News >

Follow Us

Follow @ucsdhealth