New research discovery provides therapeutic target for ALS

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Research led by Dr. Udai Pandey, Assistant Professor of Genetics at LSU Health Sciences Center New Orleans, has found that the ability of a protein made by a gene called FUS to bind to RNA is essential to the development of Amyotrophic Lateral Sclerosis (ALS). This discovery identifies a possible therapeutic target for the fatal neurological disease. The research will be available online in the Advanced Access section of the journal *Human Molecular Genetics* website, posted by December 21, 2012. It will be published in an upcoming issue of the journal.

The current project advances Dr. Pandey's ALS research by teasing out specifically how the FUS gene causes the disease. To find out whether or not the RNA binding ability of FUS was required for the disease pathogenesis, the researchers mutated FUS RNA binding sites and produced a version of FUS that couldn't bind RNA, both with and without ALS mutations. They found that not only could they eliminate FUS RNA binding, but when they blocked RNA binding, they also suppressed ALS related neurodegeneration, demonstrating that the RNA binding ability of FUS is essential to the ALS disease process.

The researchers are working with fruit flies – the first animal model of FUS-related ALS, a model Dr. Pandey developed. The fruit flies were engineered to carry and express a mutated human FUS gene. This mutated FUS gene has been shown to be one of the causes of both familial and sporadic ALS. In the fruit flies, the resulting neurodegeneration impairs their ability to walk or climb and the defect is also easily visualized in the structure of their eyes. In addition, the flies

carrying the defective FUS gene demonstrate hallmarks of the human disease, such as an age-dependent degeneration of neurons, accumulation of abnormal proteins and a decrease in life span. The fly model is a valuable resource for performing drug screens to identify drugs that could modify the effects of the mutated gene in humans.

"Our findings may pave the way for development of drugs targeting the biological processes responsible for causing ALS, and leading to treatments or prevention of this currently fatal, incurable condition, " notes Pandey. "The fly model is an inexpensive and fast way to study ALS as well as many human diseases such as cancer, Alzheimer's disease and Parkinson's disease. Many basic biological processes are well conserved between humans and fruit flies, and nearly 75% of human disease-causing genes are believed to have a functional partner (homolog) in the fly that makes these small animals a highly tractable model system."

"These intriguing findings inspire us and other researchers to search for drugs that can make the defective FUS protein less toxic by targeting is RNA binding as a potential therapeutic intervention," noted Gavin Daigle (Graduate student in the Pandey lab and leading author of the manuscript).

According to the National Institutes of Health, Amyotrophic Lateral Sclerosis, sometimes called Lou Gehrig's disease, is a rapidly progressive, invariably fatal neurological disease that attacks the nerve cells (neurons) responsible for controlling voluntary muscles. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. Motor neurons are nerve cells located in the brain, brainstem, and spinal cord that serve as controlling units and vital communication links between the nervous system and the voluntary muscles of the body. Messages from motor neurons in the brain (called upper motor neurons)

are transmitted to motor neurons in the spinal cord (called lower motor neurons) and from them to particular muscles. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, ceasing to send messages to muscles. Unable to function, the muscles gradually weaken, waste away (atrophy), and twitch (fasciculations). Eventually, the ability of the brain to start and control voluntary movement is lost.

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