Scientists identify ALS disease mechanism

28 August 2013

Researchers have tied mutations in a gene that causes amyotrophic lateral sclerosis (ALS) and other neurodegenerative disorders to the toxic buildup of certain proteins and related molecules in cells, including neurons. The research, published recently in the scientific journal *Cell*, offers a new approach for developing treatments against these devastating diseases.

Scientists at St. Jude Children's Research Hospital and the University of Colorado, Boulder, led the work.

The findings provide the first evidence that a gene named VCP plays a role in the break-up and clearance of protein and RNA molecules that accumulate in temporary structures called RNA granules. RNAs perform a variety of vital cell functions, including protein production. RNA granules support proper functioning of RNA.

In ALS and related degenerative diseases, the process of assembling and clearing RNA granules is impaired. The proteins and RNAs associated with the granules often build up in nerve cells of patients. This study shows how mutations in VCP might contribute to that process and neurodegenerative disease.

"The results go a long way to explaining the process that links a variety of neurodegenerative diseases, including ALS, frontotemporal dementia and related diseases of the brain, muscle and bone known as multisystem proteinopathies," said the study's co-corresponding author, J. Paul Taylor, M.D., Ph.D., a member of the St. Jude Department of Developmental Neurobiology. Roy Parker, Ph.D., of the University of Colorado's Department of Chemistry and Biochemistry and the Howard Hughes Medical Institute (HHMI), is the other corresponding author.

ALS, also known as Lou Gehrig's disease, is diagnosed in about 5,600 Americans annually and is associated with progressive deterioration of nerve cells in the brain and spine that govern movement, including breathing. There is no effective treatment, and death usually occurs within five years.

"A strength of this study is that it provides a unifying hypothesis about how different genetic mutations all affect stress granules, which suggests that understanding stress granule dynamics and how they can be manipulated might be beneficial for treatment of these diseases," Parker said.

Earlier work from Taylor's laboratory identified mutations in VCP as a cause of ALS and related multisystem proteinopathies. Until now, however, little was known about how those mistakes caused disease. The latest findings appeared in the June 20 issue and are highlighted in a review article published in the August 15 issue of *Cell*.

The research also ties VCP mutations to disruption of RNA regulation, which prior studies have connected to the progression of neurodegenerative diseases, said Regina-Maria Kolaitis, Ph.D., a postdoctoral fellow in Taylor's laboratory. She and Ross Buchan, Ph.D., a postdoctoral fellow in Parker's laboratory, are co-first authors.

The work focused on a class of RNA granules called stress granules. They are formed by proteins and an RNA molecule called mRNA that accumulates in the cell cytoplasm in response to stress. Stressed cells do not want to waste energy producing unnecessary proteins. Stress granules are one mechanism cells use to halt production until the cellular environment normalizes, which is when stress granules typically dissolve.

Proteins found in stress granules include RNA-binding proteins like TDP-43, FUS, hnRNPA1 and hnRNPA2B1 that regulate gene activity. Mutations in those proteins can also cause ALS and related disorders.

"VCP has many functions in cells, but it is not an RNA-binding protein and until now it was not connected to stress granules or RNA processing,"

Kolaitis said. "This study provides a new window into the disease process, highlighting VCP's role in keeping cells healthy."

For this study, researchers used yeast to identify a network of 125 genes that affect the formation and behavior of stress granules. One of the genes that appeared to play a central role in the network was CDC48, which functions like VCP in yeast. In addition, many of the genes identified are involved in a process called autophagy that cells use to break down and recycle unneeded molecules, including proteins.

Working in yeast and mammalian cells, researchers showed that stress granules are cleared by autophagy, which stalled when VCP was mutated. Researchers also reported that stress granules accumulated following mutation of either CDC48 or VCP.

"This work suggests that activating autophagy to help rid cells of stress granules offers a new approach to neurodegenerative disease treatment," Taylor said.

Provided by St. Jude Children's Research Hospital

APA citation: Scientists identify ALS disease mechanism (2013, August 28) retrieved 3 May 2021 from https://medicalxpress.com/news/2013-08-scientists-als-disease-mechanism.html

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