Loss of Key Protein Boosts Neuron Loss in ALS

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Amyotrophic lateral sclerosis, known as ALS or more popularly, Lou Gehrig's disease, is a notorious neurodegenerative condition characterized by the progressive deterioration of brain and spinal cord neurons, resulting in the gradual but catastrophic loss of muscle control and ultimately, death.

In a new paper, published in the Feb. 27 advance online edition of the journal *Nature Neuroscience*, a team of scientists at the University of California, San Diego School of Medicine and colleagues describe the profound and pervasive role of a key protein in ALS pathology called TDP-43.

The work was led by Don W. Cleveland, PhD, professor and chair of the UCSD Department of Cellular and Molecular Medicine and head of the Laboratory of Cell Biology at the Ludwig Institute for Cancer Research and Gene Yeo, PhD, assistant professor in the Department of Cellular and Molecular Medicine.

In normal cells, TDP-43 is found in the nucleus where it helps maintain proper levels of ribonucleic acid (RNA), intermediate molecules that translate genetic information from DNA to proteins – the building blocks of cells.

In the majority of ALS patients, however, TDP-43 accumulates in the cell's cytoplasm – the liquid that separates the nucleus from the outer membrane, and thus is excluded from the nucleus, which prevents it from performing its normal duties.

Using a mouse model, the researchers made three new important findings:

First, employing a comprehensive genome-wide RNA-binding mapping strategy, they discovered that more than one-third of the genes in the mouse brain are direct targets of TDP-43. In other words, the roles and functions of these genes are impacted by the presence – or absence – of normal TDP-43.

Second, the genes most affected had numerous TDP-43 binding sites on very long introns. Introns are the non-coding portions of a gene that are not used to make proteins. Typically, introns are removed (spliced out) during the development of mature messenger RNA. Introns, however, contain binding sites for RNA binding proteins such as TDP-43, to regulate the splicing process.

"This is an important finding as genes expressed in the central nervous system have much longer introns than genes expressed in any other tissues," said Yeo. "This may explain the neuronal selectivity of the disease, and why other types of cells aren't affected."

Third, TDP-43 affects the alternative splicing of many genes. In fact, it affects the alternative splicing of its own RNA message. Said Yeo: "This autoregulation keeps TDP-43 protein levels in check. The loss of TDP-43 removes this check; more TDP-43 is generated and more is likely to accumulate in the cytoplasm."

The deep and expansive impact of misaggregated TDP-43 and the concurrent loss of normal TDP-43 appear to extend beyond ALS. The protein is a central component in the pathogenesis of an ever-increasing list of neurodegenerative conditions. For example, accumulating abnormal TDP-43 in neuronal cytoplasm has been documented in frontotemporal lobar dementia, a neurological disorder that results in progressive changes in personality, the ability to concentrate, social skills, motivation and reasoning.

"It is likely that TDP-43 affects many other neurodegenerative diseases," said Yeo. "Our RNA targets probably reveal the set of genes important for maintaining the normal homeostasis of neurons."

Yeo said the team will now explore which TDP-43 binding sites are critical to how ALS begins and progresses. Ultimately, he said, the information could be used to design new drugs and therapies.

Co-authors of the paper include Magdalini Polymenidou, Clotilde Lagier-Tourenne, Jacqueline Moran, Shuo-Chien Ling, Eveline Sun, Ludwig and Holly Kordasiewicz, Ludwig Institute for Cancer Research at UCSD and the UCSD Department of Cellular and Molecular Medicine; Kasey R. Hutt, Stephanie C. Huelga and Tiffany Y. Liang, UCSD Department of Cellular and Molecular Medicine and UCSD Stem Cell Program and Institute for Genomic Medicine; Edward Wancewicz, Curt Mazur, Yalda Sedaghat and C. Frank Bennett, Isis Pharmaceuticals, Carlsbad, Ca.; John Paul Donohue and Lily Shiue, RNA Center, Department of Molecular, Cell and Developmental Biology, Sinsheimer Labs, UC Santa Cruz.

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