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Malfunctioning Gene Associated With Lou Gehrig's Disease Leads to Nerve-Cell Death in Mice

Lou Gehrig's disease, or Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Lobar Degeneration (FTLD) are characterized by protein clumps in brain and spinal-cord cells that include an RNA-binding protein called TDP-43. This protein is the major building block of the lesions formed by these clumps.

In a study published in the *Journal of Clinical Investigation*, a team led by Virginia M.-Y. Lee, PhD, Director of Penn's Center for Neurodegenerative Disease Research, describes the first direct evidence of how mutated TDP-43 can cause neurons to die? Although normally found in the nucleus where it regulates gene expression, TDP-43 was first discovered in 2006 to be the major disease protein in ALS and FTLD by the Penn team led by Lee and John Q. Trojanowski, MD, PhD, Director of the Institute on Aging at Penn. This discovery has transformed research on ALS and FTLD by linking them to the same disease protein.

"The discovery of TDP-43 as the pathological link between mechanisms of nervous system degeneration in both ALS and FTLD opened up new opportunities for drug discovery as well as biomarker development for these disorders," says Lee. "An animal model of TDP-43-mediated disease similar to ALS and FTLD will accelerate these efforts."

In the case of TDP-43, neurons could die for two reasons: One, the clumps themselves are toxic to neurons or, two, when TDP-43 is bound up in clumps outside the nucleus, it depletes the cell of normally functioning TDP-43. Normally a cell regulates the exact amount of TDP-43 in itself -- too much is bad and too little is also bad. The loss of function of TDP-43 is important in regulating disease, because it regulates gene expression.

To determine the effects of misplaced TDP-43 on the viability of neurons, the researchers made transgenic mice expressing human mutated TDP-43 in the cytoplasm and compared them to mice expressing normal human TDP-43 in the nucleus of nerve cells. Expression of either human TDP-43 led to neuron loss in vulnerable forebrain regions; degeneration of part of the spinal cord tract; and muscle spasms in the mice. These effects recapitulate key aspects of FTLD and a subtype of ALS known as primary lateral sclerosis.

The JCI study showed that a dramatic loss of function causes nerve-cell death because normal mouse TDP-43 is eliminated when human mutated TDP-43 genes are put into the mice. Since cells regulate the exact amount of TDP-43, over-expression of the human TDP-43 protein prevents the mouse TDP-43 from functioning normally. Lee and colleagues think this effect leads to neuron death rather than clumps of TDP-43 because these clumps were rare in the mouse cells observed in this study. Lee says that it is not yet clear why, clumps were rare in this mouse model, when they are so prevalent in human post-mortem brain tissue of ALS and FTLD patients?

Neurodegeneration in the mouse neurons expressing TDP-43 -- both the normal and mutated human versions -- was accompanied by a dramatic downregulation of the TDP-43 protein mice are born with. What's more, mice expressing the mutated human TDP-43 exhibited profound changes in gene expression in neurons of the brain's cortex.

The findings suggest that disturbing the normal TDP-43 in the cell nucleus results in loss of normal TDP-43 function and gene regulatory pathways, culminating in degeneration of affected neurons.

Next steps, say the researchers, will be to look for the specific genes that are regulated by TDP-43 and how mRNA splicing is involved so that the abnormal regulation of these genes can be corrected.

At the same time, notes Lee, "We soon will launch studies of novel strategies to prevent TDP-43-mediated nervous system degeneration using this mouse model of ALS and FTLD."

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