C9orf72: From Mutation to Mechanism to Therapy Development

Research Webinar: September 24, 2013
Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D.
Guest Speaker: Rita Sattler, Ph.D.

The pace of research into the causes and treatments of ALS has accelerated in the past few years, and nowhere is that more evident, and possibly more significant, that in work on the C9orf72 gene. Progress on understanding how the gene causes ALS, and ideas about reversing its effects, were the topic of a recent ALS Association-sponsored webinar with Rita Sattler, Ph.D., Principal Scientist at the Brain Science Institute at Johns Hopkins University. Dr. Sattler's work in discovering new treatments for ALS is supported by The ALS Association.

The discovery of the Corf72 gene "really changed the landscape of ALS," Dr. Sattler said, for several reasons. It is now the most common genetic cause of the disease, responsible for between a quarter and half of all familial cases, and between 5% and 20% of sporadic cases, depending on which population is studied. "This is big," she continued. "We know that if we understand the mechanism, and develop a therapeutic, we may be able to help a lot of ALS patients."

The mutation in the gene, she explained, is similar to those found in several other neurological diseases, including myotonic dystrophy, Huntington's disease, and many forms of ataxia. The normal C9orf72 gene includes a short section in which a unit of six nucleotides (the building blocks of DNA), GGGGCC, is repeated up to 30 times. In the mutant form, that section contains hundreds of these repeated units.

During the normal creation of protein, the gene is used to make a "working copy" called messenger RNA (mRNA). But when mRNA is made from the mutant gene, the repeated section creates a long, useless, and sticky section of mRNA that folds into a three-dimensional structure. This, evidence is beginning to show, can trap proteins in the cell, and may be a major source of the problem in ALS due to the mutant gene.

Dr. Sattler's lab has studied the effects of the mutation using stem cells derived from ALS patients (called iPS cells). "We feel very confident that these cells allow us to model the disease very closely," she said.

The proteins trapped include a group of proteins whose normal job is to bind to RNA, called, appropriately enough, RNA binding proteins. "The RNA binding proteins, whatever their function, cannot do their job any more. We think that is one of the mechanisms responsible for toxicity," she said. That phenomenon has been shown to be largely responsible for harm in myotonic dystrophy, and Dr. Sattler believes a similar mechanism is at work in ALS.

The effects of the RNA-protein interaction include changes in the activity of many genes, and increased sensitivity to glutamate, a normal neuronal signaling molecule that is toxic in high concentrations. Reducing the amount of expanded RNA mitigates these effects.

One potentially important difference between RNA expansion in ALS and myotonic dystrophy is that in ALS, the RNA binding proteins, rather than simply being trapped in the RNA, also seem to enhance the toxicity of the RNA by their presence. She has found that depleting certain RNA binding proteins, so they can no longer interact with the expanded RNA in C9orf72, reduces the accumulation of the RNA. "That means that these proteins are necessary for these foci, and hence play a role in toxicity," Dr. Sattler concluded, suggesting that preventing that interaction may be therapeutic.

Efforts are underway to reduce the accumulation of the toxic RNA using "antisense oligonucleotides," short nucleotide molecules that bind to the RNA and prevent interaction with RNA binding proteins. Her lab is partnering with Isis Pharmaceuticals and Biogen Idec to develop this type of therapy.

Development of antisense therapy for C9orf72 ALS is likely to proceed much faster than development of many previous ALS therapies, Dr. Sattler predicted, based on progress with antisense for SOD1 ALS, and the rapidly growing understanding of the disease mechanism.

ALS Association Chief Scientist Lucie Bruijn, Ph.D., and host of the webinar, pointed out that the C9orf72 story "brings home the complexity of ALS, and shows why we need multiple disease models, and why it is important to learn from other diseases. Every project involves many people and many different tools," she said.

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