RNA May be a Key to Understanding, and Treating, ALS and Related Diseases

In the search for new treatments for ALS and related disorders, scientists look for the ultimate cause of disease, the first "falling domino" that sets all the rest of the disease process in motion. The hope is that by designing a therapy to prevent that first domino from falling, they can interrupt the disease process in the most effective way.

Increasingly, researchers are focusing on a cell molecule called RNA as being involved in the earliest steps of ALS, and possibly related diseases as well. The discovery of the role of RNA in ALS has opened up important new areas of understanding of the ALS disease process, and promising new ideas for treatments. Here, CReATe explains what RNA is, what role it may play in ALS, and how new therapies are being developed to target it.

What is RNA?

RNA (ribonucleic acid) is a type of molecule found in every cell in every organism. Like its chemical cousin, DNA, it is composed of a long string of similar subunits, linked together like beads on a string. There are 4 different RNA subunits, abbreviated A, U, G, and C. The order in which these subunits are arranged differs from RNA molecule to RNA molecule, and the exact order determines both the final structure and the function of the RNA molecule.

What does RNA do?

In the past several decades, scientists have discovered that different RNAs play a wide variety of roles in cells. The most well-known, and one that may be most important in understanding ALS, is the function of serving as a "working copy" of a gene. Genes (made of DNA) carry the instructions for making proteins, which control most cell functions. But genes remain in the nucleus of the cell. To make a protein, the cell first makes an RNA copy of the gene. That copy (called a "messenger RNA") is processed by multiple proteins, and then finally leaves the nucleus and is "read" by the protein-making machinery to create a new protein molecule.

What goes wrong with RNA in ALS?

This depends on the genetic cause of ALS. The most common genetic cause of ALS (and frontotemporal dementia, or FTD) is a mutation in the C9orf72 gene. The mutation greatly expands a region of the gene, and when an RNA copy is made from it, the RNA copy is also greatly increased in length. Like a long strand of spaghetti, this messenger RNA folds up on itself and forms large clumps, or "foci."

These RNA foci are sticky, and may trap other important cell molecules, upsetting the balance of chemical instructions shuttling into and out of the nucleus. The long strands of RNA also lead to production of an unusual type of protein, not normally found in cells, called "dipeptide repeat proteins," or DPRs. It is currently unknown whether DPRs are toxic. Scientists are exploring whether the foci, the DPRs, or both, represent the "first domino" in the disease process for ALS and FTD due to the C9orf72 gene mutation.

How is RNA involved in other forms of ALS?

Other genetic causes of ALS, including mutations in TDP43 and FUS, are thought to impair the processing of RNA, in ways that are not yet clear. By understanding more about the function of these genes, and what goes wrong in ALS, researchers hope to gain a better understanding of non-genetic (sporadic) ALS as well. It is possible that RNA handling plays an early role in these forms of the disease as well.

How are treatments being developed to prevent problems with RNA?

Among the most promising treatments in development for ALS due to known genes, including C9orf72, is "antisense" therapy. An antisense molecule is similar in structure to RNA itself, and is designed to bind to the RNA that is causing the disease—that first domino in the disease process. The binding of an antisense molecule to an RNA causes cellular defense mechanisms to destroy the RNA, releasing the antisense molecule to bind to another RNA.

Antisense treatment has been shown to be safe in one form of ALS, due to mutations in the SOD1 gene. Experiments in lab models of ALS indicate that antisense can slow disease progression. A clinical trial of antisense in C9orf72 ALS/FTD is being planned, and is slated to begin in late 2016.

You can find out more about current clinical trials in ALS and FTD at www.clinicaltrials.gov