Clumps of the protein called TDP-43 appear in motor neurons in almost every form of ALS, but what is their relationship to development of disease? Philip Wong, Ph.D., Professor of Pathology at Johns Hopkins University in Baltimore, explored that question and how answering it may lead to new therapeutic strategies in ALS. Dr. Wong spoke in a recent webinar hosted by Lucie Bruijn, Ph.D., M.B.A., Chief Scientist for The ALS Association.

“Dr. Wong’s work, which is partially funded by The ALS Association, provides important new insights into the role of TDP-43 in the healthy motor neuron, and into how disruption of that role may contribute to disease,” Dr. Bruijn said.

Aggregates of TDP-43 are found in 97% of ALS cases. While mutations in the gene coding for the TDP-43 protein are a rare cause of ALS, in all other cases, there is nothing wrong with the protein itself. Instead, researchers are coming to believe the problem is that the protein aggregates when too much of it is present in the wrong place. TDP-43 is normally found mostly in the cell nucleus, but it shuttles in and out of the nucleus as part of its job. When too much of it accumulates outside the nucleus, it forms clumps. New evidence suggests that accumulation occurs because the normal machinery to transport it back into the nucleus is defective.

But how might this cause ALS? To understand that, “we need to understand TDP-43’s job,” Dr. Wong said. The structure of the protein indicates it binds readily with RNA. Cells use RNA for many different purposes in the cell, but the bulk of it functions as the “working copy” of the DNA’s instructions for making proteins. Dr. Wong’s work indicates that TDP-43 plays an essential role as the “quality control manager” for making that working copy.

To understand how, it is helpful to remember that the gene for a protein is a long string of DNA letters, broken up into useful segments called exons, and useless bits called introns. After introns are removed, exons can be spliced together to form a final “messenger RNA.”

Recently, it was discovered that introns contain sequences that may be mistaken for exons, called “cryptic exons.” If cryptic exons were included in the messenger RNA, the resulting protein would be nonfunctional. The role of TDP-43 is to suppress the inclusion of cryptic exons, “to make sure these do not get into the final messenger RNA,” Dr. Wong said, “so it won’t disrupt the normal exon pattern. This is why we say that TDP-43 is a manager of quality control.” But if the level of TDP-43 in the nucleus is decreased, as it appears to be in at least some forms of ALS, that could prevent the exclusion of cryptic exons, leading to proteins that are misformed or never made in the first place, which may lead to motor neuron death.
Dr. Wong and his team showed that loss of TDP-43 in mice led to more cryptic exons being incorporated into messenger RNA and increased death. They also found that cryptic exons were more commonly included in messenger RNA in brain tissue of people with ALS and frontotemporal dementia, a related disease, than in healthy control brain. “This strongly argues that this problem is caused by loss of TDP-43,” Dr. Wong said.

“So how are we going to fix it?” he asked. “By building a better quality control manager.” Dr. Wong has created and is currently testing a similar protein that is resistant to aggregation, helping it last long enough to return to the nucleus. When he introduced the protein to cells lacking TDP-43, they rescued the dying cells. He is currently testing it in animal models.

If those studies support further development, he envisions that the gene for the new protein could be delivered by gene therapy to the brain and spinal cord, using delivery vectors that are currently being tested in other conditions. “If that works well, it will allow us to bring this to clinical trials,” he said.

“We share your excitement in developing this new avenue for understanding the disease and developing treatment,” Dr. Bruijn said. “As we learn more about the role of TDP-43, it becomes increasingly important to explore all avenues for correcting the problems caused by its aggregation.”

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