New Discoveries in RNA Processing Point to New Therapeutic Targets
Research Webinar: December 18, 2013
Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D.
Guest Speaker: Paul Taylor, M.D., Ph.D.

Ribonucleic acid (RNA) processing has emerged as a central focus for understanding the causes of ALS. Paul Taylor, M.D., Ph.D., explained the importance of the dynamic processes that regulate RNA transport and discussed recent discoveries from his laboratory at St. Jude’s Children’s Hospital in Memphis, Tennessee, in a recent webinar sponsored by The ALS Association. Dr. Taylor’s work has been supported by The Association.

Dr. Taylor’s discovery of a new ALS gene began with a woman with ALS whose daughter had inclusion body myositis, a muscle disorder. Extensive genetic analysis led him to the realization, that in this family, these two seemingly unrelated diseases were in fact caused by mutation in the same gene, called valosin-containing protein (VCP). The same gene can also cause dementia and a bone disorder. This mutation-related collection of diseases is now called multisystem proteinopathy (MSP).

“We thought that if mutations in this one gene could lead to all these diseases, it must be important,” Dr. Taylor said; so his lab set out to understand more about it.

He explained that VCP is a gear-shaped protein that can attach to and pull on other proteins, removing them from large complexes, “like bricks out of a Jenga game,” helping to disassemble the complexes. That type of disassembly is critical for many cell processes, he said, “so many that it is hard to figure out which is essential for ALS.”

Dr. Taylor embarked on a large-scale genetic “screen” for other genes that worked with VCP, or, in cell biology parlance, were in the same “pathway.” He performed the screen, “like casting a net into the genome,” in fruit flies. These workhorses of the laboratory are perfect for such a screen for three reasons. First, VCP mutations in the fly cause not only motor neuron loss, but also neurodegeneration of the eye, a large and easily monitored structure. Second, the fly genome is very well characterized. And third, fly and human genomes are highly similar, with three quarters of all human genes having an obvious counterpart in the fly.

So his lab set out to study the effects of mutating each of the 13,000 fly genes, one by one, to see which made the eye degeneration better, and which made it worse, “meaning that those genes are either compensating or exacerbating the problem,” Dr. Taylor said. Genes with such an effect “are virtually always in the same biological pathway, so this is a way to find other gene products functionally related to VCP.”

The laborious search paid off. “We struck gold,” Dr. Taylor said. He found that VCP interacted with three proteins: hnRNPA1, hnRNPA2, and TDP-43. The three have much in common. TDP-43 mutations can cause ALS, and clumps of TDP-43 are found in the dying motor neurons of
almost all people with ALS. Recently, mutations in both hnRNPA1 and hnRNPA2 have been discovered to cause some cases of MSP, of which motor neuron disease is one manifestation.

Furthermore, all three proteins bind to the cellular messenger called RNA. Messenger RNA is a “working copy” of a gene, used to make protein. Messenger RNAs are often transported long distances in neurons, and these binding proteins help protect them during transport.

So how does VCP interact with these proteins? And how do these three mutant proteins cause disease? The answers are only beginning to emerge, but Dr. Taylor believes a key comes from looking at similarities in the structure of the three proteins. Each has a region that Dr. Taylor likens to Velcro, in that it acts to link the protein into a much larger assembly called an RNA granule. These granules are dynamic structures used by neurons as a kind of “holding cell” for RNA molecules during transport or times of stress. Each of the three proteins binds to its own set of RNAs, and then links into an RNA granule.

Disassembling RNA granules when the time is right is just as important as making them in the first place, and disassembly seems to be the problem in MSP and ALS. Recall that VCP’s job is to disassemble large protein complexes. It turns out that RNA granules are one of its targets, and VCP mutations inhibit this disassembly. Similarly, mutations in hnRNPA1, hnRNPA2, or TDP-43 also inhibit disassembly.

As a result, the RNA granules don’t disassemble properly. “The granules get stuck, and our hypothesis is that these lead to formation of the protein inclusions seen in ALS patients,” Dr. Taylor said. The inclusions may then trap other proteins, ultimately crippling the motor neuron.

“We are trying to understand normal assembly and disassembly of granules. We think this process is out of balance, and that it may be therapeutic to restore that balance.” Evidence for that is beginning to emerge, including from a recent study showing that inhibiting a granule-promoting process reduced neurodegeneration in flies.

“These studies are a good illustration of the power of an appropriate disease model to lead to rapid insights into disease mechanisms,” said Lucie Bruijn, PhD, Chief Scientist for The ALS Association. “They also support the idea that the many genes that cause ALS may ultimately work through a smaller number of pathways, and that studying many of these less common genes can lead to valuable insights about ALS from many different causes.”

To view Dr. Taylor’s full presentation on RNA processing, visit https://alsa.webex.com/alsa/ldr.php?RCID=260eedb4d52235853c192c25cadbe560.