New study opens new door for ALS drug discovery

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Credit: National Cancer Institute

To create treatments for a disease without any, scientists need to study and understand the driving forces behind the faulty biology. Today, researchers at the University of North Carolina School of Medicine announced the first-ever evidence-based description of the neuronal protein clumps thought to be important in Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, a fatal neurodegenerative

condition.

The study, published online today in *Proceedings of the National Academy of Sciences*, also provides the first definitive evidence that these protein clumps are indeed toxic to the type of neurons that die in patients with ALS.

This research development could be a crucial step toward developing drugs to stop the creation of the clumps and stem the progression of the disease. Cures for ALS and other neurodegenerative diseases have long eluded researchers, largely because their causes have remained mysterious.

"One of the biggest puzzles in health care is how to address neurodegenerative diseases; unlike many cancers and other conditions, we currently have no leverage against these neurodegenerative diseases," said senior study author Nikolay Dokholyan, PhD, the Michael Hooker Distinguished Professor of Biochemistry and Biophysics at UNC. "This study is a big breakthrough because it sheds light on the origin of motor neuron death and could be very important for drug discovery."

Patients with ALS suffer gradual paralysis and early death as a result of the loss of motor neurons, which are crucial to moving, speaking, swallowing, and breathing.

The study focuses on a subset of ALS cases - an estimated 1 to 2 percent - that are associated with variations in a protein known as SOD1. However, even in patients without mutations in their SOD1 gene, this protein has been shown to form potentially toxic clumps. The researchers discovered that the protein forms temporary clumps of three, known as a "trimer," and that these clumps are capable of killing motor neuron-like cells grown in the laboratory.

"This is a major step because nobody has known exactly what toxic interactions are behind the death of motor neurons in patients with ALS," said Elizabeth Proctor, PhD, a graduate student in Dokholyan's laboratory at the time of the study and the paper's first author. "Knowing what these trimers look like, we can try to design drugs that would stop them from forming, or sequester them before they can do damage. We are very excited about the possibilities."

Researchers zeroed in on SOD1 after genetic mutations affecting the protein were linked with ALS in the early 1990s. But the exact form of aggregated protein that is responsible for killing neurons has been hard to identify, and many of the clumps that are thought to be toxic disintegrate almost as soon as they form, making them exceedingly difficult to study.

"It is thought that part of what makes them so toxic is their instability," said Proctor, who is now a postdoctoral researcher at MIT. "Their unstable nature makes them more reactive with parts of the cell that they should not be affecting."

Until now, researchers did not know what these fleeting clumps looked like or how they might affect cells.

To crack the mystery, the research team used a combination of computational modeling and experiments in live cells. Proctor spent two years developing a custom algorithm to determine the trimers' structure, an aspect of the study Dokholyan described as "an outstanding tour de force" akin to mapping the structure of a ball of yarn after taking snippets of just its outermost layer and then figuring out how they fit together.

Once the trimers' structure was established, the team spent several more years developing methods to test the trimers' effects on motor neuron-

like cells grown in the laboratory. The results were clear: SOD1 proteins that were tightly bound into trimers were lethal to the motor neuron-like cells, while non-clumped SOD1 proteins were not.

The team plans to further investigate the "glue" that holds the trimers together in order to find drugs that could break them apart or keep them from forming.

In addition, these findings could help shed light on other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's.

"There are many similarities among neurodegenerative diseases," said Dokholyan. "What we have found here seems to corroborate what is known about Alzheimer's already, and if we can figure out more about what is going on here, we could potentially open up a framework to be able to understand the roots of other neurodegenerative diseases."

More information: Nonnative SOD1 trimer is toxic to motor neurons in a model of amyotrophic lateral sclerosis, www.pnas.org/cgi/doi/10.1073/pnas.1516725113

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