Suppressing single protein greatly extends life span of mice with form of ALS

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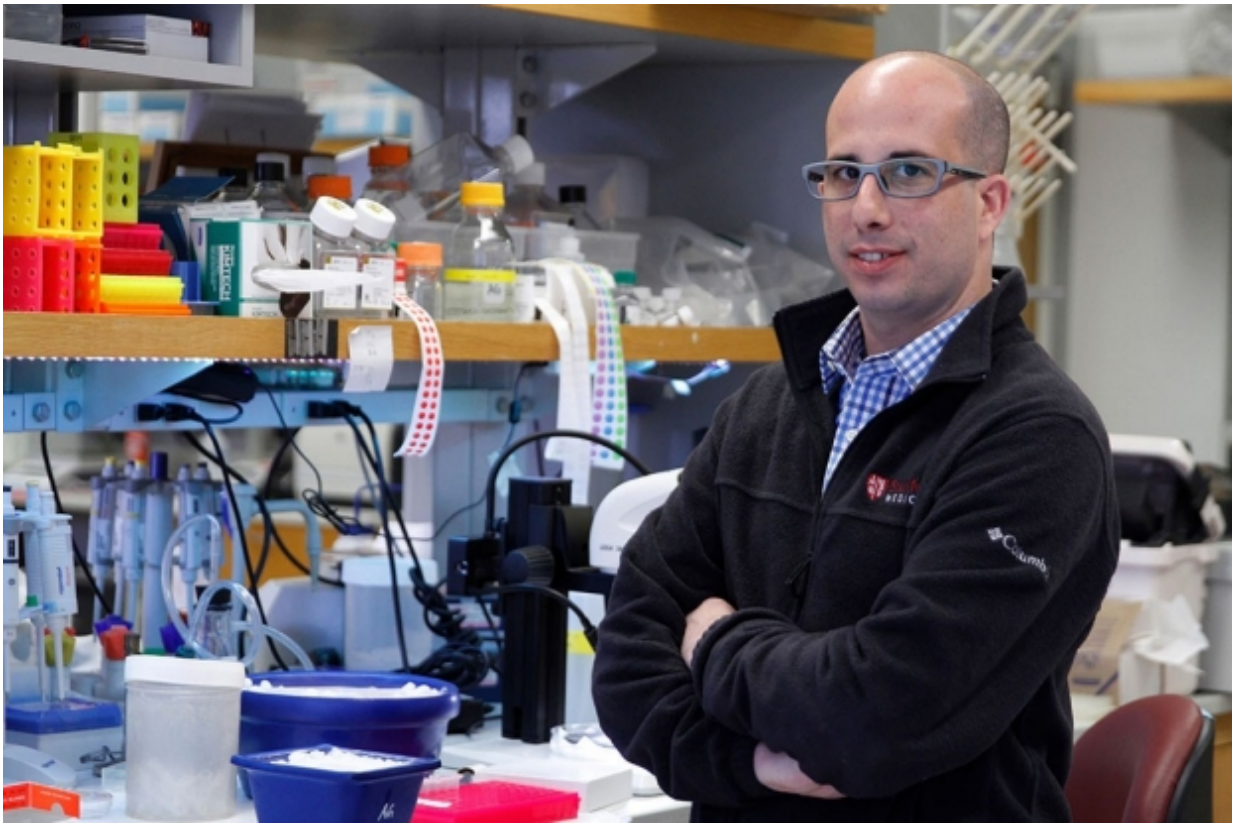

Aaron Gitler and his colleagues found that suppressing a protein in mice with a form of ALS allowed them to live longer and improved their motor function. Credit: Paul Sakuma

A study led by researchers at Stanford University School of Medicine

has revealed a possible new therapeutic approach for amyotrophic lateral sclerosis, a progressive neurodegenerative disease.

The Stanford-led team performed a series of experiments showing that suppressing a certain protein in a mouse model of ALS, or Lou Gehrig's disease, could markedly extend the animal's life span. In one experiment, none of the untreated mice lived longer than 29 days, while some of the treated mice lived over 400 days.

A paper describing the work was published online April 12 in *Nature*. The paper—by senior author Aaron Gitler, PhD, associate professor of genetics, and lead author Lindsay Becker, a graduate student—details a series of experiments that together suggest a possible strategy for treating ALS.

Finding a different approach

ALS is a disease in which the nerve cells in the brain and spinal cord degenerate, leading to wasting of the muscles. Patients gradually lose the ability to move, speak, eat or breathe, often leading to paralysis and death within two to five years. It is associated with environmental risk factors, such as old age and military service. In addition, mutations in certain genes can cause ALS. Exactly how ALS works is still poorly understood, but knowing which genes are involved can point researchers toward processes inside cells that would be good targets for drugs.

One indicator of ALS, as well as other neurodegenerative diseases, is clumps of protein in the brain. In ALS, these clumps, or aggregates, are made up of a protein called TDP-43. Eliminating TDP-43, and therefore the TDP-43 aggregates, might seem like a good way to prevent or cure ALS. But cells need TDP-43 to survive, so suppressing TDP-43 itself is not a good idea.

A different approach was needed. The researchers knew that a second protein, ataxin 2, helped cells survive when TDP-43 formed toxic clumps. Unlike TDP-43, ataxin 2 is not essential for a cell's survival, making it a reasonable therapeutic target, Gitler said.

In a previous study, the Stanford-led team had shown that when ataxin 2 is suppressed or blocked in yeast cultures and fruit flies that carry the human TDP-43 gene, cells are more resistant to the potential toxic effects of the clumping TDP-43 protein.

In still another study, Gitler and his colleagues had shown that versions of the human ataxin 2 gene that resulted in a more stable ataxin 2 protein—and therefore more of the protein—increased the risk for developing ALS. The researchers reasoned that if mutations that increased the amount of ataxin 2 raised the risk of ALS, maybe lowering the amount of ataxin 2 would protect a person from ALS.

Becker used genetically engineered mice whose neurons produced human TDP-43 protein at high levels. These mice exhibit some features that resemble human ALS, including a buildup of clumps of TDP-43 in their neurons. These mice also have difficulty walking and typically have life spans of no more than 30 days.

"We wanted to find out if we could protect these mice from the consequences of TDP-43 by lowering the amount of ataxin 2," said Gitler. Becker genetically engineered these ALS mice to have half the normal amount of ataxin 2, and also engineered other mice to completely lack the protein. She found that with half the ataxin 2, the ALS-like mice survived much longer. "But what was really astounding," said Becker, "was that when we completely removed ataxin 2, there was really an unprecedented survival; some of the mice lived hundreds and hundreds of days."

A preventive that worked in mice

Gitler's team next tried something that could have a more direct therapeutic value: treating mice with a type of DNA-like drug, designed to block the production of ataxin 2. These so called "antisense oligonucleotides" are strands of synthetic DNA that target a gene and block the expression of the protein that it encodes. Delivery of the antisense oligonucleotides to the nervous systems of some of the ALS mice enabled them to maintain their health much longer than the ALS mice treated with a placebo.

A similar antisense oligonucleotide was recently approved for safety trials in pediatric patients with spinal muscular atrophy, and other antisense oligonucleotides have passed safety trials—factors that Gitler said give him hope for a similar strategy for ALS.

Becker said the study showed that suppressing ataxin 2 delayed onset and slowed the progression of the ALS-like disease in mice that were not yet showing symptoms. Whether oligonucleotides or other protein-blocking treatments could reverse symptoms in mice that are already sick is another question. "That's the next set of experiments that we are working on," she said. Because TDP-43 clumping occurs in nearly all ALS cases, targeting ataxin 2 could be a broadly effective therapeutic strategy, she said.

More information: Lindsay A. Becker et al. Therapeutic reduction of ataxin-2 extends lifespan and reduces pathology in TDP-43 mice, *Nature* (2017). DOI: 10.1038/nature22038

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