



Can Vaccination Stop SOD Protein's Toxic Effects?

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Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D.

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What is the best strategy for treating ALS caused by mutations in the SOD1 gene? The answer may be immunization, stimulating the body's own immune system to clear out the damaging protein. That's the strategy being pursued by Janice Robertson, Ph.D., Associate Professor at The University of Toronto, Canada, who explained her research in a recent webinar sponsored by The ALS Association.

"Dr. Robertson has been instrumental in focusing on SOD1 and uncovering important clues to treatment," said Lucie Bruijn, Ph.D., Chief Scientist of The ALS Association, who hosted the webinar. Dr. Robertson thanked The Association for support both early in her career, and currently.

SOD1 was the first gene discovered to cause ALS, and it accounts for about 15% to 20% of all familial cases, or about 2% of all ALS. The gene is the "instruction manual" for making the superoxide dismutase (SOD) protein, one of the most abundant proteins in the brain. Its job is to help detoxify certain byproducts of the brain's activity, called free radicals.

Misfolding is the Key to SOD Protein's Toxic Effects

Like all proteins, the SOD protein is first formed as a long string, and then is carefully folded up into its active shape, which determines its function. When the gene is mutated, the protein no longer folds normally; and therefore, no longer functions normally.

However, SOD1 mutation doesn't appear to cause ALS through loss of the protein's normal function. Instead, the altered protein takes on a new shape and a new, toxic function within the cell.

"Proteins depend on their shape to determine their function," Dr. Robertson said. "The new, misfolded, shape can cause interactions that shouldn't occur. We think this is happening in ALS. These abnormal interactions likely underlie the cause of the disease."

It is still not clear what those new interactions are, and there may be several. But what does seem clear, Dr. Robertson said, is that the mutations that cause ALS all disrupt a key property of the SOD protein molecule, the ability to bind to another SOD protein molecule to make a so-called "homo-dimer." Without that ability, the mutant protein forms aggregates or clumps of protein within the cell. These aggregates may themselves be toxic.

The disruption of the homo-dimer may be the root of the problem, but it may also be the Achilles' heel that makes the protein vulnerable to a therapeutic immunization strategy. To understand why, it is important to know something about how antibodies protect the body

against foreign invaders. Antibodies recognize the shape of foreign proteins, and bind to them. Other parts of the immune system then dispose of the antibody-foreigner combination, preventing harm to the body.

Immunization Against Toxic SOD Helps in the Animal Model

Immunization takes advantage of this natural system. A vaccination is an injection with a foreign protein, which stimulates the immune system to make antibodies against it. Later, when you are exposed to the organism that has that protein (such as a tuberculosis bacterium), the antibodies you made after the vaccination, and the cells that make those antibodies, stand ready to defend you. Vaccination, therefore, allows you to remove a dangerous protein.

Dr. Robertson wants to use this strategy against mutant SOD protein. She has identified a unique feature of the mutant protein, the one feature that distinguishes it from the normal one. When normal SOD proteins link together, they do so along a particular surface of each of the individual proteins, or monomers. This surface is normally hidden between the two proteins, but is exposed when the protein misfolds and remains a monomer.

By using that part of the molecule in the vaccine, she stimulates the immune system to make antibodies specifically against it, without inadvertently making antibodies against the other, normal parts of the SOD protein. This allows any normal SOD protein to remain.

The vaccine strategy, then, is to inject the “SOD exposed dimer interface,” or SEDI, which causes the immune system to make an antibody to it. Working in the ALS mouse model, which creates large amounts of mutant SOD protein, she has obtained promising results. Immunized (vaccinated) animals maintained their motor performance better and for a longer time. Treatment delayed disease onset, and the animals lived longer. Their motor neurons were preserved, and measurements of mutant SOD protein show that it had been reduced, just as expected.

Good versus Bad Immune Responses

Very importantly, she said, the particular type of immune response mounted by the animals was a “TH2,” not a “TH1,” response. The reason this distinction is important, she said, is that TH1 promotes inflammation as part of the response, and inflammation usually causes harm in the central nervous system. A recent immunization trial in Alzheimer’s disease was halted due to the occurrence of TH1 responses, which led to patient deaths. That unfortunate event has made government regulators very cautious about approving other vaccination trials. “We are optimistic in moving forward, but this fear is holding things up at the moment,” Dr. Robertson said.

Currently, she is planning further vaccination trials in the dog model of ALS, to determine if they too will mount a TH2, rather than TH1, response. If so, that would be further evidence that human treatment is likely to be safe.

It is not clear whether the same treatment may be useful in people with ALS who do not carry SOD1 mutations, and whose disease is due to other factors. There is some evidence that even normal SOD may play a toxic role once the disease begins, though Dr. Robertson is not yet convinced this is so. "But it is still worth investigating even if it is only to treat the 2% of patients with the SOD1 mutation," she said. And should the treatment be beneficial in such patients, understanding on the cellular level exactly what changes is likely to benefit all people with ALS.

You can view the presentation in its entirety here:

<https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&rID=65699477&rKey=ef6a6333f5805e21>