

# Researchers clarify protein's role in multiple sclerosis

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A protein found primarily in the lens of the eye could be the critical "tipping point" in the spiral of inflammation and damage that occurs in multiple sclerosis, researchers at the Stanford University School of Medicine report.

This protein - alphaB-crystallin - is not normally found in the brain, but develops in response to the injuries inflicted on nerve cells by multiple sclerosis. The nerve-cell injuries can cause people to suffer loss of motor control and even paralysis.

"The big breakthrough in this paper is answering the question 'What is alphaB-crystallin doing?'" said Lawrence Steinman, MD, professor of neurology and neurological sciences. Steinman and his team demonstrated that the protein plays a protective role in a mouse model of multiple sclerosis - and when injected in mice, it can reverse paralysis. Their findings will be published in the June 13 advance online edition of *Nature*.

In multiple sclerosis, the immune system launches an attack against the myelin sheath surrounding nerve cells, causing them to misfire. According to the Multiple Sclerosis Foundation, up to 500,000 people in the United States have been diagnosed with the condition, which causes varying symptoms depending on the location and extent of the scarring of the myelin sheath. Common symptoms include fatigue, weakness, vertigo, numbness and vision problems.

For reasons not yet understood, the immune system considers the expression of the alphaB-crystallin protein in the brain a danger signal and attacks this healing substance. "Like a runaway truck careening down a mountain and then having the brakes fall off, the immune attack against alphaB-crystallin worsens the situation," said Steinman. And remarkably, he noted, addition of that protein works like restoring the failing brakes, returning control.

If the same recovery is seen in humans, the protein might someday be used to treat multiple sclerosis. "It is a real delight to see that the same material that is naturally produced, that has these protective effects, could potentially be harnessed and used as a therapeutic itself," said Steinman.

The team is optimistic about the protein being used as a therapy, but Steinman and Shalina Ousman, PhD, a postdoctoral researcher in his laboratory and the first author of the publication, emphasized that it is still a long way from being tested in humans.

The recognition of this protein's role in multiple sclerosis began more than a decade ago, when Dutch researcher Johannes Van Noort, PhD, found that the main stimulant of the immune system's attack on the brain was not the presumed culprit of one of the parts of myelin, but alphaB-crystallin, the major structural protein of the lens of the eye.

"For some reason, the protein gets turned on in the brain where it's not expected to be," said Steinman, who wrote an editorial about Van Noort's finding in 1995 when it was published in *Nature*. Since then, Steinman and others in the field wondered what it means that a protein normally found in the lens of the eye suddenly appears in the brain. In 2001, Steinman published work in *Science* cataloging the proteins most abundant in multiple sclerosis, and found that alphaB-crystallin ranked first.

This finding led him and his colleagues to perform a series of experiments on the mouse model of multiple sclerosis-experimental autoimmune encephalomyelitis. They showed in a variety of ways how alphaB-crystallin in mice decreases inflammation and reduces other pathological conditions associated with multiple sclerosis, such as cell death. Also, they demonstrated that the removal of the protein increased the neurological symptoms in the mice.

"We have to remember that repair mechanisms normally exist in response to injury and stress," said Ousman. "In some cases however, those repair mechanisms fail to overcome the injurious responses. It is important to ask why these mechanisms fail and could their protective function be restored."

When they gave injections of the protein to mice that had the mouse equivalent of M.S., their paralysis was reversed. The protein restored order by suppressing the cellular processes causing the damage, explained Ousman. Steinman speculated that the mechanism is tolerization - similar to the process used in allergy shots, when a person with an allergy gets an injection of the protein that is causing problems for the body, so it can learn to ignore it.

Once the researchers had a grasp of what was occurring in mice, they turned to humans. Using a collection of spinal fluid samples from a collaborator at Harvard Medical School, Steinman's team tested them on their antibody arrays. The arrays - developed with Stanford colleagues William Robinson, MD, PhD, assistant professor of medicine, and P.J. Utz, MD, associate professor of medicine - are glass slides spotted with minute amounts of hundreds of myelin sheath proteins to provide a profile of the antibodies' targets.

They found that in humans, too, the highest antibody response was directed against alphaB-crystallin, leading the researchers to speculate

that the protein could possibly reverse the damage in humans as it does in mice. "I am going to strenuously work to bring this from our benches to the bedside," said Steinman, "either through collaborations with existing companies, or we will start a new one."

Source: Stanford University

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