Mutant Protein in Muscle Linked to Neuromuscular Disorder

A new therapeutic target for Kennedy's disease and a potential treatment

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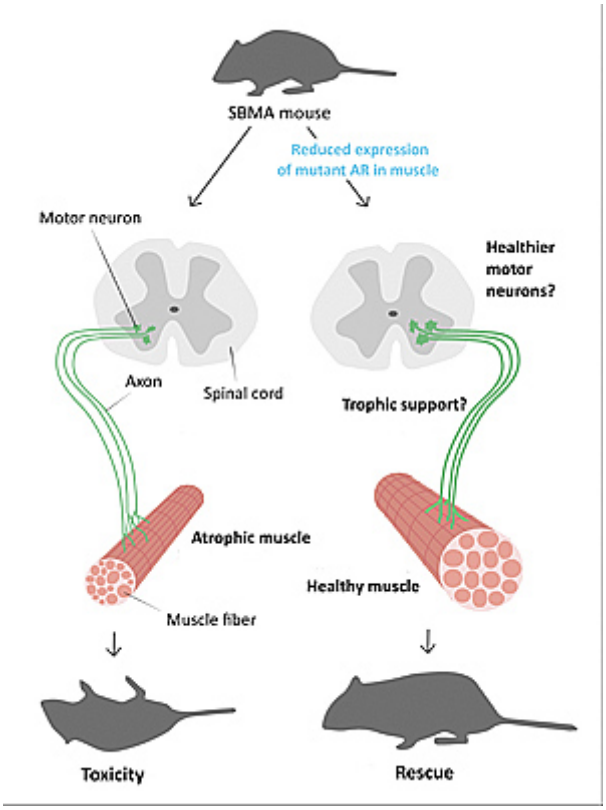
Sometimes known as Kennedy's disease, spinal and bulbar muscular atrophy (SBMA) is a rare inherited neuromuscular disorder characterized by slowly progressive muscle weakness and atrophy. Researchers have long considered it to be essentially an affliction of primary motor neurons – the cells in the spinal cord and brainstem that control muscle movement.

But in a new study published in the April 16, 2014 online issue of *Neuron*, a team of scientists at the University of California, San Diego School of Medicine say novel mouse studies indicate that mutant protein levels in muscle cells, not motor neurons, are fundamentally involved in SBMA, suggesting an alternative and promising new avenue of treatment for a condition that is currently incurable.



SBMA is an X-linked recessive disease that affects only males, though females carrying the defective gene have a 50:50 chance of passing it along to a son. It belongs to a group of diseases, such as Huntington's disease, in which a C-A-G DNA sequence is repeated too many times, resulting in a protein with too many glutamines (an amino acid), causing the diseased protein to misfold and produce harmful consequences for affected cells. Thus far, human clinical trials of treatments to protect against these repeat toxicities have failed.

In the new paper, a team led by principal investigator Albert La Spada, MD, PhD, professor of pediatrics, cellular and molecular medicine, and neurosciences, and the associate director of the Institute for Genomic Medicine at UC San Diego, propose a different therapeutic target. After creating a new mouse model of SBMA, they discovered that skeletal muscle was the site of mutant protein toxicity and that measures which mitigated the protein's influence in muscle suppressed symptoms of SBMA in treated mice, such as weight loss and progressive weakness, and increased survival.

In a related paper, published in the April 16, 2014 online issue of *Cell Reports*, La Spada and colleagues describe a potential treatment for SBMA. Currently, there is none.

The scientists developed antisense oligonucleotides – sequences of synthesized genetic material – that suppressed androgen receptor (AR) gene expression in peripheral tissues, but not in the central nervous system. Mutations in the AR gene are the cause of SBMA, a discovery that La Spada made more than 20 years ago while a MD-PhD student.

La Spada said that antisense therapy helped mice modeling SBMA to recover lost muscle weight and strength and extended survival.

"The main points of these papers is that we have identified both a genetic cure and a drug cure for SBMA – at least in mice. The goal now is to further develop and refine these ideas so that we can ultimately test them in people," La Spada said.

Co-authors of the *Neuron* paper include Constanza J. Cortes, Taiji Tsunemi, Linda Ly and Edith Lopez, UCSD Department of Pediatrics; Shuo-Chien Ling, Selya Tokunaga and Don W. Cleveland, UCSD Department of Cellular and Molecular Medicine; Ling T. Guo and G. Diane Shelton, UCSD Department of Pathology; Gene Hung and C. Frank Bennett, Isis Pharmaceuticals; and Bryce L. Sopher, University of Washington.

Funding for this study came, in part, from National Institutes of Health grants R01NS041648 and R01NS027036, the Muscular Dystrophy Association, the Ludwig Institute and the National Institute of Aging.

Co-authors of the *Cell Reports* paper include Andrew P. Lieberman and Zhigang Yu, UCSD Department of Pathology; Sue Murray, Raechel Peralta, Audrey Low, Shuling Guo, Xing Xian Yu, C. Frank Bennett, Brett P. Monia and Gene Hung, Isis Pharmaceuticals; and Constanza J. Cortez, UCSD departments of cellular and molecular medicine, neuroscience and pediatrics.

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