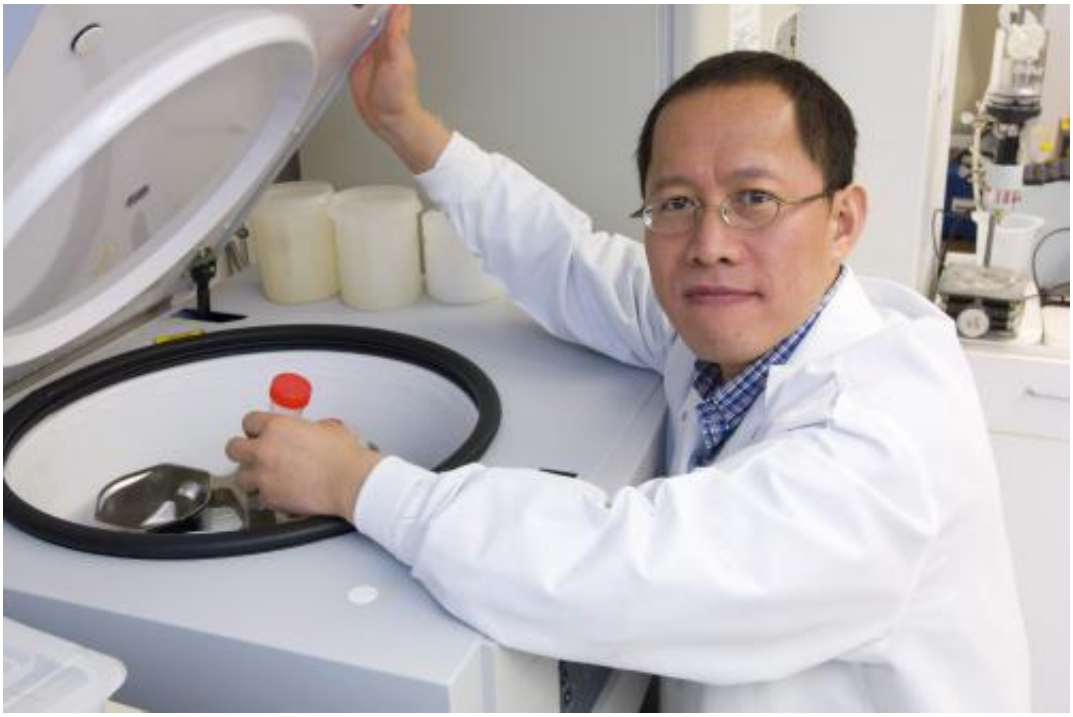
Scientists discover 'needle in a haystack' for muscular dystrophy patients

January 22 2013



MU scientist Dongsheng Duan, Ph.D., and colleagues have identified significant sections of a gene that are essential in helping muscle tissues function. Their findings, described this month in the *Proceedings of the National Academy of Sciences*, could provide hope to young patients with muscular dystrophy. Credit: University of Missouri School of Medicine

(Medical Xpress)—Muscular dystrophy is caused by the largest human gene, a complex chemical leviathan that has confounded scientists for decades. Research conducted at the University of Missouri and

described this month in the *Proceedings of the National Academy of Sciences* has identified significant sections of the gene that could provide hope to young patients and families.

MU scientists Dongsheng Duan, PhD, and Yi Lai, PhD, identified a sequence in the dystrophin gene that is essential for helping muscle tissues function, a breakthrough discovery that could lead to treatments for the deadly hereditary disease. The MU researchers "found the proverbial needle in a haystack," according to Scott Harper, PhD, a muscular dystrophy expert at The Ohio State University who is not involved in the study.

Duchenne muscular dystrophy (DMD), predominantly affecting males, is the most common type of muscular dystrophy. Children with DMD face a future of rapidly weakening muscles, which usually leads to death by respiratory or cardiac failure before their 30th birthday.

Patients with DMD have a gene mutation that disrupts the production of dystrophin, a protein essential for muscle cell survival and function. Absence of dystrophin starts a chain reaction that eventually leads to muscle cell degeneration and death. While dystrophin is vital for muscle development, the protein also needs several "helpers" to maintain the muscle tissue. One of these "helper" molecular compounds is nNOS, which produces nitric oxide that can keep muscle cells healthy during exercise.

"Dystrophin not only helps build muscle cells, it's also a key factor to attracting nNOS to the muscle cell membrane, which is important during exercise," Lai said. "Prior to this discovery, we didn't know how dystrophin made nNOS bind to the cell membrane. What we found was that dystrophin has a special 'claw' that is used to grab nNOS and bring it to the muscle cell membrane. Now that we have that key, we hope to begin the process of developing a therapy for patients."

Duan and Lai, scientists with MU's Department of Molecular Microbiology and Immunology, found that two particular sections of the dystrophin gene must be present for nNOS to bind to the muscle cell membrane. The sections of the gene, known as "repeaters 16 & 17," contain a "claw" that can grab nNOS and bring it to the muscle cell membrane so that it will prevent ischemic damage from muscle activity. Without this "claw," nNOS doesn't bind to the cell membrane and the muscle cells are damaged, leading to further problems associated with muscular dystrophy.

The other key to this puzzle is dystrophin. If the protein is not present in the body, no "claw" exists and nNOS would never make it to the muscle cell membrane. For years, scientists have been attempting to find ways to make the body manufacture dystrophin, and thus get nNOS to the muscle cell membrane. Duan and Lai said the answer might lie elsewhere.

"Everybody, including those individuals with muscular dystrophy, has another protein known as 'utrophin,' " said Duan, a Margaret Proctor Mulligan Distinguished Professor in Medical Research at MU. "Utrophin is nearly identical to dystrophin except that it is missing repeaters 16 & 17, so it cannot attract nNOS to the muscle cell membrane. In our study, we were able to modify utrophin so that it had the repeaters, and thus, the ability to grab nNOS and bring it to the muscle cell membrane to protect muscle. Our study was completed in mice, but if we can do the same thing in larger animals, we could eventually have a therapy for humans with this devastating disease."

Harper described the MU research as "as an exquisite example of a basic study with potentially important translational implications for therapy of Duchenne muscular dystrophy. … The data from the Duan laboratory, reported in this paper and previous studies, demonstrates that the structural elements required for proper nNOS localization should be

included in any DMD therapy for which dystrophin restoration is the goal."

For more than 10 years, Duan has been a leader in muscular dystrophy, gene therapy and biology research at MU. In addition to his recently published study in PNAS, Duan's lab continues to examine the basic scientific mechanisms behind muscular dystrophy as well as strategies for treating the disease. For example, his lab is studying the effectiveness of a gene therapy for treating heart failure associated with Duchenne muscular dystrophy.

Using viruses as a means for delivering gene therapy, Duan is also testing how synthetic microgenes could improve muscle function in dystrophic dog and mouse models. In 2011, he and Lai were granted a patent for a synthetic microgene developed in his lab that has now proved to enhance muscle function in dogs. Those results were also published this month in the journal *Molecular Therapy*.

More information: www.pnas.org/content/110/2/387.full

Provided by University of Missouri School of Medicine