Another muscular dystrophy mystery solved; MU scientists inch closer to a therapy for patients

7 December 2012

Approximately 250,000 people in the United States suffer from muscular dystrophy, which occurs when damaged muscle tissue is replaced with fibrous, bony or fatty tissue and loses function. Three years ago, University of Missouri scientists found a molecular compound that is vital to curing the disease, but they didn't know how to make the compound bind to the muscle cells. In a new study, published in the *Proceedings of the National Academies of Science*, MU School of Medicine scientists Yi Lai and Dongsheng Duan have discovered the missing pieces to this puzzle that could ultimately lead to a therapy and, potentially, a longer lifespan for patients suffering from the disease.

Duchenne muscular dystrophy (DMD), predominantly affecting males, is the most common type of muscular dystrophy. Patients with Duchenne muscular dystrophy 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 after exercise.

"Dystrophin not only helps build muscle cells, it's also a key factor to attracting nNOS to the muscles cells and helping nNOS bind to the cell and help repair it following activity," said Lai, a research assistant professor in the Department of Molecular Microbiology and Immunology. "Prior to this discovery, we didn't know how dystrophin made nNOS bind to the cells. What we found was that dystrophin has a special 'claw' that is used to grab nNOS and bring it close to the muscle cell. Now that we have that key, we hope to begin the process of developing a therapy for patients."

In their study, Lai and Duan found that two particular sections of the dystrophin gene must be present for nNOS to bind to the muscle cells. The sections of the gene, known as "repeaters 16 & 17," contain a "claw" that can grab nNOS and bring it to the muscle cells so that it will bind and repair any damage from regular use. Without this "claw," nNOS doesn't bind to the cells and the damage is not repaired, 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 cells. For years, scientists have been attempting to find ways to make the body manufacture more dystrophin, and thus get more nNOS to the muscle cells. 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 professor of molecular microbiology and immunology. "Utrophin is nearly identical to dystrophin except that it is missing repeaters 16 & 17, so it cannot attract nNOS to the muscle cells. 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 cells for repair. Our study was completed in mice; if we can do the same thing in larger animals, we could eventually have a significant therapy for humans with this devastating disease."

Provided by University of Missouri-Columbia