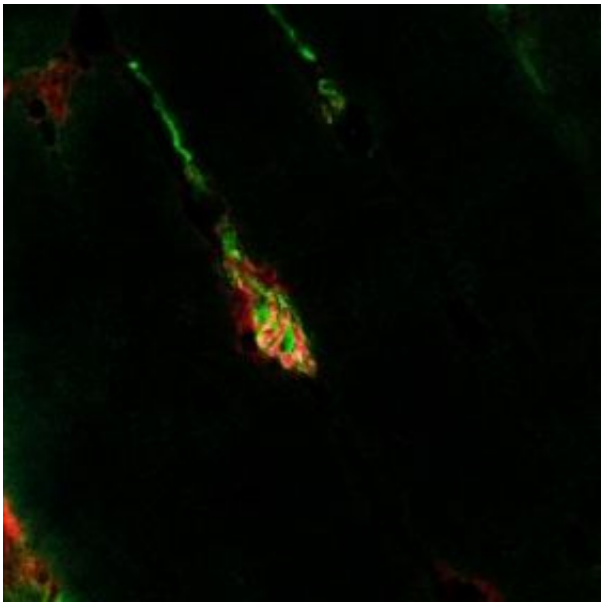
Penn researchers find a new target for muscular dystrophy drug therapy

July 12 2007



Expression of utrophin (green) at the synapse of normal skeletal muscles and nerves (red). Credit: Santhosh M. Baby, PhD; Tejvir S. Khurana, MD, PhD, University of Pennsylvania School of Medicine

Researchers at the University of Pennsylvania School of Medicine report how the gene for utrophin, which codes for a protein very similar to dystrophin, the defective protein in Duchenne muscular dystrophy (DMD), puts the brakes on its own expression in muscle cells, thereby suggesting a new target for treatment. The findings were published online in *Molecular Biology Cell*, in advance of print publication.

The production of utrophin slows in fetal muscles soon after birth, after which dystrophin takes over as the primary muscle-associated protein. How this normal utrophin silencing occurs has been a mystery, until now. If the brakes on utrophin production could be removed by drug intervention, then increased utrophin expression could substitute for dystrophin as a possible therapy for DMD, which affects 1 in 3,500 males.

Utrophin is normally made at the junction where nerves meet muscles, an area called the neuromuscular junction or synapse. In the present study, the Penn team discovered that silencing is applied by a protein called Ets-2 repressor factor (ERF) sitting on a small piece of the utrophin gene called the N-box.

“We demonstrated that ERF significantly reduces or represses the activity of utrophin’s N-box in muscle cells of mice,” says senior author Tejvir S. Khurana, MD, PhD, Associate Professor of Physiology and Member of the Pennsylvania Muscle Institute. When the N-box was deleted from the utrophin gene, ERF had no effect on silencing the utrophin gene, as measured by an increase in utrophin gene-promoter activity. In another experiment in which ERF was repressed, the researchers found utrophin mRNA production increased.

“This approach of ‘repressing the repressor’ is medically relevant to treating muscular dystrophy in that we hope to one day be able to upregulate utrophin production,” explains Khurana.

Because utrophin is over 80 percent identical to dystrophin in its gene sequence, utrophin could substitute for it in muscle cells. In normal muscle cells dystrophin is part of a large complex of proteins that attaches muscle cells to surrounding tissues. In DMD muscle cells, dystrophin cannot perform this function and the muscles slowly fall apart. DMD patients begin to have muscle weakness and motor

difficulties as children, and the condition worsens with age, eventually proving fatal around the third decade of life.

“Dr. Khurana's work hints at what could be an important new drug target for DMD–the more options we have with this disease, the better,” says Sharon Hesterlee, PhD, Vice President for Translational Research at the Muscular Dystrophy Association. “We've known for a while that increasing utrophin expression can reduce symptoms of the disease, but it's very difficult to use a drug to increase gene activity. What's nice about this work is that now we can try to ‘block a blocker’ to get the same effect–it's a more drug-friendly approach.”

Other therapeutic strategies for DMD involve muscle-cell implantation, stem-cell treatment, and gene therapy. While there has been some progress with these approaches, there have been many difficulties with graft vs. host rejection and gene delivery. This new research suggests that blocking ERF, either with drugs or by interfering with its RNA, may be more generally feasible in most DMD patients.

There are several animal models of DMD, most notably the mdx mouse. Khurana and his colleagues are currently investigating whether repressing ERF in mdx mouse muscle reduces muscle deterioration.

“We have worked on this problem for a number of years, and our current findings are a logical incremental step in understanding how utrophin could become an effective tool for treating DMD,” states Khurana. He cautions that while he hopes his work will lead to an effective treatment someday, there are many steps and hurdles to get through first.

Source: University of Pennsylvania School of Medicine