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Aberrant splicing saps the strength of 'slow' muscle fibers

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When you sprint, the "fast" muscle fibers give you that winning kick. In a marathon or just day-to-day activity, however, the "slow," or type 1 fibers, keep you going for hours.

In people with myotonic dystrophy, the second most common form of muscular dystrophy and the one most likely to occur in adults, these slow or type 1 fibers do not work well, wasting away as the genetic disorder takes its grim toll. In a report that appears online in the *Proceedings of the National Academy of Sciences*, Dr. Thomas A. Cooper, professor of pathology & immunology at Baylor College of Medicine, and Dr. Zhihua Gao, a postdoctoral associate at BCM, showed how an aberrant alternative splicing program changes the form of an enzyme (pyruvate kinase of PKM) involved in the fundamental metabolism of these muscle cells, leaving them unable to sustain exercise. The enzyme reverts to the embryonic form (PKM2), which changes its activity in the cell.

Alternative splicing is one of the secrets as to how the estimated 25,000 human genes code for the 100,000 or more proteins important to the functioning of the human body. For one gene to make different proteins, it has to alter the genetic message, choosing which coding parts of the gene called exons are included in the protein "recipe" used by the cell's protein-making machinery.

"In the case of PKM2, this enzyme represents a shift back to the fetal splicing pattern," said Cooper. "What was striking was that if you look at the histology (the tissues seen at a microscopic level) of the skeletal

muscle, only the slow fiber types – the ones affected in myotonic dystrophy – have this splicing event switch." The slow fibers are those most affected in myotonic dystrophy.

"We don't know what it is doing to the metabolism, but it seems to be pushing it in the opposite direction from what slow fibers do," said Cooper. "This is related to the loss of slow fibers in myotonic dystrophy."

To figure out how this happens, Cooper and his colleagues used antisense oligonucleotides (snippets of genetic material designed to target specific areas of a gene) to bind to the precursor RNA (genetic material that carries the code for a protein) for PKM, and thus force it in the other direction – to the embryonic form.

"Doing this, we showed there could be a change in metabolism in myotonic dystrophy and we showed it in the whole animal," said Cooper.

Myotonic dystrophy occurs when the nucleotides CTG (cytosine, thymine, guanine) repeat an abnormal number of times. When the CTG in the DNA is transcribed into CUG in RNA, the resulting aberrant protein is toxic and disrupts the activity of RNA factors (MBNL1 AND CELF1), which are two RNA splicing factors. The resultant splicing changes somehow drive the skeletal and heart muscle wasting seen in the disease.

"To my knowledge, this is the first time anyone has looked at this alternative splicing event and associated it with a disease other than cancer," said Cooper. "The muscle wasting in this disease could be due to an imbalance of metabolism."

More information: Reexpression of pyruvate kinase M2 in type 1 myofibers correlates with altered glucose metabolism in myotonic

dystrophy, www.pnas.org/cgi/doi/10.1073/pnas.1308806110