Role of gene regulator in skeletal muscles demonstrated

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Fast muscles, such as the thigh muscle in a sprinter, deliver energy quickly but fatigue quickly. Slow muscles, such as the soleus muscle in the lower calf, are less forceful but important for posture and endurance. Researchers from the University of Texas Southwestern Medical Center and Virginia Tech have discovered one gene regulator that maintains the fast muscle type and inhibits the development of a slow muscle type.

The research was posted in the Proceedings of the National Academy of Sciences' online early edition on June 1 in the article, "Concerted regulation of myofiber-specific gene expression and muscle performance by the transcriptional repressor Sox6," by Daniel Quiat of UT Southwestern, Kevin Voelker of Virginia Tech, Jimin Pei and Nick V. Grishin of UT Southwestern, Robert Grange of Virginia Tech, and Rhonda Bassel-Duby and Eric N. Olson of UT Southwestern.

"Based on previous studies by our group and others, we knew that a gene regulator called Sox6 promotes development of fast muscle in the embryo," said Olson, professor of molecular biology. "But the function of Sox6 in adult muscle was unknown."

By studying adult mice that lacked Sox6 in fast muscles, the researchers observed that fast muscle took on the performance attributes of slow muscles.

Virginia Tech's role in the research project was to measure muscle performance. "We demonstrated experimentally that there were

functional changes that supported the development of slow muscle," said Grange, associate professor of human nutrition, food, and exercise in the College of Agriculture and Life Sciences. At Virginia Tech, he worked with Voelker, a postdoctoral associate in the department.

"The most obvious change is the speed at which muscle can shorten," said Grange. "Fast muscle shortens quickly; but, in the absence of Sox6, our measurements showed that fast muscle shortened more slowly and the muscle was less fatigued after contracting for several minutes. Both of these muscle performance changes demonstrated that a fast muscle that lacked Sox6 became more like a slow muscle."

"Skeletal muscles can adapt based on the stress imposed," explains Grange. "For example, if you lift weights, your muscles become stronger; if you run long distances, your muscles become less fatigued. What we don't yet know fully is how adaptations occur at the gene level and protein level in response to these different stresses. The current study is an important step to understand how muscle adaptation occurs."

Although applications of the new information are distant, Grange points out, "The more you know about how the body works, the easier it is to keep it healthy."

"We might be able to manipulate gene regulators by training in a certain way. We don't know what that is, but that is one of the objectives. From a muscle disease perspective, there may be characteristics that lead back to the proteins that control adaptations, such as Sox6," said Grange.

"You cannot have adaptations in the muscle unless there are changes in the genes turned on and those turned off. The genes turned on produce the proteins responsible for the muscle adaptation" he said. "The most exciting aspect of the study was that we clearly demonstrated changes in muscle function from a fast type to a slow type of skeletal muscle that

was dependent on the absence of Sox6."

More information: Concerted regulation of myofiber-specific gene expression and muscle performance by the transcriptional repressor Sox6, *PNAS*, Published online before print June 1, 2011, doi: 10.1073/pnas.1107413108

Abstract
In response to physiological stimuli, skeletal muscle alters its myofiber composition to significantly affect muscle performance and metabolism. This process requires concerted regulation of myofiber-specific isoforms of sarcomeric and calcium regulatory proteins that couple action potentials to the generation of contractile force. Here, we identify Sox6 as a fast myofiber-enriched repressor of slow muscle gene expression in vivo. Mice lacking Sox6 specifically in skeletal muscle have an increased number of slow myofibers, elevated mitochondrial activity, and exhibit down-regulation of the fast myofiber gene program, resulting in enhanced muscular endurance. In addition, microarray profiling of Sox6 knockout muscle revealed extensive muscle fiber-type remodeling, and identified numerous genes that display distinctive fiber-type enrichment. Sox6 directly represses the transcription of slow myofiber-enriched genes by binding to conserved cis-regulatory elements. These results identify Sox6 as a robust regulator of muscle contractile phenotype and metabolism, and elucidate a mechanism by which functionally related muscle fiber-type specific gene isoforms are collectively controlled.

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