Lift weights to lower blood sugar? White muscle helps keep blood glucose levels under control

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Researchers in the Life Sciences Institute at the University of Michigan have challenged a long-held belief that whitening of skeletal muscle in diabetes is harmful.

In fact, the white muscle that increases with resistance training, age and diabetes helps keep blood sugar in check, the researchers showed.

In addition, the insights from the molecular pathways involved in this phenomenon and identified in the study may point the way to potential drug targets for obesity and metabolic disease.

"We wanted to figure out the relationship between muscle types and body metabolism, how the muscles were made, and also what kind of influence they have on diseases like type 2 diabetes," said Jiandie Lin, Life Sciences Institute faculty member and associate professor at the U-M Medical School.

Lin's findings are scheduled to be published online April 7 in *Nature Medicine*.

Much like poultry has light and dark meat, mammals have a range of muscles: red, white and those in between. Red muscle, which gets its color in part from mitochondria, prevails in people who engage in endurance training, such as marathon runners. White muscle dominates

in the bodies of weightlifters and sprinters—people who require short, intense bursts of energy.

"Most people are in the middle and have a mix of red and white," Lin said.

When you exercise, nerves signal your muscles to contract, and the muscle needs energy. In response to a signal to lift a heavy weight, white muscles use glycogen to generate adenosine triphosphate (ATP)—energy the cells can use to complete the task. While this process, called glycolysis, can produce a lot of power for a short time, the glycogen fuel soon depletes.

However, if the brain tells the muscle to run a slow and steady long-distance race, the mitochondria in red muscles primarily use fat oxidation instead of glycogen breakdown to generate ATP. The supply of energy lasts much longer but doesn't provide the burst of strength that comes from glycolysis.

People with diabetes see whitening of the mix of muscle.

"For a long time, the red-to-white shift was thought to make muscle less responsive to insulin, a hormone that lowers blood sugar," Lin said. "But this idea is far from proven. You lose red muscle when you age or develop diabetes, but is that really the culprit?"

To find out, the team set out to find a protein that drives the formation of white muscle. They sifted through microarray data sets from public databases and identified a list of candidate proteins that were prevalent in white muscle but not in red.

Further studies led the team to focus on a protein called BAF60c, a sort of "zip code" mechanism that tells the cells when and how to express

certain genes. The Lin team made a transgenic mouse model to increase BAF60c only in the skeletal muscle. One of the first things they noticed was that mice with more BAF60c had muscles that looked paler.

"That was a good hint that we were going in the white-muscle direction," said lead author Zhuo-xian Meng, a research fellow in Lin's lab.

They used electron microscopy to see the abundance of mitochondria within the muscle, and confirmed that muscle from BAF60c transgenic mice had less mitochondria than the normal controls.

"We saw predicted changes in molecular markers, but the ultimate test would be seeing how the mouse could run," Lin said.

If the BAF60c mice could run powerfully for short distances but tired quickly, the scientists would be able to confirm that the BAF60c pathway was a key part of the creation of white muscle.

Using mouse treadmills, they compared the endurance of BAF60c mice to a control group of normal mice, and found that the BAF60c transgenic mice could only run about 60 percent of the time that the control group could before tiring.

"White muscle uses glycogen, and the transgenic mice depleted their muscles' supplies of glycogen very quickly," Lin said.

After some follow-up experiments to figure out exactly which molecules were controlled by BAF60c, Lin and his team were confident that they had identified major players responsible for promoting white muscle formation. Now that they knew how to make more white muscle in animals, they wanted to determine whether white muscle was a deleterious or an adaptive characteristic of diabetes.

The team induced obesity in mice by feeding them the "Super Size Me" diet, Lin said. On a high-fat diet, a mouse will double its body weight in two to three months. They found that obese mice with BAF60c transgene were much better at controlling blood glucose.

"The results are a bit of a surprise to many people," Lin said. "It really points to the complexity in thinking about muscle metabolism and diabetes."

In humans, resistance training promotes the growth of white muscle and helps in lowering blood glucose. If future studies in humans determine that the BAF60c pathway is indeed the way in which cells form white muscle and in turn optimize metabolic function, the finding could lead to researching the pathway as a drug target.

"We know that this molecular pathway also works in human cells. The real challenge is to find a way to target these factors," Lin said.

Provided by University of Michigan

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