Medical Xpress

Scientists discover cause of and potential treatment for muscle weakness and loss due to aging

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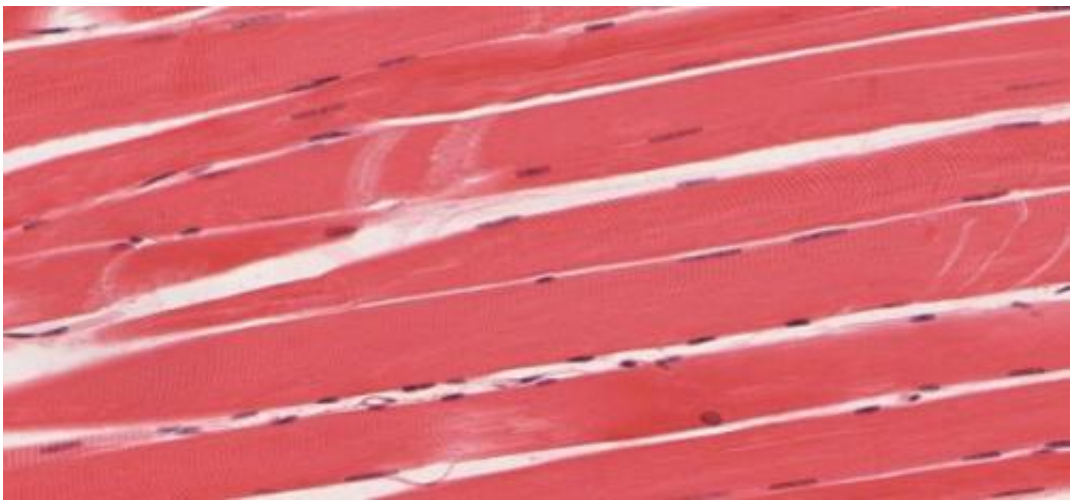

Skeletal muscle tissue. Credit: University of Michigan Medical School

As we grow older, we lose strength and muscle mass. However, the cause of age-related muscle weakness and atrophy has remained a mystery.

Scientists at the University of Iowa have discovered the first example of a protein that causes muscle weakness and loss during aging. The protein, ATF4, is a transcription factor that alters gene expression in skeletal muscle, causing reduction of muscle protein synthesis, strength, and mass. The UI study also identifies two natural compounds, one found in apples and one found in green tomatoes, which reduce ATF4

activity in aged skeletal muscle. The findings, which were published online Sept. 3 in the *Journal of Biological Chemistry*, could lead to new therapies for age-related muscle weakness and atrophy.

"Many of us know from our own experiences that muscle weakness and atrophy are big problems as we become older," says Christopher Adams, MD, PhD, UI professor of internal medicine and senior study author. "These problems have a major impact on our quality of life and health."

Previously, Adams and his team had identified ursolic acid, which is found in apple peel, and tomatidine, which comes from green tomatoes, as small molecules that can prevent acute muscle wasting caused by starvation and inactivity. Those studies set the stage for testing whether ursolic acid and tomatidine might be effective in blocking the largest cause of muscle weakness and atrophy: aging.

In their latest study, Adams' team found that ursolic acid and tomatidine dramatically reduce age-related muscle weakness and atrophy in mice. Elderly mice with age-related muscle weakness and atrophy were fed diets lacking or containing either 0.27 percent ursolic acid, or 0.05 percent tomatidine for two months. The scientists found that both compounds increased muscle mass by 10 percent, and more importantly, increased muscle quality, or strength, by 30 percent. The sizes of these effects suggest that the compounds largely restored muscle mass and strength to young adult levels.

"Based on these results, ursolic acid and tomatidine appear to have a lot of potential as tools for dealing with muscle weakness and atrophy during aging," Adams says. "We also thought we might be able to use ursolic acid and tomatidine as tools to find a root cause of muscle weakness and atrophy during aging."

Adams' team investigated the molecular effects of ursolic acid and

tomatidine in aged skeletal muscle. They found that both compounds turn off a group of genes that are turned on by the transcription factor ATF4. This led them to engineer and study a new strain of mice that lack ATF4 in skeletal muscle. Like old muscles that were treated with ursolic acid and tomatidine, old muscles lacking ATF4 were resistant to the effects of aging.

"By reducing ATF4 activity, ursolic acid and tomatidine allow skeletal muscle to recover from effects of aging," says Adams, who also is a member of the Fraternal Order of Eagles Diabetes Research Center at the UI and a staff physician with the Iowa City Veterans Affairs Medical Center.

The UI study was done in collaboration with Emmyon, Inc., a UI-based biotechnology company founded by Adams, that is now working to translate ursolic acid and tomatidine into foods, supplements, and pharmaceuticals that can help preserve or recover strength and muscle mass as people grow older.

More information: *Journal of Biological Chemistry*, www.jbc.org/content/early/2015 … 9/03/jbc.M115.681445

Provided by University of Iowa