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Loss of antioxidant protein Nrf2 represses regeneration of muscle lost to aging

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Good news for lifelong exercisers: Along with its salutary effects on the heart, weight, and other facets of health, physical activity also helps to regenerate muscle mass, which tends to diminish as people age.

In a study published in the journal *Free Radical Biology and Medicine*, researchers from the University of Utah and other institutions found that aged mice lacking Nrf2 that underwent two weeks of endurance exercise stress on treadmills showed poor stem cell regeneration, which is likely to hinder the recovery of lost muscle mass. Nrf2 is protein that regulates the production of antioxidants in the body.

"Physical activity is the key to everything," says Raj Soorappan, Ph.D., assistant research professor of medicine at the University of Utah and senior author on the study. "After this study, we believe that moderate exercise could be one of the key ways to induce stem cells to regenerate especially during senescence."

Sarcopenia – age-related loss of skeletal muscle mass – occurs naturally and begins in most people around age 30. Fortunately, to help stem this tide, the body produces antioxidants, which are molecules that help maintain muscle mass through the regeneration of stem cells that become muscle cells.

For reasons not yet entirely known, as people age, their bodies produce fewer antioxidants. This can result in oxidative stress, a condition in which the level of molecules called free radicals – rogue electrons that

travel through the body triggering chemical reactions that damage proteins and cells – exceeds that of antioxidants. When this happens, stem cell regeneration and, consequently, formation of muscle cells doesn't keep up with muscle mass loss.

Nrf2 is a protein and transcription factor that turns on and off the genes that produce antioxidants. To test the role of Nrf2 in regeneration of skeletal muscle during aging, Soorappan tested two groups of mice that were 23 months or older – the murine equivalent of senior citizens. In one group of mice the gene that codes for Nrf2 had been knocked out while the other group of mice was able to produce the protein. Each group underwent endurance training to create a profound oxidative stress setting.

Typically, regeneration, maintenance and repair of adult skeletal muscle damage due to aging and/or chronic stress states require activation of satellite cells (stem cells). In the group that couldn't produce Nrf2, endurance exercise stress on the treadmills affected stem cell protein expression and limited skeletal muscle regenerative capacity.

"Now we know that the antioxidant protein Nrf2 guards the muscle regeneration process in the elderly mice and loss of Nrf2, when combined with endurance exercise stress, can cause severe muscle stem cell impairment," said Madhusudhanan Narasimhan, Ph.D., a U of U senior research associate and the study's first author.

Understanding Nfr2's role on muscle regeneration is essential to optimize effective strategies for muscle repair during aging, Soorappan said.

Going forward, Soorappan plans to continue his studies to see whether spontaneous exercise (active lifestyle) favors stem cells and muscle regeneration. But he's also looking into studies to see whether exercise

affects Nfr2 activation in people.

Although the results of this study haven't been replicated in people yet, Soorappan believes there's a clear message for couch potatoes: "If you don't use your muscles, you will lose them. At the same time, overdoing endurance training may detract from muscle regeneration," he cautions.

More information: The study appeared Thursday, March 6, 2014, in *Free Radical Biology and Medicine* online.

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