

Mitochondria may metabolize ADP differently in aging muscle, despite exercise resistance

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Mitochondria. Credit: Wikipedia commons

Most adults reach their peak levels of muscle mass in their late 30s or early 40s. Even for those who exercise regularly, strength and function start to decline after that point. For those who don't exercise, the drops



can be dramatic. Now, a study of twenty men published March 13 in the journal *Cell Reports* provides new clues about the cellular mechanisms of aging muscles, showing a key role for how mitochondria, the powerhouses of the cell, process ADP, which provides energy to cells.

ADP, or adenosine diphosphate, plays a role in how our cells release and store energy. But previous lab models that have looked at the mechanisms of aging in human <u>cells</u> have not included ADP. When ADP is metabolized in the mitochondria, it stimulates cellular respiration and decreases reactive oxidative species (ROS; also known as free radicals). Higher ROS levels are linked to damage in different components of the cell, a process also called oxidative stress.

In the study, the investigators developed an in vitro system employing individual muscle fibers taken from muscle biopsies. The fibers were put into a system in which mitochondrial function and respiration could be measured across a range of ADP concentrations that are relevant to those found in the human body. "The way people normally measure ROS is in a system that has ADP removed," says senior author Graham Holloway, an associate professor at the University of Guelph in Ontario. "But biologically, we always have ADP in the system. We started to think that maybe how we get ADP into the mitochondria is important for aging."

In the first part of the paper, the researchers compared muscle from ten healthy men in their 20s with muscle from ten healthy men in their early 70s. They found that there was an 8- to 10-fold decrease in ADP sensitivity, and therefore, when ADP was added to the system, there was a 2- to 3-fold higher rate of ROS emission in the muscle taken from the <u>older men</u>. ROS levels were determined by measuring emissions of hydrogen peroxide, a byproduct of activity in the cell.

The findings suggested that mitochondrial ADP sensitivity was somehow impaired in the muscles of the older men and that increased levels of



ROS were contributing to sarcopenia, or the degenerative loss of <u>muscle</u> <u>mass</u>. "The magnitude of change was quite striking to us," Holloway explains. "For humans, it's remarkable to have such a big difference."

In the second part, the older men undertook a program of supervised resistance training, which included leg presses and upper-body exercises. But, after 12 weeks, there were no changes in the levels of <u>hydrogen</u> <u>peroxide</u> emitted, suggesting no improvements in age-associated cellular stress.

"This doesn't mean there's no hope for building strength in aging <u>muscle</u>," Holloway says. "I actually think that endurance training would be potentially beneficial, because we know with that kind of training you get increases in mitochondrial content." Endurance training includes aerobic exercise like cycling and swimming. "Moving forward, we plan to look at other types of exercise, to see if it can improve the dynamic response of mitochondria to ADP," he adds.

Other future work will use rodent models to delve into the cause-andeffect relationships of the molecular mechanisms of ADP metabolism. The investigators also plan to extend their studies to looking at different types of exercise in aging women. Early research in healthy young people has indicated that there are differences in sensitivity to ADP between men and women.

More information: *Cell Reports*, Holloway et al. "Age-associated impairments in mitochondrial ADP sensitivity contribute to redox stress in senescent human skeletal muscle." <u>www.cell.com/cell-reports/full ...</u> <u>2211-1247(18)30264-X</u>, <u>DOI: 10.1016/j.celrep.2018.02.069</u>

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