Clearing a path for non-invasive muscle therapy for the elderly

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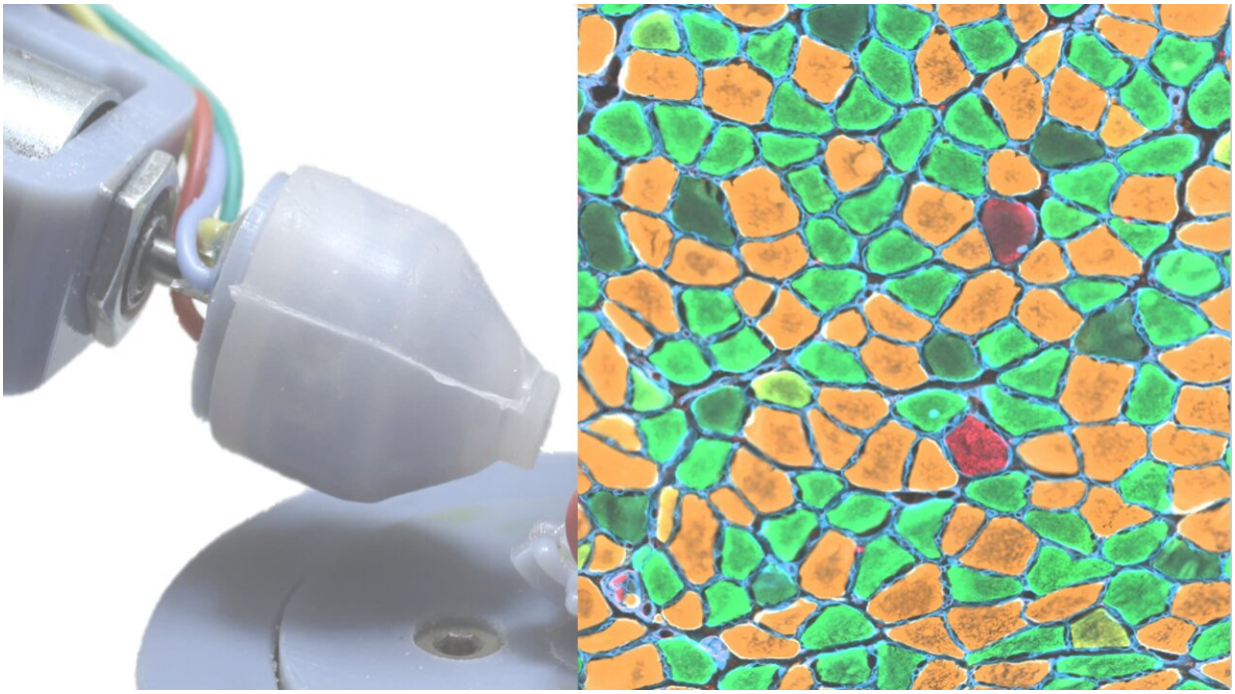

Uncovering age-dependent differences in how injured muscle responds to Mechanotherapy using force feedback-controlled robotics. Credit: Seth Kroll and Stephanie McNamara

Mechanotherapy, the concept of using mechanical forces to stimulate tissue healing, has been used for decades as a form of physical therapy to help heal injured muscles. However, the biological basis and optimal settings for mechanotherapies are still poorly understood, especially with

respect to elderly patients. Given the well-known decline in healing ability that occurs with age, elderly patients stand to benefit greatly from an effective, non-invasive musculoskeletal treatment approach.

A new multidisciplinary study helps close this knowledge gap of mechanotherapies' effectiveness in aged muscle. The study was performed by researchers at the Wyss Institute for Biologically Inspired Engineering and the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS) led by Wyss Core Faculty member David Mooney, Ph.D. in collaboration with Associate Faculty member and Paul A. Maeder Professor of Engineering and Applied Sciences, Conor Walsh, Ph.D.

In previous work, the collaborators used Walsh's Lab's expertise in wearable robotic systems to develop a robotic mechanotherapy device that functions like a highly advanced massage gun. This technology enabled precise delivery of non-invasive mechanotherapy to injured muscles of mice, allowing the team to measure its biological effects. The researchers had used this device to optimize the magnitude, duration, and frequency of force applied to the muscles of young animals to accelerate healing, and found that mechanotherapy accelerated muscle healing by mitigating inflammation after injury.

Now, using this device on aged muscle, the researchers found that the same mechanotherapy treatment that helps young muscle heal faster after injury actually has the opposite effect with aging—the settings that promoted healing in young muscle *exacerbated* injury in old muscle. In search for an explanation for these results, the team found that mechanotherapy amplified rather than alleviated inflammation in aged muscle, ultimately hindering the normal healing process by disrupting the behavior of muscle stem cells, a subset of cells responsible for replacing damaged muscle tissue.

Prompted by these findings, the researchers next asked if controlling inflammation along with delivering mechanotherapy could help achieve healing effects in aged muscles. They found that this was indeed the case: combining mechanotherapy with anti-inflammatory treatment significantly improved healing in aged muscles and was superior to anti-inflammatory treatment alone. This work, published in *Science Robotics*, opens an exciting non-invasive therapeutic avenue for healing muscle injuries in elderly patients.

"Our study highlights critical differences in how muscle stem cells and immune cells respond to mechanical forces in the context of age, and how upregulated inflammation additionally compromises the function of aged stem cells needed for the regeneration of old muscles," said Mooney who also is the Robert P. Pinkas Family Professor of Bioengineering at SEAS. "Muscle mechanotherapies likely thus won't be a 'one-size-fits-all." To realize their benefits, they will have to be tailored to patient populations, and specifically for aged individuals, it will be key to modulate inflammation."

From surprise to solution

Following their surprising discovery that mechanotherapy alone actually hinders the normal regeneration process of aged muscles by interacting with the immune system, the team took a deeper look at the muscles' stem cells. Applying a mechanical load to muscle, as is done during mechanotherapy treatment, influences muscle cell behavior via several molecular "mechanotransduction pathways" that also affect stem cells.

"We showed that although aged stem cell behavior was disrupted by the elevated inflammation, they were still able to 'feel' the mechanical forces of loading as we demonstrated by the activation of these pathways," said first-author Stephanie McNamara, who is a graduate student on Mooney's team and currently enrolled in the joint Harvard/MIT MD-

Ph.D. program. "This actually was what prompted us to ask whether controlling inflammation might enable these cells to respond to the mechanical stimuli—and indeed it did."

The team found that administering anti-inflammatory therapy in the form of glucocorticoids alongside mechanotherapy suppressed key pro-inflammatory pathways and reduced overall inflammation levels in injured aged muscle to those seen in injured young muscle. Yet at a cellular level the muscle cells continued to experience mechanotransduction, and by removing the negative impacts of inflammation, injured aged muscles could positively respond to the robot-delivered mechanical loading.

"It is well-known that, with age, many of the normal processes of muscle healing and inflammation change. It's important to question whether the same mechanisms seen in studies performed in young animals stay the same as the body ages," McNamara says. "By leveraging what we learned in this study and our previous work and combining it with growing expertise in wearable soft robotic systems, we believe that in the future personalized mechanotherapeutic approaches can be developed to heal injuries across all ages."

"This discovery that a non-invasive mechanotherapy can stimulate muscle repair in the elderly when combined with anti-inflammatory therapy opens an entirely new path for regeneration and repair in older populations. Mechanotherapies clearly have immense potential to change the lives of patients, but it is truly cross-disciplinary collaborations, such as the one between Dave Mooney's and Conor Walsh's groups at the Wyss Institute, that set the stage for advancing them into clinical realities," said Wyss Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and Boston Children's Hospital, and the Hansjörg Wyss Professor of Bioinspired Engineering at the Harvard John A. Paulson

School of Engineering and Applied Sciences.

More information: David Mooney et al, Anti-inflammatory therapy enables robot-actuated regeneration of aged muscle, *Science Robotics* (2023). DOI: 10.1126/scirobotics.add9369.
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