Out-of-step cells spur muscle fibrosis in Duchenne muscular dystrophy patients

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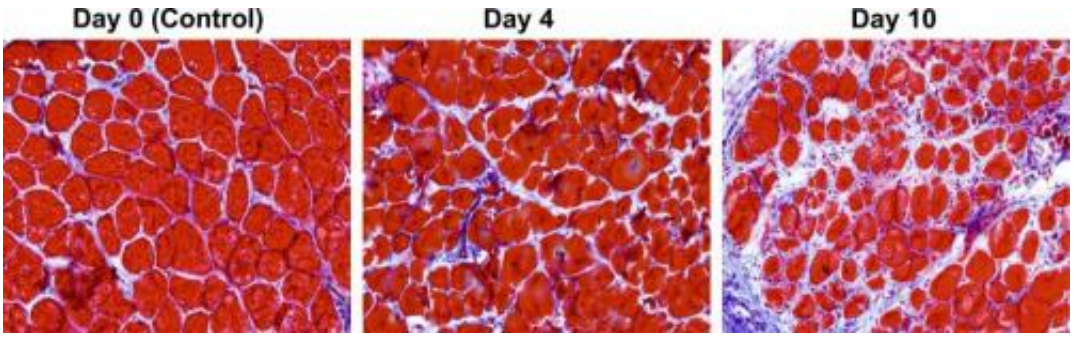

This time series shows the proliferation of stiff connective tissue, or fibrosis, in a section of mouse muscle located between two distinct sites undergoing asynchronous regeneration. Credit: Rockefeller University

Like a marching band falling out of step, muscle cells fail to perform in unison in patients with Duchenne muscular dystrophy. A new study in *The Journal of Cell Biology* reveals how this breakdown leads to the proliferation of stiff fibrotic tissue within muscles.

Duchenne muscular dystrophy is a genetic disorder affecting around 1 in 3,600 boys. Children with this condition usually don't show symptoms right away. Instead, their muscles become progressively weaker over time as normal tissue is replaced by rigid connective tissue, a process known as fibrosis. It's been unclear whether fibrosis causes the failure of muscle repair or regeneration, or rather failure of regeneration leads to fibrosis.

To find answers to this chicken-or-egg conundrum, researchers at the Children's National Medical Center in Washington, DC, analyzed muscle biopsies from patients at different stages of several dystrophic diseases and found that they expressed a collection of genes associated with both normal tissue repair and progressive fibrosis. They then looked at the expression of these genes in normally regenerating mouse muscle and found that, although the same genes were expressed, their activities were ordered and spread out over time in the healthy tissue, with every cell arriving at the same stage of the repair process alongside its neighbors. In contrast, cells in dystrophic muscle underwent these processes asynchronously, which could cause regeneration failure.

In order to test this hypothesis, the researchers created a mouse model of asynchronous muscle repair by injecting a toxin into nearby spots of muscle at different time intervals. When they analyzed the gene expression patterns over a period of 10 days, they found that muscle recovery stalled in areas of tissue between the two injury sites.

"The areas between the injections got frozen or fixed in a developmental time frame and had trouble getting out of it," explains senior author Eric Hoffman. "Because they were getting mixed signals from their neighbors as to where they should be in this regenerative process, they couldn't do the right thing."

Rather than progressing through normal recovery and regeneration, the muscle tissue was being replaced by fibrotic tissue. These results therefore suggest that asynchronous regeneration of cells within muscle tissue leads to the development of fibrosis in patients with Duchenne muscular dystrophy. Hoffman's group is working to develop steroids that can resynchronize regenerative processes with the hope that such drugs can be used to treat or prevent fibrosis in muscle and other tissues, such as the heart, lung, and liver.

More information: Dadgar, S., et al. 2014. J. *Cell Biol.* DOI: 10.1083/jcb.201402079