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Stem cells police themselves to reduce scarring

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Treating mice with a compound that increases the expression of an inactive protein helped them heal from injury with less scarring, according to a study by researchers at the Stanford University School of Medicine.

The researchers are hopeful that their findings could one day be used to help keep muscles supple during normal aging and to treat people with diseases like muscular dystrophy.

"Fibrosis occurs in many degenerative diseases and also in normal aging," said Thomas Rando, MD, PhD, a professor of neurology and neurological sciences. "It negatively impacts muscle regeneration by altering the stem cell niche and inhibiting the stem cell function. In addition, as more scarring occurs, muscles become stiff and can't contract and relax smoothly."

Rando, who is the director of Stanford's Glenn Center for the Biology of Aging, is the senior author of the study, which will be published online Nov. 28 in *Nature*. Former graduate student Alisa Mueller, MD, PhD, is the lead author.

Self-policing stem cells

The researchers discovered that stem cells embedded in muscle fibers do some fancy gene-expression footwork in order to respond appropriately

to injury, disease or aging. In particular, the cells toggle between producing a full-length, active version of a protein that responds to external signals to divide and a shorter, inactive version of the same protein that attenuates the growth signal and prevents an overly enthusiastic response that can lead to scarring or fibrosis.

The researchers studied a protein called platelet-derived growth factor receptor alpha, or PDGFR alpha, that sits on the surface of muscle-embedded stem cells called fibro-adipogenic progenitors, or FAPs. These stem cells are responsible for generating the connective tissue scaffolding necessary to support muscle development and regeneration.

PDGFR alpha straddles the cell membrane. The portion outside the cell serves as a landing pad for external signals that encourage the FAPs to begin dividing, or proliferating. The interior portion of the protein passes the signal along to other proteins inside the cell to get the ball rolling. Although some proliferation is necessary to repair an injury, an overly enthusiastic response can lead to scarring and fibrosis that inhibits muscle function. So it's imperative the cells strike the right balance in their response.

The researchers found that the cells have devised a novel, unexpected way to police themselves. The cells found a way to generate a shortened version of the protein that is missing the interior portion of its structure. This shortened version hangs out on the cells' membranes and sequesters the growth signals away from the active form of PDGFR. Without the interior part of the protein, the message to grow is stopped in its tracks.

"We've found that the cells actively regulate the production of the inhibitory form of the protein, which is very surprising," said Rando. "If they make less, the degree of fibrosis increases; if they make more, it decreases."

The cells produce the shortened form of the protein by recognizing and using a specific series of nucleotides in the messenger RNA that encodes the instructions to make the PDGFR alpha protein. The nucleotide code tells the cell's messenger RNA-processing machinery to create a shorter-than-normal message. As a result, the protein that is made from that messenger RNA is also truncated.

Artificially increasing, decreasing expression

Mueller, Rando and their colleagues used a type of small molecule called a vivo-morpholino that can bind and block access to small sections of messenger RNA to artificially increase or decrease expression of the inhibitory version of the PDGFR alpha protein. They found that increasing the amounts of the inhibitory version allowed both young and old mice to heal from injury with less fibrosis and scarring. Conversely, decreasing the amount increased the severity of fibrosis.

"We'd like to test this approach in a mouse model of muscular dystrophy next," said Rando. "Interestingly, the vivo-morpholino we used is similar to a small oligonucleotide therapy currently being tested in clinical trials to stimulate the production of proteins missing in patients with Duchenne muscular dystrophy. Perhaps we could also use this approach to reduce fibrosis in this disease."

More information: Intronic polyadenylation of PDGFRα in resident stem cells attenuates muscle fibrosis, *Nature*, nature.com/articles/doi:10.1038/nature20160

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