Gene controls regeneration of injured muscle by adult stem cells

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A key gene enables the repair of injured muscle throughout life. This is the finding of a study in mice led by researchers at NYU Langone Medical Center and the University of Colorado at Boulder, and published online July 21 in *Cell Reports*.

The study results further suggest that this "overlooked" gene may play an important role in sarcopenia, the loss of muscle tissues with age.

Specifically, the research team found that levels of a single protein known as AUF1 determine whether pools of stem cells retain the ability to regenerate muscle after injury and as mice age. Changes in the action of AUF1 have also been linked by past studies to human muscle diseases.

More than 30 genetic diseases, collectively known as myopathies, feature defects in this regeneration process and cause muscles to weaken or waste away. Clinical presentation and age of diagnosis vary; Duchenne muscular dystrophy develops in infants, limb girdle muscular dystrophy weakens the torso and limb muscles beginning in young adulthood, and sarcopenia occurs in older patients.

"This work places the origin of certain muscle diseases squarely within muscle stem cells, and shows that AUF1 is a vital controller of adult muscle stem cell fate," says Robert Schneider, PhD, the Albert B. Sabin Professor of Microbiology and Molecular Pathogenesis, and associate dean for the Office of Therapeutics Alliances at NYU Langone.

"The stem cell supply is remarkably depleted when the AUF1 signal is defective, leaving muscles to deteriorate a little more each time repair fails after an injury," says Schneider.

Tagged for Destruction

The study results revolve around one part of gene expression, in which the instructions encoded in DNA chains for the building of proteins are carried by intermediates known as messenger RNAs (mRNAs). Proteins comprise the body's structures, enzymes and signals. The expression of certain genes that need to be turned on and off quickly is controlled in part by the targeted destruction of their mRNA intermediates, a job assigned to proteins like AUF1.

The investigators found that among the functions controlled by mRNA stability is the fate of stem cells, which descend from the human embryo, and then multiply and specialize in the womb until they become our bones, skin, muscles, and other tissue types. Some tissues maintain specialized pools of stem cells into adulthood, ready to mature into replacement cells and regenerate damaged tissues as needed.

Following skeletal muscle injury, muscle stem cells receive a signal to multiply and repair damaged tissue, a process that the researchers found is controlled by AUF1. Among the mRNA targets of AUF1 in muscle stem cells, they discovered one that encodes a "master regulator" of adult muscle regeneration, a protein known as MMP9. This enzyme breaks down other proteins, ultimately controlling their expression levels.

The current study found that mice engineered to lack the AUF1 gene showed increased MMP9 activity and reduced stem-cell-driven repair. This "self-sabotages" the stem cell pools that normally repair muscle and destroys the niche in which their muscle stem cells reside as they await activation. Together, this results in a dramatic and continuous breakdown of skeletal muscle.

The investigators showed that they could restore normal muscle stem cell function and related muscle regeneration in mice lacking AUF1 by repurposing a drug developed for cancer treatment that blocks MMP9 activity.

"This provides a potential path to clinical treatments that accelerate muscle regeneration following traumatic injury, or in patients with certain types of adult onset muscular dystrophy," says Schneider. "We may be able to treat a variety of degenerative diseases by enhancing resident tissue stem cells through targeting MMP9 and its pathways, even those with normal AUF1."

"It was once thought that AUF1 did no more than tag mRNAs that were not needed so they could be disposed of, a utilitarian protein of little interest," says first author Devon Chenette, a graduate student who pioneered the work in Schneider's lab. "To the contrary, our results suggest that AUF1 has evolved to be a key regulator of stem cell fate and the related regenerative ability of adult tissues."

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