Protein found to bolster growth of damaged muscle tissue

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Johns Hopkins University biologists have found that a protein that plays a key role in the lives of stem cells can bolster the growth of damaged muscle tissue, a step that could potentially contribute to treatments for muscle degeneration caused by old age and diseases such as muscular dystrophy.

The results, published online by the journal *Nature Medicine*, show that a particular type of protein called integrin is present on the stem cell surface and used by stem cells to interact with, or "sense" their surroundings. How stem cells sense their surroundings, also known as the stem cell "niche," affects how they live and last for regeneration. The presence of the protein ?1-integrin was shown to help promote the transformation of those undifferentiated stem cells into muscle after the tissue has degraded, and improve regenerated muscle fiber growth as much as 50 percent.

While the presence of ?1-integrin in adult stem cells is apparent, "its role in these cells has not been examined," especially its influence on the biochemical signals promoting stem cell growth, wrote the three authors, Chen-Ming Fan, an adjunct biology professor; Michelle Rozo, who completed her doctorate in biology at Johns Hopkins this year; and doctoral student Liangji Li.

The experiment shows that ?1-integrin - one of 28 types of integrin - maintains a link between the stem cell and its environment, and interacts biochemically with a growth factor called fibroblast growth factor [FGF] to promote stem cell growth and restoration after muscle tissue injury. Aged stem cells do not respond to FGF, and the results also show that ?1-integrin restores aged stem cell's ability to respond to FGF to grow and improve muscle regeneration.

By tracking an array of proteins inside the stem cells, the researchers tested the effects of removing ?1-integrin from the stem cell. This is based on the understanding that the activities of stem cells - undifferentiated cells that can become specialized - are dependent on their environment and supported by the proteins found there.

"If we take out ?1-integrin, all these other (proteins) are gone," said Fan, the study's senior author and a staff member at the Carnegie Institution for Science in Washington and Baltimore.

Why that is the case is not clear, but the experiment showed that without ?1-integrin, stem cells could not sustain growth after muscle tissue injury.

By examining ?1-integrin molecules and the array of proteins that they used to track stem cell activity in aged muscles, the authors found that all of these proteins looked like they had been removed from aged stem cells. They injected an antibody to boost ?1-integrin function into aged muscles to test whether this treatment would enhance muscle regeneration. Measurements of muscle fiber growth with and without boosting the function of ?1-integrin showed that the protein led to as much as 50-percent more regeneration in cases of injury in aged mice.

When the same ?1-integrin function-boosting strategy was applied to mice with muscular dystrophy, the muscle was able to increase strength by about 35 percent.

Fan said the team's research will next try to determine what is happening inside the stem cells as they react with their immediate environment, as a step to understanding more about the interaction of the two. That, in turn, could help refine the application of integrin as a therapy for muscular dystrophy and other diseases, and for age-related muscle degeneration.

"We provide here a proof-of-principle study that may be broadly applicable to muscle diseases that

involve SC (stem cell) niche dysfunction," the authors wrote. "But further refinement is needed for this method to become a viable treatment."

More information: Michelle Rozo et al, Targeting ?1-integrin signaling enhances regeneration in aged and dystrophic muscle in mice, *Nature Medicine* (2016). DOI: 10.1038/nm.4116

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