Researchers track muscle stem cell dynamics in response to injury and aging

December 14 2017

SBP's Alessandra Sacco, Ph.D., investigates how muscle stem cells become activated to repair damage, paving the way for stem cell-based therapies for muscle wasting and muscular dystrophy. Credit: Sanford Burnham Prebys Medical Discovery Institute (SBP)

A new study led by researchers at Sanford Burnham Prebys Medical

Discovery Institute (SBP) describes the biology behind why muscle stem cells respond differently to aging or injury. The findings, published in *Cell Stem Cell*, have important implications for therapeutic strategies to regenerate skeletal muscle in response to the normal wear and tear of aging, or in cases of injury or muscle diseases such as muscular dystrophy.

"Our study is one of the first to look at muscle stem cells in their native tissue with resolution at the level of a single clone," says Alessandra Sacco, Ph.D., professor at SBP. "This allowed us to probe the dynamic heterogeneity of the cells, a measure of their flexibility to respond to exercise, injury, and the normal wear and tear that occurs with aging. Using this approach, we found surprising differences in the degree to which stem cells can maintain this heterogeneity, depending on what they are asked to do."

Adult muscle stem cells are essential for repairing and regenerating muscle throughout life. These cells are located between muscle fibers and exist as a heterogeneous population that need to "self-renew" to maintain the stem cell population, as well as differentiate into myogenic cells that proliferate, differentiate, and fuse to create new muscle fibers.

"Muscle stem cells must maintain a spectrum of functional abilities to be prepared for the overall changes that occur from injuries, diseases and aging," says Sacco. "Here, we focused on studying how the pool of muscle stem cells responds to age or after an injury to the muscle.

"Our goal is to understand how stem cells uniquely cope with or yield to these different pressures. Then, we can use this information to create new approaches designed to specifically prevent muscle stem cell loss and/or dysfunction linked to sarcopenia—the medical term for age-related loss of skeletal muscle mass and strength—or in association with muscle diseases that are characterized by chronic tissue damage, such as

dystrophies," adds Sacco.

Sacco's research team used a technology called in vivo multi lineage tracing to follow the self-renewal capacity and range of progeny produced by individual stem cells. Repetitive injuries cause muscles to undergo multiple rounds of repair, and are used as a model for diseases characterized by progressive muscle degeneration and weakness, such as muscular dystrophies.

"The results were quite different from what we expected—aged muscle stem cells maintained a diverse assortment of cells in the overall pool, despite being less able to proliferate and multiply sufficiently. The outcome was flipped when we caused an injury and watched how the pool responded to tissue damage," explains Matthew Tierney, Ph.D., a former graduate student of Sacco, now a postdoctoral researcher at The Rockefeller University. "In the case of injury, the stem cell pool becomes less diverse, but maintains its proliferative capacity.

"Our findings lead to several interesting questions about the potential causes of these observed differences—muscle stem cells are asked to function in a very different local environment with age or during regeneration due to injury, and we suspect this may contribute to some of the distinct behaviors we observed," adds Tierney.

"This study has shown clear-cut differences in the dynamics of muscle stem cell pools during the aging process compared to a sudden injury," says Sacco. "This means that there probably isn't a 'one size fits all' approach to prevent the decline of muscle stem cells. Therapeutic strategies to maintain muscle mass and strength in seniors will most likely need to differ from those for patients with degenerative diseases."

Provided by Sanford-Burnham Prebys Medical Discovery Institute