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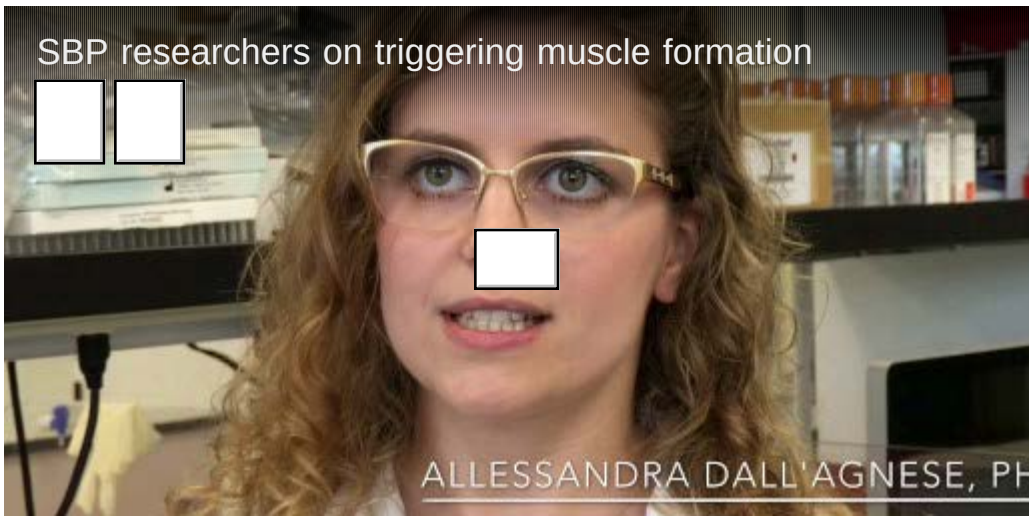
New Insights on Triggering Muscle Formation

Research uncovers molecular reasons why aged muscle loses the ability to regenerate



Kristen Cusato, SBP

Scientists from the labs of Lorenzo Puri, M.D., Ph.D., and Alessandra Sacco, Ph.D., uncover the molecular reasons why aged muscles lose their ability to regenerate.

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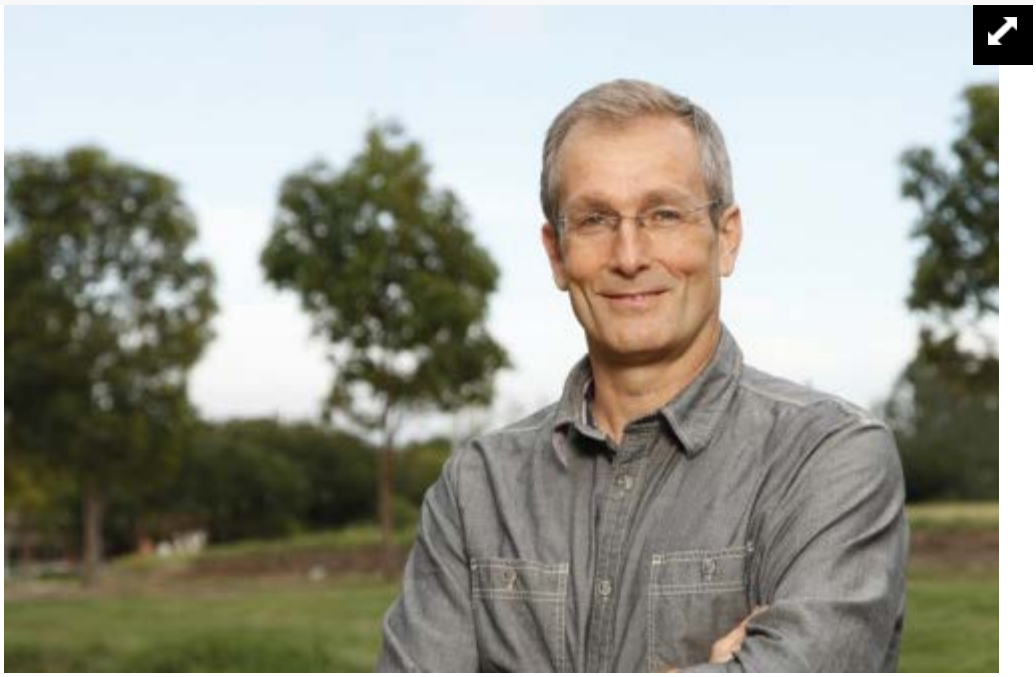

Credit: Sanford Burnham Prebys Medical Discovery Institute

Lorenzo Puri, M.D., Ph.D.

Newswise — La Jolla, Calif., April 25, 2017 (embargoed until 5:00 P.M. EST) — Researchers at Sanford Burnham Prebys Medical Discovery Institute (SBP) have identified a previously unrecognized step in stem cell-mediated muscle regeneration. The study, published in *Genes and Development*, provides new insights on the molecular mechanisms that impair muscle stem cells (MuSCs) during the age-associated decline in muscle function that typically occurs in geriatric individuals. It also provides further insight into the connection between accelerated MuSC aging and muscular dystrophies.

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Aging, Cell Biology, Genetics, Stem Cells, Local - California

KEYWORDS

"In adult skeletal muscle, the process of generating muscle—myogenesis—depends on activating MuSCs that are in a resting, or quiescent, state. As we age, our MuSCs transition to a permanently inactive state called senescence, from which they can't be 'woken up' to form new muscle fibers," says Lorenzo Puri, M.D., Ph.D., professor in the Development, Aging and Regeneration Program at SBP.

"If we could encourage senescent MuSCs to start replicating and advance through myogenesis—perhaps

through pharmacological interventions—we may have a way to help build muscle in patients that need it," adds Puri.

The goal of the study was to define the molecular determinants that lead to irreversible MuSC senescence. Using a combination of a mouse model and human fibroblasts, the team found that the reason old MuSCs can't be activated to generate muscle cells is that they spontaneously activate a DNA damage response (DDR) even in the absence of exposure to exogenous genotoxic agents. This senescence-associated DDR chronically turns on the machinery needed to repair breaks and errors in DNA, and activate cell cycle checkpoints, which inhibit cells from dividing.

"In our study, we found that the senescence-associated DDR prevents MUSCs from differentiating by disabling MyoD-mediated activation of the muscle gene program," explains Puri. "We also learned that a prerequisite for activating the muscle gene program is progression into the cell cycle, a process that is irreversibly inhibited in senescent cells."

"We did identify experimental strategies to get senescent cells to move through the cell cycle and activate myogenesis, which is a promising result. However, we also discovered that enforcing old MuSCs to form new muscles might lead to the formation of myofibers with nuclear abnormalities resulting from genomic alterations generated during aging."

"Given the tremendous impact that decline in muscle function has on aging and lifespan, research that elucidates pathways and networks that contribute to the progressive impairment of MuSCs—such as that reported here—may lead to targeted pharmacological interventions that improve human health," Puri notes. "However, the findings from this study should warn against overenthusiasm for strategies aimed at rejuvenating muscle of elderly individuals by enforcing the regeneration process, as they might carry a sort of trade-off at the expense of the genomic and possibly functional integrity of the newly formed muscles."

This research was performed through a collaboration among the laboratories of Pier Lorenzo Puri, Alessandra Sacco (SBP) and Lucia Latella (IRCCS Fondazione Santa Lucia and the National Research Council of Italy). Funding was provided by the National Institutes of Health, the Ellison Medical Foundation, Epigen Progetto Bandiera Epigenomica (an initiative of the Italian Ministry of Education, University and Research and the National Research Council), and the Glenn Foundation for Medical Research.

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About SBP

Sanford Burnham Prebys Medical Discovery Institute (SBP) is an independent nonprofit medical research organization that conducts world-class, collaborative, biological research and translates its discoveries for the benefit of patients. SBP focuses its research on cancer, immunity, neurodegeneration, metabolic disorders and rare children's diseases. The Institute invests in talent, technology and partnerships to

accelerate the translation of laboratory discoveries that will have the greatest impact on patients. Recognized for its world-class NCI-designated Cancer Center and the Conrad Prebys Center for Chemical Genomics, SBP employs about 1,100 scientists and staff in San Diego (La Jolla), Calif., and Orlando (Lake Nona), Fla. For more information, visit us at SBPdiscovery.org or on Facebook at facebook.com/SBPdiscovery and on Twitter @SBPdiscovery.