A novel role for satellite cells in adult skeletal muscle

Skeletal muscle stem cells, otherwise known as satellite cells, are essential for postnatal muscle development and for repairing or replacing injured or degenerated muscle fibres. **Professor Charlotte Peterson**, and her collaborators Professor Esther Dupont-Versteegden and Professor John McCarthy at the University of Kentucky are using a genetic mouse model to investigate the contribution of satellite cells to normal muscle maintenance and adaptation to physical activity. Their research has highlighted a new role for satellite cells that could one day be utilised to treat muscle fibrosis associated with age and disease.

Skeletal muscle has a remarkable ability to repair and regenerate due to the presence of muscle stem cells. These cells are referred to as satellite cells due to their satellite-like position along the boundary of muscle fibres. Following muscle injury, satellite cells divide and fuse into damaged muscle fibres to repair them, or fuse together to form a new fibre, replacing degenerated muscle fibres. Less well studied is the role of satellite cells in normal muscle maintenance or adaptation to different types and levels of physical activity. Understanding the role of satellite cells could help scientists to develop strategies which utilise these cells to treat muscle disease and wasting, and muscle loss with age. Professor Peterson and her colleagues are studying satellite cell function using a genetic mouse model in which they can specifically kill satellite cells at any point in the life of the mouse, and the results have been surprising.

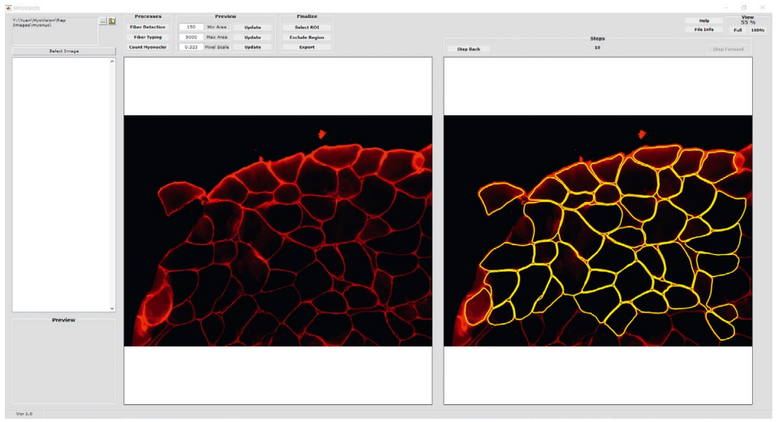
AGEING

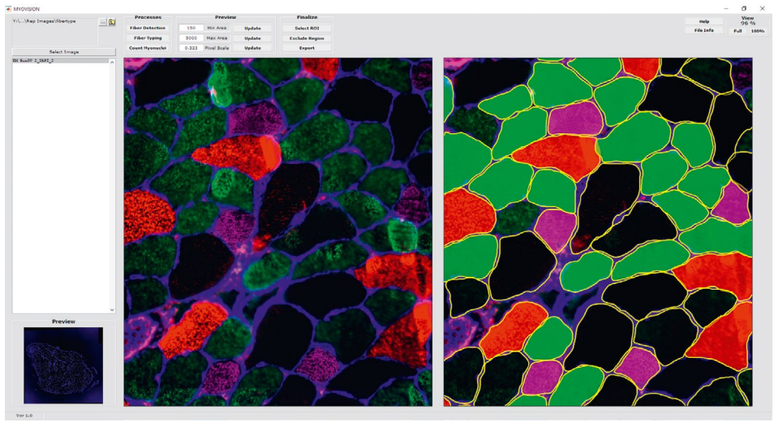
Satellite cells are lost and become less active as we age, and it has been suggested that normal age-associated loss of muscle mass – called sarcopenia – is caused by this diminishing satellite cell activity. However, when Professor Peterson and her team eliminated satellite cells in the mouse model they found that average muscle fibre size was not affected. Furthermore, the decrease in muscle size associated with normal ageing in the mice was not exacerbated. Increased extracellular matrix was observed in the muscles of satellite cell-depleted mice, suggesting that loss of satellite cells may contribute to age-related fibrosis.

RUNNING

Skeletal muscle can adapt to aerobic activity. The team used the genetic mouse model to characterise the role of satellite cells in muscle adaptation to running. Interestingly, satellite cell-depleted mice ran around 27% less distance and were around 23% slower than their non-depleted counterparts. This difference wasn't because satellite cell-depleted muscle produced energy less efficiently. Instead, the difference was caused by accumulation of extracellular

Understanding the role of satellite cells could help scientists to develop strategies which utilise these cells to treat muscle disease





MyoVision improves efficiency and consistency of microscopic analysis of muscle. Upper panels: laminin or dystrophin immunofluorescence is used to delineate, measure and count myofibres on cross section. Lower panels: laminin (blue) combined with fibre type-specific myosin heavy chain immunofluorescence (green, pink, red or black) is used to measure size and distribution of different fibre types.

matrix in limb muscle, which compromised the function of special muscle fibres that control co-ordination. Unlike limb muscle, fibrosis did not occur in the diaphragm, a muscle involved in breathing, where it appears that an alternative stem cell population may compensate for absent satellite cells during adaptation to running.

LIFTING

Weightlifting is associated with growth (or hypertrophy) of muscles. Satellite cells normally fuse with growing adult muscle fibres as an adaptive response to weightlifting, and have been considered essential for the hypertrophic response. Professor Peterson and her colleagues investigated this using the genetic mouse model. Surprisingly, they found that even in the absence of satellite cells, hypertrophy proceeded in adult mice, such that muscle fibres grew without fusing with satellite cells. However, elimination of satellite cells caused the accumulation of excess extracellular matrix surrounding the muscle fibres after several weeks, which may ultimately limit the growth of muscle fibres.

Skeletal muscle has a remarkable ability to repair and regenerate due to the presence of muscle stem cells – satellite cells

Q&A

How does the mouse model work?

A gene encoding a toxin, diphtheria toxin, is engineered into the genome of the mice, but is silent. The toxin gene can be turned on so toxin accumulates only in satellite cells, because gene expression is under the inducible control of another genetic regulatory sequence which is only expressed in satellite cells in muscle. The induction of the gene to kill the satellite cells can be done in the mouse at any age and the satellite cells do not recover over the life of the mouse.

The research has shown that sarcopenia is probably not caused by the loss of activity of satellite cells with age. What other factors could be responsible?

Several factors intrinsic to muscle fibres probably contribute to sarcopenia. These include 1) inability of protein synthesis to be increased in response to a hypertrophic condition or the inability to recover muscle mass after a period of atrophy which can happen in response to illness; 2) reduced capacity to recycle damaged proteins and organelles, causing an accumulation of less functional cellular components; 3) decreased muscle quality through accumulation of lipid inside the fibres, causing loss of muscle force generation. Loss of the nerves that stimulate muscles to contract may also contribute to sarcopenia.

What degenerative muscle diseases could potentially be treated by utilising satellite cells?

Many labs are currently studying the potential of satellite cells to treat muscular dystrophies, particularly Duchenne Muscular Dystrophy. This disease is characterised by degeneration of muscle fibres, as well as extensive fibrosis and fat infiltration in muscle.

MyoVision is a fantastic resource. Has the software been used in any published research so far?

We have been using MyoVision in our publications for the last year. Most recently we used the program to measure fibre cross-sectional area and showed that muscle hypertrophy is impaired if satellite cells are depleted in young, growing mice. Apparently immature muscles require satellite cells to respond to an additional hypertrophic stimulus (Murach, K.A., S.H. White, A. Ho, E.E. Dupont-Versteegden, J.J. McCarthy, C.A. Peterson. 2017. Differential requirement for satellite cells during overload-induced muscle hypertrophy in growing versus mature mice. *Skeletal Muscle* 7:14-27. DOI 10.1186/s13395-017-0132-z). We have now developed the user-friendly interface so that other researchers can use the program.

How did you first become interested in satellite cells?

I was first attracted to the study of muscle because it is an amazingly adaptive tissue, with a much higher regenerative capacity than most adult tissues, such as brain or heart. This is largely due to the activity of satellite cells. Given that muscle is the largest organ in the human body, satellite cells are readily accessible to enable study of the properties of adult stem cells to understand and harness their reparative potential.

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REGULATION OF THE ECM

These studies have defined an important new role for satellite cells in regulating the environment surrounding muscle fibres. The extracellular matrix surrounding muscle fibres is made up of fibrous collagen molecules secreted by interstitial fibrogenic cells (IFCs). During hypertrophy, satellite cells are activated, divide and give rise to myogenic progenitor cells (MPCs). Recent research in Professor Peterson's laboratory has shown that these MPCs interact with IFCs to ensure proper extracellular matrix deposition and ensure optimal muscle remodelling. MPCs secrete molecules that repress the synthesis of collagen by IFCs to prevent excessive deposition of collagen. This work has given insight into how satellite cells can interact with other cell types to regulate the extracellular matrix environment for muscle tissue maintenance and adaptation. Thus, in addition to therapeutic potential of satellite cells in treating degenerative muscle diseases by promoting regeneration, satellite cells may be useful in reducing fibrosis associated with ageing and some muscle diseases.

AUTOMATED ANALYSIS

Professor Peterson has been recently selected for a University Research Professorship, demonstrating the excellence and impact of her work. The team has recently developed software for automated muscle image analysis. Microscopic analysis of rodent muscles and human muscle biopsies is an important technique in muscle biology and is used extensively in Professor Peterson's laboratory. However, quantification of the microscope images requires extensive human input, slowing progress and introducing the possibility of user-bias. For these reasons, Professor Peterson and her colleagues have produced MyoVision – a software package that automates the analysis of microscope images of muscle. The software has an accuracy of around 94% compared to manual quantification when taking basic measurements such as the number of muscle fibres and their cross-sectional area. The software is available for any scientist to download and use for free at www.uky.edu/chs/muscle/myovision. Professor Peterson hopes that this software will improve the efficiency and consistency of the microscopic analysis of muscle and helps reduce the burden of routine image quantification in muscle biology.

Detail

RESEARCH OBJECTIVES

Professor Peterson's research explores the cellular and molecular mechanisms controlling skeletal muscle structure and function. Her long-term goal is to develop new strategies to prevent frailty and loss of functional independence.

FUNDING

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BIO

Charlotte A. Peterson received her PhD from University of Virginia and completed two postdoctoral fellowships at the National Eye Institute and at Stanford University Medical Center. She is currently the Joseph Hamburg Endowed Professor and Director of the Center for Muscle Biology at University of Kentucky, and scientific advisor to the National Institutes of Health.

Esther E. Dupont-Versteegden received her PhD from University of Texas Health Science Center San Antonio, and received postdoctoral training at University of Arkansas for Medical Sciences. She is currently an Endowed Professor in Health Sciences and Director of the PhD program in Rehabilitation Sciences at the University of Kentucky.

John J. McCarthy received his PhD from University of Oregon with postdoctoral training at the University of Illinois and University of Missouri. He is currently an Associate Professor in the Department of Physiology at the University of Kentucky.

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