New regulator of muscle regeneration discovered

Researchers at the Leibniz Institute on Aging—Fritz Lipmann Institute (FLI) in Jena and the BTU Cottbus-Senftenberg in Senftenberg have identified a previously unknown regulator of muscle stem cell differentiation. When new muscle fibers develop from these cells, the protein leiomodin 1 (LMOD1) is activated at an early stage. In the absence of LMOD1, muscle fiber formation is significantly impaired; conversely, when its production is increased, the formation of new muscle fibers is accelerated. The study, published in "eLife," also shows that LMOD1 interacts with the enzyme SIRT1, which plays a key role in differentiation. The findings provide new insights into the molecular basis of muscle regeneration and raise new questions about how these processes change with age.

Jena/Cottbus-Senftenberg. Skeletal muscles are capable of regenerating themselves following an injury, a process depending on muscle stem cells. In healthy resting muscle, these cells are predominantly in a quiescent state. However, following an injury, they are activated, begin to proliferate, and subsequently start to develop into specialized skeletal muscle cells (differentiation). These cells then fuse with one another or with existing muscle fibers, thereby generating new or repaired muscle fibers.

This entire process is critically important for the repair and regeneration of skeletal muscle tissue. However, the ability to regenerate declines with increasing age. Diseases can also impair the formation of new muscle fibers. The exact molecular switches determining when a muscle stem cell transitions from its resting state into differentiation is still only partially understood. This is precisely where the study recently published in "eLife" comes in.

A research team led by Dr. Alessandro Ori of the Leibniz Institute on Aging—Fritz Lipmann Institute (FLI) in Jena and Prof. Julia von Maltzahn of the BTU Cottbus-Senftenberg investigated the changes that occur in the overall protein profile of a muscle stem cell as it becomes a differentiated skeletal muscle cell.

Analysis of thousands of proteins over time

For their study, the researchers used mass spectrometry-based proteomics to analyze more than 6,000 proteins in primary mouse muscle cells at various stages of differentiation. This allowed them not only to identify which proteins were present but also to track how their levels changed during the development of the muscle cells.

"One protein in particular caught our attention because its levels changed drastically right at the beginning of the differentiation process," reports Dr. Alessandro Ori. The protein leiomodin 1 (LMOD1) belongs to the group of so-called actin nucleators and helps to build new actin filaments. Actin is an important component of the cytoskeleton—the dynamic framework that gives cells their shape and is involved in numerous processes of movement, growth, and remodeling. However, the study results showed that LMOD1 apparently has additional functions, as its levels rise early during muscle cell differentiation and influence whether these cells can successfully form new muscle fibers.

Without LMOD1, the formation of new muscle fibers stalls

To determine whether LMOD1 is required for muscle formation or merely occurs in parallel with it, the amount of the protein was specifically reduced in primary muscle cells. With the reduction of LMOD1 levels, the formation of myotubes—the precursors of new muscle fibers—was significantly impaired. As a result, there was an accumulation of cells that had not successfully completed the differentiation process, leading to the formation of only shorter structures with fewer cell nuclei.

In contrast, increased production of LMOD1 led to significantly faster formation of new muscle fibers. The cells formed fully differentiated myotubes earlier, which were also longer and contained more cell nuclei. Proteomic analyses confirmed that, under these conditions, the cells adopted a characteristic molecular pattern of early muscle formation.

This correlation was also demonstrated in a living organism: Following a muscle injury, the level of LMOD1 increased in the regenerating muscle in a mouse model. During the early phase of muscle fiber regeneration, the protein was clearly detectable there. Thus, the results provide clear evidence that LMOD1 actively supports myogenic differentiation.

“We were surprised to see how early this protein plays a role in the differentiation process,” says Prof. Julia von Maltzahn form the BTU Cottbus-Senftenberg in Senftenberg. “Our results demonstrate that LMOD1 is far more than just a component of the cytoskeleton: It influences the central regulatory process that determines how muscle stem cells form new muscle fibers.”

Molecular interaction with SIRT1

Another finding was particularly interesting. LMOD1 apparently does not act alone but interacts with SIRT1—an enzyme that, among other functions, regulates the activity of proteins and genes and is already known to play a role in muscle cell differentiation.

The researchers were able to show that LMOD1 and SIRT1 interact with each other and that LMOD1 influences the spatial distribution of SIRT1 within the cell. This relationship is particularly pronounced at the very beginning of differentiation. When LMOD1 expression is increased, the distribution of SIRT1 changes: the proportion of SIRT1 in the cell nucleus decreases. “Our study thus paints a new picture: LMOD1 is not only a component of the cytoskeleton but also appears to play a role in regulating the genetic program of muscle cell differentiation by controlling the spatial distribution and activity of SIRT1,” explains Dr. Ellen Späth, former PhD student at the FLI, lead author of the study and now Postdoc at Genentech Inc., USA.

Connection to the aging process

Of particular interest to aging research is the observation that elevated levels of LMOD1 protein were found to be elevated in muscle stem cells of old mice. This raises an important new question: Could the altered regulation of LMOD1 contribute to age-related changes in muscle stem cells? After all, these changes occur during a phase of life in which the muscles’ ability to regenerate gradually declines.

“Our study expands our understanding of how muscle stem cells control their program for forming new muscle fibers,” says Dr. Svenja Schuler, former PhD student at FLI, co-leader of the study and now Postdoc at Sherbrook University in Canada. “For future research, the key questions are why LMOD1 levels change in aging muscle and what consequences do these changes have for the regenerative capacity of muscle stem cells. It should also be investigated whether the observed mechanism plays a comparable role in human muscle.”

The results thus provide a new building block for understanding skeletal muscle aging. In the long term, however, they could help to better understand the molecular causes of declining muscle regeneration in old age and identify potential targets for future strategies to maintain muscle health.

Publication

Proteome dynamics reveal Leiomodin 1 as a key regulator of myogenic differentiation. Späth E, Schüler SC, Heinze I, Dau T, Minetti A, Hofmann M, Hönzke K, von Maltzahn J, Ori A. Elife. 2026 Aug 4;14:RP104331. doi: 10.7554/eLife.104331.

https://elifesciences.org/articles/104331

Picture

The protein LMOD1 plays a central role in the differentiation of muscle stem cells and promotes the formation of new muscle fibers. Its interaction with SIRT1 provides new insights into the molecular mechanisms of muscle regeneration.
(Image: Sunisa / AdobeStock_1996686217.jpeg / stock.adobe.com)

Contact

Dr. Kerstin Wagner
Press & Public Relations
Phone: 03641-656378, Email: presse@leibniz-fli.de

Background

The Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena is a federal and state government-funded research institute and member of the Leibniz Association (Leibniz-Gemeinschaft). FLI conducts internationally recognized, high-impact research on the biology of aging at the molecular, cellular, and systems levels. Scientists from around 40 countries investigate the mechanisms of aging to uncover its root causes and pave the way for strategies that promote healthy aging. Further information: www.leibniz-fli.de.

The **Leibniz Association** connects 96 independent research institutions that range in focus from natural, engineering, and environmental sciences to economics, spatial, and social sciences and the humanities.

Leibniz Institutes address issues of social, economic, and ecological relevance. They conduct knowledge-driven and applied basic research, maintain scientific infrastructure and provide research-based services.

The Leibniz Association identifies focus areas for knowledge transfer to policy-makers, academia, business and the public. Leibniz institutions collaborate intensively with universities – in the form of “Leibniz ScienceCampi” (thematic partnerships between university and non-university research institutes), for example – as well as with industry and other partners at home and abroad.

They are subject to an independent evaluation procedure that is unparalleled in its transparency. Due to the importance of the institutions for the country as a whole, they are funded jointly by the Federation and the Länder, employing some 21,400 individuals, including 12,200 researchers. The entire budget of all the institutes is approximately 2,3 billion Euros. For more information: www.leibniz-gemeinschaft.de/en/.