New muscle power from the lab

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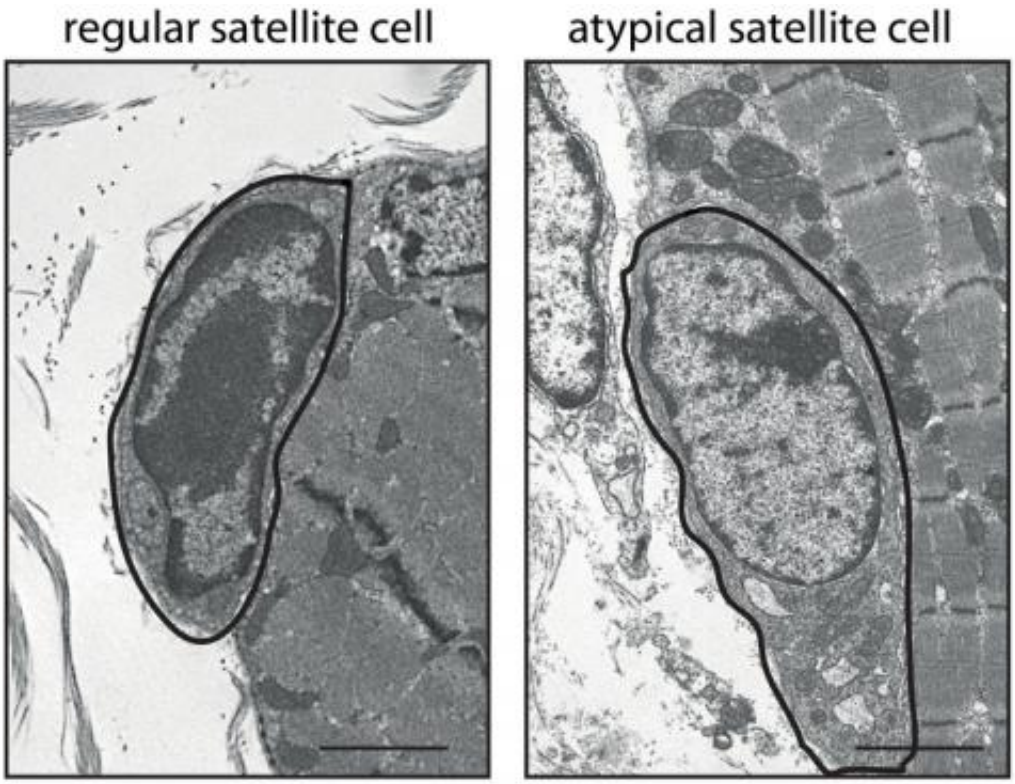

Out of shape. Whereas the heterochromatin in the cell nucleus of a normal satellite cell (marked cell, left) exhibits a characteristic dark colouration under the electron microscope, the DNA string in a satellite cell without Pax7 (right) is much less tightly condensed, making the cell nucleus appear lighter. Credit: MPI for Heart and Lung Research

(Medical Xpress)—Unlike the heart muscle, the musculature of the locomotive organs has the capacity to heal itself. What makes this possible are muscle-specific stem cells known as satellite cells. Located

on the muscle fibres, these cells can multiply when necessary and replace damaged muscle cells. Scientists from the Max Planck Institute for Heart and Lung Research recently succeeded in elucidating the role of an important factor in the regulation of self-healing. One of the ways this knowledge could be used in the future is in engineering optimal conditions for creating replacement stem cells in the lab, thereby producing a potential way of treating degenerative muscle diseases.

From muscle ache to a pulled muscle - damage to the skeletal muscles can be painful but is often healed within a few days. The regeneration happens at this speed because of the satellite cells. These are stem cells which are present in very small quantities in muscular tissue exclusively. They take their name from their isolated position around the muscle fibres. When a muscle becomes damaged, the satellite cells multiply rapidly and copiously through cell division and replace the damaged muscles by fusing together to form new muscle cells. And the cells themselves ensure that the body's supply of satellite cells never completely runs out. However, as the body ages, they reduce in number, with the result that muscle damage takes longer to heal and muscle strength diminishes in old age.

How the musculature regenerates and the satellite cells preserve themselves at the molecular level was something that was insufficiently understood until now. Scientists from Thomas Braun's Research Group at the Max Planck Institute for Heart and Lung Research in Bad Nauheim have now been able to clarify the importance of a factor known as Pax7, which is instrumental in the regulation of muscle regeneration.

In the context of satellite cells, Pax7 is not an unknown factor. It is, in fact, the most important marker of satellite cells. In the past, however, scientists doubted the protein's importance for muscle regeneration; they believed it was only relevant for certain processes shortly after birth. The

scientists in Bad Nauheim have now reached a different conclusion based on an innovative type of experiment.

The scientists experimented on genetically engineered mice, in which they were able to deactivate the Pax7 functionality in the satellite cells of adult animals. Consequently, the number of satellite cells in the musculature reduced dramatically. The researchers then induced specific muscle damage by injecting a toxin. "In the mice with no Pax7, muscle regeneration was significantly reduced compared with the control group. By the same token, we found that the mice without any Pax7 had far more damaged or dead muscle fibres," commented Stefan Günther, lead author of the study. This is a clear indication of the significant role of Pax7 in muscle regeneration – and specifically in the stem cell expansion that occurs at the start of regeneration.

In a bid to identify the means by which Pax7 acts, the muscle tissue was placed under an electron microscope: "Where there is no Pax7, the few remaining satellite cells exhibit characteristic changes which distinguish them markedly from the normal stem cells. There is barely any trace left of heterochromatin ? the tightly packed form of DNA typical of stem cells," explains Günther. Not only were the typical condensed chromatin structures missing, the cell organelles and cytoplasm were also abnormal.

Similar changes can be observed when keeping isolated satellite cells in culture in the lab for a certain period of time. The Max Planck scientists therefore decided to deactivate Pax7 in isolated satellite cells. They found that cell division stopped within a very short period of time, causing one of the characteristic functions of stem cells to be lost. Conversely, the researchers discovered that an overabundance of Pax7 in these cells immediately led to a drastic increase in cell division activity, which they took as further evidence of the key role of Pax7 in regulating satellite cell function.

Not only have the scientists in Bad Nauheim concluded from their study that Pax7 is important in sustaining the function of a stem cell, they also see in it a potential therapy: "When it comes to degenerative muscle diseases like muscular dystrophy, attempts are currently being made improve the muscle tissue's capacity for self-healing, for instance by implanting muscle stem cells," explains Thomas Braun, Director at the Max Planck Institute. "The comprehensive understanding of how Pax7 works should enable satellite cells to be modified in such a way as to make them more active in repairing muscle damage. This could revolutionise future therapies and should also aid the maintenance of muscle strength in old age."

Background: Muscle strength and mobility in old age are key factors in preventing cardiovascular and metabolic diseases. Improved mobility also adds to enhanced quality of life. Hopes that muscle strength and muscle regeneration can be bettered by specific molecular intervention in the muscle's satellite cells will now be explored in a series of follow-up studies.

More information: Stefan Günther, Johnny Kim, Sawa Kostin, Christoph Lepper, Chen-Ming Fan, Thomas Braun, Myf5-Positive Satellite Cells Contribute to Pax7-Dependent Long-Term Maintenance of Adult Muscle Stem Cells. *Cell Stem Cell* (2013)

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