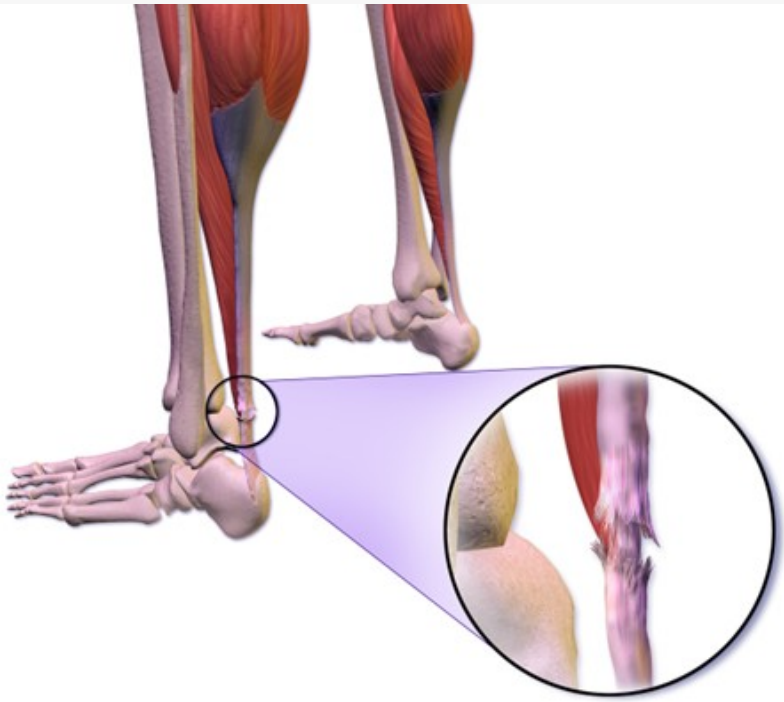
Aging-Linked Cells Emerge as Unexpected Allies in Tendon Healing

Cells expressing a protein called p16INK4a, once thought to be associated with aging, have been found to aid tendon regeneration



New study reveals that aging-associated cells were found to aid tendon healing

CHINA, July 3, 2026 /EINPresswire.com/ -- Chinese researchers led by Prof. Shen Liu from the Department of Orthopedics of the Shanghai Jiao Tong University School of Medicine have discovered that certain supporting cells expressing a protein marker called p16INK4a, once associated with aging or stressed cells, were found to be key drivers of tendon healing. JMJD3, a molecular "switch," helped them turn on the repair genes. This pathway can be targeted to develop new treatment strategies for tendon injuries.

Tendon injuries, though very common, frequently heal with scar tissue, which is less flexible and more prone to future injury. Better insights into the biological mechanisms that promote stronger and more complete tendon repair are necessary to develop effective treatment measures. Meanwhile, a group of cells that has attracted attention is cells expressing a protein called p16INK4a. Cells producing this protein are designated as p16INK4a+, and were traditionally seen as non-beneficial as they were associated with aging, cellular stress, and a process called senescence, in which cells stop dividing. However, a few recent studies in other tissues suggested that these cells might sometimes help repair injured tissue.

In a recent study published online on June 11, 2026, in the journal Bone Research, researchers from China, led by Prof. Shen Liu from the Department of Orthopedics, Shanghai Sixth People's Hospital, affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, explored whether p16INK4a+ cells play any role in tendon injuries. "Because tendons rarely heal well even

with surgery, we were curious to know if p16INK4a+ cells could help in the repair of injured tendons as had been demonstrated in skin and lungs," says Prof. Liu. They used mice with Achilles tendon injuries and tracked p16INK4a+ cells over time and analyzed the types of cells present in injured tendons at various time points, using a technique called single-cell RNA sequencing that measures gene activity in individual cells.

Around seven days after tendon injury, the number of p16INK4a+ cells increased markedly within the damaged tissue. In healthy, uninjured tendons, these cells were very rare. Removing them from injured tissue resulted in poorer healing and weaker, less mature tendons. Collagen fibers, the major proteins that make up the tendons, were disorganized with fewer repair cells and increased inflammation around the site of injury. This suggested that p16INK4a+ cells contributed to repair rather than causing damage. Further studies revealed that p16INK4a+ cells are actually mesenchymal cells, a type of connective tissue cell. They produce high levels of collagen and factors that promote the formation of new blood vessels and nerves, all crucial for normal tendon function.

As these cells were thought to be associated with aging and not beneficial, how these cells switch into "repair mode" was examined. They suspected the answer might involve 'epigenetics', which is the "switch" cells use to turn genes on and off. They focused on a protein called 'JMJD3', which removes the "gene off" epigenetic mark 'H3K27me3', of the repair genes. The study found that p16INK4a+ mesenchymal cells in injured tendon contained high levels of JMJD3 and low levels of H3K27me3. They concluded that H3K27me3 suppresses the activity of repair genes in normal tendons. When injured, JMJD3 removes this suppressive mark and allows genes to be expressed. Furthermore, when JMJD3 was removed, the overall tissue repair was impaired.

To add a further layer of evidence, the researchers created tendon-injury-like p16-positive cells in culture using a drug called doxorubicin. Then, they blocked JMJD3 with a drug called GSK-J4. This increased H3K27me3, the repair genes' off switch, reducing collagen production and worsening healing. Then they did the opposite experiment. EZH2, an enzyme that creates H3K27me3 was blocked, decreasing H3K27me3. This improved collagen organization, increased tendon-specific repair markers, and enhanced the mechanical strength of repaired tendons.

In conclusion, these experiments gave a new perspective on p16INK4a+ cells thought to be non-beneficial. "We didn't want to compromise on the quality of evidence. This study could be a game changer in how we understand and approach tendon repair in the future," says Prof. Xiaonan Liu, the first author. It showed how epigenetic modification could drive the cell from 'senescence mode' to 'repair mode' and regenerate strong tendons with organized collagen structure and healthy blood vessel and nerve growth. In the future, targeting epigenetic pathways is a promising strategy for improving tendon healing.

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Reference

Title of original paper: JMD33-driven epigenetic reprogramming of p16INK4a positive cells promotes tendon regeneration
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Prof. Xiaonan Liu is working at the Department of Orthopaedics, Shanghai Sixth People's Hospital, affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. He completed his M.D on Orthopedics from Southern Medical University, Guangzhou and Postdoctoral education from Johns Hopkins University, USA. He is a member of International Chinese Musculoskeletal Research Society, Hong Kong, China, American Society for Bone and Mineral Research, Washington DC, USA, Orthopedic Research Society, Illinois, USA, and OA Centers for Orthopedics, Portland, USA. He works on bone biology, senescence, aging, osteoporosis, osteoarthritis, and spine degeneration with nearly 30 works to his credit.

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