

Single-Cell Atlas Reveals Why Rotator Cuff Injuries Heal with Damaging Scars

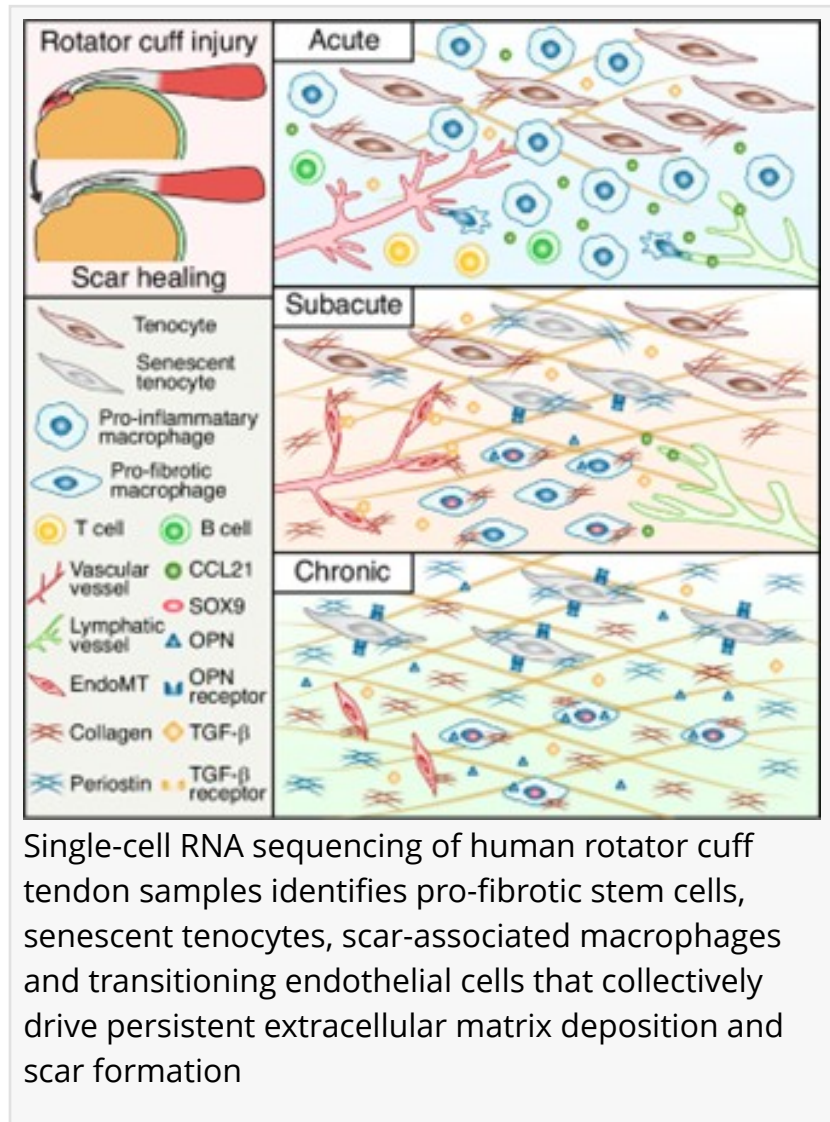
Researchers uncover how distinct cell populations and fibrotic signals drive permanent scarring after rotator cuff tears

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/EINPresswire.com/ -- Rotator cuff tears often heal with stiff, dysfunctional scar tissue, limiting recovery. A new study reveals why tendon regeneration fails after injury. Using single-cell profiling of tens of thousands of cells from patient tendon samples, the study maps the first atlas of human tendon scarring and identifies pro-fibrotic stem cells, senescent tendon cells, scar-forming macrophages, and transitioning endothelial cells. Targeting key fibrotic signals reduced scarring in animal models, suggesting new therapeutic strategies.

Rotator cuff tears are among the most common and debilitating musculoskeletal injuries, frequently causing chronic pain, reduced shoulder

mobility, and a high risk of re-injury even after surgical repair. Although modern surgical techniques can reconnect injured tendons to bone, healing outcomes remain inconsistent. Unlike fetal tendons, which are capable of regenerating without scarring, adult human tendons typically repair themselves by forming dense fibrotic tissue. This scar tissue lacks the highly organized collagen architecture and elastic mechanical properties of healthy tendon, ultimately compromising strength, flexibility, and long-term recovery. Despite the major clinical burden of rotator cuff disease, the cellular and molecular mechanisms that lock adult tendons into this scarring response have remained poorly understood.



To address this gap, researchers analyzed tendon tissue from patients with acute, subacute, and chronic rotator cuff tears using a combination of histological imaging and single-cell RNA sequencing. This integrated approach enabled scar formation to be examined at unprecedented resolution, with nearly 90,000 individual cells profiled from injured human tendons. By comparing samples across different stages of injury, the team was able to capture both early and persistent changes in tendon structure and cell behavior. The analysis revealed marked architectural disruption following injury, including severely disorganized collagen fibers, an imbalance in the ratio of collagen types I and III, and abnormally thin collagen fibrils that persisted even months after the initial tear. These structural abnormalities closely mirrored the long-term functional deficits commonly observed in patients. The findings were published on February 5, 2026, in Volume 14, Issue 17 of the [journal Bone Research](#).

The research was led by Professor Jianzhong Hu from the Department of Spine Surgery and Orthopaedics and Professor Hongbin Lu from the Department of Sports Medicine at Xiangya Hospital, Central South University, China.

At the cellular level, the study uncovered a surprisingly complex and self-reinforcing fibrotic microenvironment. Tendon stem cells and progenitor cells, which normally contribute to tissue repair, failed to fully differentiate into mature, functional tendon cells. Instead, they remained in a prolonged activated state, continuously secreting extracellular matrix components that contributed to scar buildup. In parallel, a large fraction of resident tenocytes entered a senescent state. These aging cells lost their capacity to remodel damaged tissue but remained metabolically active, releasing signals that further promoted collagen accumulation. “We were struck by how tendon cells that should support healing instead became drivers of fibrosis,” said Prof. Hu. “This helps explain why scarring persists even long after inflammation subsides.”

Immune cells were also found to play a central role in sustaining fibrosis. While most inflammatory cells gradually declined as injury progressed, macrophages persisted at the injury site and underwent a striking functional transition. These cells adopted a distinct scar-associated phenotype characterized by direct production of collagen and other fibrotic proteins. The study showed that this transition was driven by the transcription factor SOX9, which reprogrammed macrophages into matrix-secreting cells. “These macrophages are not just bystanders,” explained Prof. Lu. “They actively build scar tissue, creating a self-sustaining fibrotic environment that is difficult to reverse.”

Beyond identifying cellular mechanisms, the study highlights meaningful translational opportunities. In the short term, targeting key fibrotic pathways such as osteopontin (OPN) and transforming growth factor- β (TGF- β) signaling could be used alongside surgery to reduce scar formation and lower the risk of re-tear.

Over the longer term, the cellular roadmap provided by this work may enable regenerative therapies that actively redirect tendon healing toward true tissue restoration. The findings also

point to broader relevance, as similar fibrotic mechanisms operate in heart, lung, and liver diseases. Understanding scar biology at single-cell resolution extends well beyond orthopedics, bringing the field closer to therapies that help tissues heal properly rather than merely closing wounds.

Reference

Title of original paper: Single cell atlas decodes the molecular dynamics of scar repair after human rotator cuff tear

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