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RESEARCH NEWS STORY

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Chiba University

Pathological Mechanism of Mechanosensitive Cells Driving the Growth of Keloids

Researchers discover a type of fibroblast that may contribute to the formation and recurrence of overgrown scars

Keloids are overgrown scars that often cause chronic pain, itching, and restricted movement, but their biological origins remain unclear. In a recent study, researchers from Japan discovered a distinct subset of fibroblasts that senses mechanical tension through a protein called PIEZO2. These cells drive abnormal extracellular matrix collagen production and lead to scar recurrence, highlighting a potential therapeutic target and opening new avenues for the diagnosis and treatment of keloids.

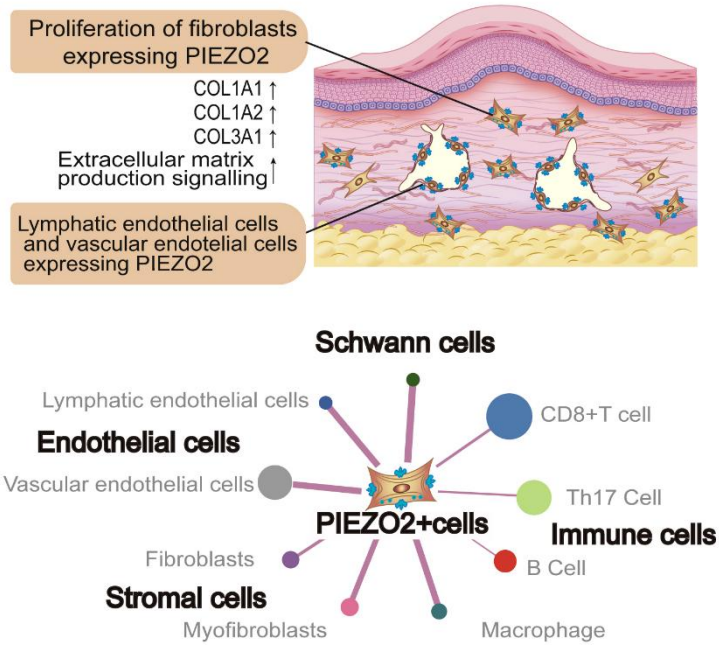

Image title: Cells expressing PIEZO2 mechanoreceptors may drive the pathology of keloids
Image caption: This schematic diagram shows how a specific population of fibroblast expressing PIEZO2 protein contribute to the formation and growth of keloids.
Image credit: Professor Yuzuru Ikehara from Chiba University, Japan
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Keloids are raised, overgrown scars that can develop after skin injuries or surgery, often extending beyond the original wound boundaries. For many people, keloids are more than just a cosmetic concern; they often cause distressing symptoms such as chronic pain, itching, and restricted movement. While various treatment options exist, such as surgical removal, steroid injections, and radiation, keloids are notoriously difficult to manage, with recurrence rates reaching as high as 30%.

Even after decades of study, it is still unclear why keloids grow uncontrollably, unlike hypertrophic scars. The current understanding is that an overproduction of extracellular matrix collagen by fibroblasts—cells that produce elements of connective tissue—is involved and that repeated mechanical tension on the skin contributes to keloid formation. However, the precise cellular and molecular mechanisms driving this uncontrolled scarring are unclear. More specifically, we don't know how or which cells sense the mechanical pressure and ultimately translate it into abnormal tissue growth.

Now, a study made available online on July 31, 2025, and published in Volume 267, Issue 1 of *The Journal of Pathology* on September 01, 2025, provides a new piece to this puzzle. A research team led by Professor Yuzuru Ikehara, along with co-first authors Dr. Shinsuke Akita and Dr. Sanae Ikehara, and co-authors Prof. Kiyoshi Hirahara, and Prof. Nobuyuki Mitsukawa, all from the Graduate School of Medicine at Chiba University, Japan, investigated the histological, genetic, and molecular differences between keloids and other fibrotic conditions to pinpoint the unique drivers of keloid formation and recurrence.

"While analyzing fibrotic tissue from lymphedema in collaboration with plastic surgeons, I conceived the idea that comparing it with keloid tissue might help identify pathological alterations specific to keloid fibroblasts. Although both conditions involve fibrosis, their underlying physiological contexts and etiologies differ substantially," explains Prof. Ikehara, describing the motivation behind the study.

The study involved a comprehensive analysis of human tissue samples. The team compared keloid tissues with those from lymphedema, a condition characterized by fibrous overgrowth but not primarily driven by mechanical tension, along with healthy skin samples. They employed several advanced techniques, including global gene expression analysis and single-cell RNA sequencing; these methods allowed them to examine gene activity in individual cells and precisely characterize the cell types involved. Through this detailed approach, the researchers sought to pinpoint mechanosensitive cells and molecules contributing to keloid pathology and recurrence.

A key discovery was that keloid tissues exhibited significantly higher expression levels of a mechanosensitive ion channel called PIEZO2, compared to lymphedema tissues. Simply put, PIEZO2 acts as a microscopic sensor, allowing cells to detect and respond to mechanical forces. The researchers observed that keloids with a history of recurrence after surgery showed even higher levels of PIEZO2.

Further investigation using single-cell analysis identified a previously unknown subpopulation of fibroblasts that specifically expressed high levels of PIEZO2. These PIEZO2-expressing fibroblasts (called FB^{PZ2+}) were found to be highly active in the production of collagen and

other components of the extracellular matrix, which are the building blocks of scar tissue. The team also observed that these FB^{PZ2+} cells clustered around blood and lymphatic vessels in keloid tissue, particularly in actively growing areas.

"Connective tissue is not composed merely of fibroblasts—it also contains immune cells, blood vessels, and nerves, all of which work together to maintain the proper homeostasis, a critical factor in supporting organ-specific functions," explains Prof. Ikehara. *"Therefore, just as studies of immune and neural cell components have advanced our understanding of neurodegenerative and allergic diseases, investigating fibroblasts may help uncover the mechanisms underlying keloid formation."* Indeed, this study represents a significant step in that direction by highlighting the unique role of FB^{PZ2+}cells.

Most importantly, the identification of these PIEZO2-expressing fibroblasts has profound implications for the future diagnosis and treatment of keloids. The study findings reveal that keloid formation is not merely a generalized overgrowth but a unique process driven by specific tension-sensing cells.

"*Our work offers new insights into the pathogenesis of keloids and opens the door to novel diagnostic and therapeutic strategies,*" says Prof. Ikehara. "*For example, PIEZO2 inhibitors, which are a type of calcium ion channel blocker, may help alleviate pain and itching associated with keloids. If such targeted therapies become clinically available, they could greatly improve the quality of life for patients suffering from keloid-related discomfort.*"

Taken together, this study contributes to the development of therapeutic strategies to restore healthy connective tissue, ultimately improving patient outcomes.

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About Professor Yuzuru Ikehara from Chiba University, Japan
Dr. Yuzuru Ikehara is a Professor in the Department of Pathology at the Graduate School of Medicine, Chiba University, Japan. His research expertise spans surgical pathology, medical application of plasma technology, molecular and biochemical analysis, and the development of medical device systems. He has authored more than 200 peer-reviewed publications in these fields and has received numerous honors, including the Plasma Medicine Award (2022, Utrecht) from the International Society of Plasma Medicine and the Academic Research Award (2012, Nagoya) from the Japanese Society of Pathology. His work bridges basic science and translational research by identifying deviations from physiological norms through interdisciplinary methods—paving the way for innovative medical technologies.

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Reference:
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