News Release

BCAT1 Drives Excessive Collagen Production in the Fibrotic Heart

-The enzyme boosts proline production in cardiac myofibroblasts and could serve as a therapeutic target for fibrosis -

Key Points

- Fibrosis, in which excessive collagen accumulates in organs, contributes to idiopathic pulmonary fibrosis, cardiac hypertrophy, liver cirrhosis, chronic kidney failure, and treatment-resistant cancers, but no definitive therapy currently targets the process itself.
- The researchers identified branched-chain amino acid transaminase 1 (BCAT1) as a molecule that increases production of proline, an amino acid that makes up approximately 20% of collagen, in collagen-producing cardiac myofibroblasts.
- Deleting Bcat1 or administering a BCAT1 inhibitor reduced proline and collagen levels in infarcted mouse hearts and limited cardiac dysfunction, suggesting that BCAT1 could be a target for new antifibrotic therapies.

Summary

A research group led by Professor Michio Nakaya of the Research Institute of Environmental Medicine and Graduate School of Medicine, Nagoya University, in collaboration with Professor Kenji Hamase and Professor Go Hirai of Kyushu University and Professor Hidetaka Kosako of Tokushima University, has found that BCAT1 promotes collagen production in the fibrotic heart by increasing production of proline, a major amino acid building block of collagen.

Collagen is essential for maintaining the shape and elasticity of organs and for repairing injured tissue. During chronic inflammation or disease, however, collagen can be produced in excess and accumulate in organs. This process, known as fibrosis(*1), stiffens tissue, impairs organ function, and contributes to the progression of many serious diseases.

The team discovered that BCAT1 was barely detectable in healthy hearts but was strongly induced in collagen-producing myofibroblasts(*2) after myocardial infarction. BCAT1 activated pathways that increase the cellular supply of proline, which accounts for approximately one fifth of the amino acid composition of collagen, thereby supporting large-scale collagen production. BCAT1 expression was also elevated in hearts from patients with heart failure.

Mice lacking Bcat1 accumulated less proline and collagen after myocardial infarction and showed less deterioration of cardiac function. Treatment of wild-type mice with a BCAT1 inhibitor produced similar protective effects, including when treatment began after fibrosis had started to develop. The findings identify BCAT1 as an active driver of cardiac fibrosis and a potential target for therapies designed to suppress pathological collagen production.

The study was published in the Journal of Clinical Investigation on September 1, 2026.

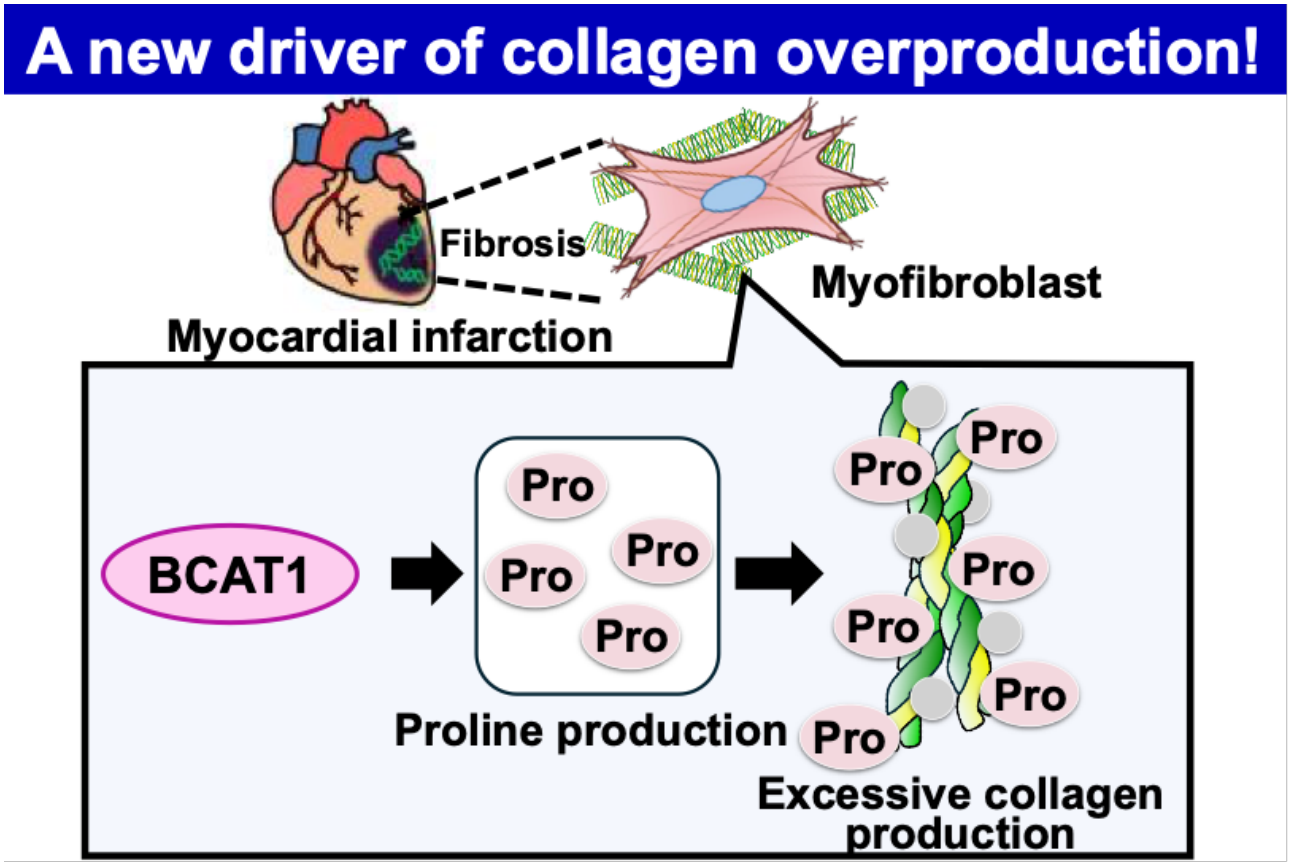

Figure. BCAT1 promotes excessive collagen production in the fibrotic heart.
After myocardial infarction, BCAT1 is induced in cardiac myofibroblasts and increases the supply of proline, a major building block of collagen.

Research Background

Extracellular matrix proteins such as collagen are indispensable for maintaining the shape of organs and tissues and providing appropriate strength and elasticity. Under normal conditions, only the required amount is produced. Disease and chronic inflammation, however, can cause these proteins to be produced in excess.

When excessive extracellular matrix accumulates in an organ, the tissue becomes stiff and loses its normal function. This condition is called fibrosis.

Fibrosis is observed in idiopathic pulmonary fibrosis, cardiac hypertrophy, liver cirrhosis, chronic kidney failure, and treatment-resistant cancers such as pancreatic cancer. It is deeply involved in disease progression and severity and has been estimated to contribute to approximately 45% of deaths in developed countries.

Despite its broad impact, there is no definitive therapy that directly suppresses fibrosis. Clarifying how the process occurs and identifying the proteins that drive its progression are therefore important for developing new treatments.

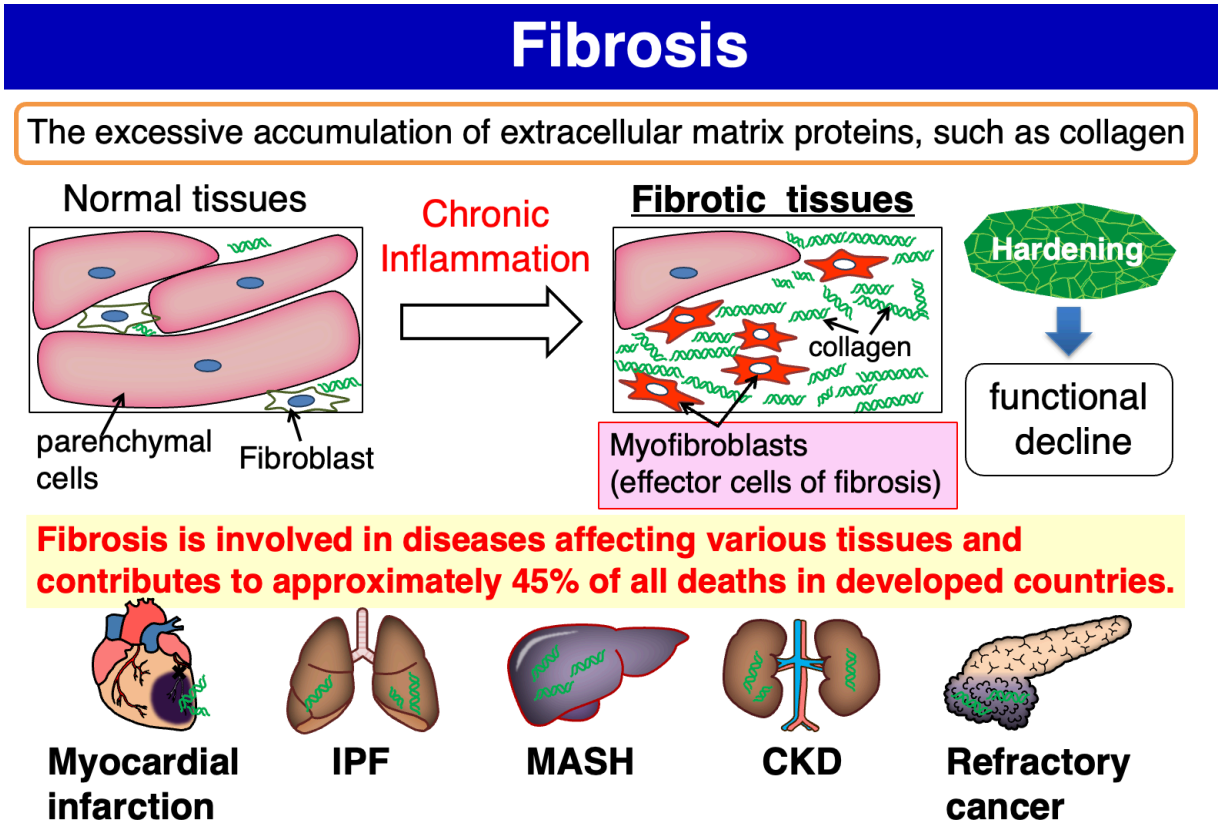

Figure. Overview of Fibrosis.
Chronic inflammation activates fibroblasts and promotes their differentiation into myofibroblasts, leading to excessive collagen deposition. The resulting tissue hardening and functional decline contributes to diseases in various organs, including the heart, lungs, liver, kidneys, and cancer.

Research Results

1. BCAT1 is induced in collagen-producing cells after myocardial infarction

Following myocardial infarction, collagen is produced to reinforce and repair the injured heart. Although this response is necessary for wound repair, excessive collagen deposition causes cardiac fibrosis. As fibrosis advances, the heart can no longer contract and relax efficiently, which can lead to the onset or

worsening of heart failure. The mechanisms that sustain excessive collagen production in the heart have remained incompletely understood.

The researchers found that the enzyme BCAT1 increased in collagen-producing cells after myocardial infarction. BCAT1 was barely detectable in healthy mouse hearts, but it became strongly expressed in myofibroblasts as fibrosis developed. The team also observed increased BCAT1 expression in hearts from patients with heart failure, supporting the relevance of this response to human disease.

2. BCAT1 increases the cellular supply of proline for collagen production

Collagen consists of long chains of amino acids, and approximately 20% of its amino acid composition is proline. The research group showed that BCAT1 activates a cellular pathway that ensures an adequate supply of proline and thereby supports the large-scale production of collagen. BCAT1 therefore functions as part of the material-supply system used by fibrotic cells to manufacture collagen.

3. Genetic deletion or pharmacological inhibition of BCAT1 protects the heart

In mice lacking Bcat1, proline levels in the heart fell after myocardial infarction, collagen accumulation decreased, and the decline in cardiac function was less severe than in control mice. The researchers then administered a BCAT1 inhibitor to wild-type mice. This treatment also suppressed cardiac fibrosis and limited the deterioration of cardiac function. The protective effect was observed not only when treatment began immediately after myocardial infarction but also when it began after fibrosis had started to develop. Together, these results show that BCAT1 is not simply a marker of fibrotic cells; it actively promotes excessive collagen production and cardiac fibrosis.

Research Summary and Future Perspective

This study identifies BCAT1 as a key molecule that promotes pathological collagen production in the heart by increasing the supply of proline. Because BCAT1 was barely detectable in healthy hearts and was concentrated in myofibroblasts in fibrotic hearts, targeting BCAT1 may make it possible to suppress excessive collagen production while limiting effects on normal tissue. BCAT1 was also increased in fibrotic liver tissue. The group will therefore investigate whether the pathway can be targeted in liver disease and other fibrotic disorders, with the goal of developing treatments that can be applied across multiple organs. Further work will be required to evaluate the safety,

dosing, and clinical efficacy of BCAT1-directed therapies.

Glossary

∗1)Fibrosis: A condition in which collagen and other extracellular matrix proteins accumulate excessively in an organ, causing the tissue to become stiff.

∗2)Myofibroblasts: Cells that emerge after tissue injury or inflammation and produce collagen and other extracellular matrix proteins during repair and fibrosis. They are rare in healthy organs and arise when fibroblasts and other cells become activated.

Publication

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