

News Release

Discovery of fibroblasts that suppress intestinal fibrosis in Crohn's disease

- Possibility of a new drug therapy targeting fibroblasts -

Key Points

- In intestinal strictures of patients with Crohn's disease, the characteristics of fibroblasts were found to change, and Meflin-positive fibroblasts, which act to suppress fibrosis, were significantly decreased.
- Using animal models, we clarified that Meflin suppresses the progression of intestinal fibrosis through the WNT5A-ROR2 pathway.
- Administration of AM80, a synthetic retinoid drug, was shown to change fibroblasts derived from patients with Crohn's disease into Meflin-positive cells and, in mouse models, to potentially suppress the progression of fibrosis by increasing Meflin-positive fibroblasts.

Summary

A collaborative research team led by Researcher Jingxi Mu (first author), Hospital Lecturer Keiko Maeda (corresponding author), and Professor Hiroki Kawashima of the Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine; Professor Atsushi Enomoto (corresponding author) of Tumor Pathology; Associate Professor Goro Nakayama of Surgery (currently at Nagoya Memorial Hospital); and Professor Mitsuhiro Fujishiro of the Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, has discovered fibroblasts that suppress the progression of intestinal fibrosis in Crohn's disease.

Crohn's disease is an intractable disease that causes inflammation of unknown causes in the gastrointestinal tract. Repeated inflammation leads to the progression of fibrosis and narrowing of the intestine. At present, there is no effective drug therapy for strictures caused by intestinal fibrosis, and surgery is the main treatment when strictures progress. Therefore, the development of medical therapies that suppress the progression of fibrosis and prevent intestinal strictures is needed. Fibroblasts play an important role in fibrosis, but their functions have not been fully clarified, and their diversity has attracted attention. In this study, we focused on fibroblasts with the aim of developing a medical therapy to suppress the progression of intestinal fibrosis.

Analysis of surgical specimens from patients with Crohn's disease who underwent surgery for intestinal strictures showed that fibroblast populations differed

between strictured and non-strictured intestinal regions, and that Meflin-positive fibroblasts were decreased in strictured regions. Animal experiments further showed that, in mice lacking Meflin, progression of intestinal fibrosis was aggravated through the WNT5A-ROR2 pathway. In addition, using the existing synthetic retinoid drug AM80, we clarified that pharmacologically increasing Meflin-positive fibroblasts suppressed the progression of intestinal fibrosis in mouse models and in fibroblasts derived from patients with Crohn's disease.

This study interprets intestinal fibrosis in Crohn's disease from the perspective of the functional diversity of fibroblasts. The findings are expected to lead to the development of medical treatment strategies targeting fibroblasts.

This research was published in The Journal of Clinical Investigation on May 19, 2026.

Research Background

Crohn's disease is a designated intractable disease that causes chronic inflammation of unknown cause in the gastrointestinal tract, and fibrosis triggered by inflammation causes intestinal strictures. Although drugs that suppress inflammation have been developed, drug therapies that suppress the progression of fibrosis have not been established, and surgery is the main treatment when strictures progress. Repeated surgery is often required, and the development of medical treatment is desired.

Intestinal fibrosis is a condition in which, triggered by regeneration of injured epithelial cells, fibroblasts excessively produce extracellular matrix, making the organ hard and impairing its normal function. Fibroblasts play a central role in fibrosis, but it has become clear that their functions are diverse. However, it has not been sufficiently clarified which fibroblasts promote or suppress fibrosis. Against this background, this study focused on the diverse functions of fibroblasts and aimed to clarify the pathophysiology of intestinal fibrosis in Crohn's disease and to develop medical treatment.

Research Results

In this study, we analyzed fibroblasts using surgical specimens from patients with Crohn's disease who underwent surgery for small-intestinal strictures. Compared with non-strictured regions, fibroblast populations were altered in intestinal strictured regions, and among them, Meflin-positive fibroblasts were found to be decreased. Meflin is a protein expressed in fibroblasts and is known to be associated with cancer progression and fibrosis of the heart and lung.

Next, using animal experiments, we examined the function of Meflin in intestinal fibrosis. In mice lacking Meflin, progression of intestinal fibrosis was promoted. In addition, analyses of isolated fibroblasts showed that the WNT5A-ROR2 pathway

was involved in the progression of fibrosis.

Furthermore, AM80, an existing drug that induces Meflin expression in fibroblasts, was examined using fibroblasts isolated from patients with Crohn's disease and a mouse model of fibrosis. As a result, secretion of fibrosis-promoting factors (such as TGF- β and IL-6) from patient-derived fibroblasts was suppressed, and progression of intestinal fibrosis was also suppressed in the mouse fibrosis model.

Research Summary and Future Perspective

This study revealed fibroblasts that suppress the progression of intestinal fibrosis in Crohn's disease and showed the possibility that the progression of fibrosis can be suppressed by controlling the properties of fibroblasts with drugs. In the future, toward the development of treatments targeting fibroblasts, we aim to further examine safety and efficacy and to connect these findings to clarification of the pathophysiology and development of treatments for other diseases caused by chronic inflammation.

Publication

Journal: The Journal of Clinical Investigation

Article title: Meflin confers antifibrotic properties to intestinal fibroblasts in inflammatory bowel disease

Authors: Jingxi Mu, Keiko Maeda*, Tadashi Iida, Shinji Mii, Nobutoshi Esaki, Yukihiro Shiraki, Yasuyuki Mizutani, Masanao Nakamura, Takeshi Yamamura, Tsunaki Sawada, Eri Ishikawa, Kentaro Murate, Takashi Hirose, Kazuhiro Furukawa, Akina Oishi, Haruhiko Suzuki, Takayoshi Kishida, Goro Nakayama, Mitsuhiro Fujishiro, Hiroki Kawashima, Atsushi Enomoto*

DOI: [10.1172/JCI192804](https://doi.org/10.1172/JCI192804)

Japanese ver.

https://www.med.nagoya-u.ac.jp/medicalJ/research/pdf/Jou_260610.pdf