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EDITORIAL

Myofibroblast-Driven Crohn's Disease Fiber Stricture Fibrotic Microenvironment: High-Resolution Spatial Transcriptomic Analysis

Crohn's disease (CD) is a major challenge in the field of gastroenterology, with fibrotic strictures being one of its most troublesome complications.[1] The pathological features of its complications are mainly intestinal wall structural remodeling and excessive deposition of the extracellular matrix (ECM). More than one-half of patients with CD will develop fibrotic strictures as the disease progresses.[2] A significant pathological feature of fibrous stenosis is the proliferation of myofibroblasts in the submucosa[3]; however, the identity and origin of these cells remain unclear, and the molecular mechanisms driving their abnormal proliferation have not been fully elucidated. Currently, single-cell RNA sequencing (scRNA-seq) technology has made significant progress. Traditional research methods indeed have limitations, such as difficulty in effectively capturing cell subpopulations embedded in the ECM and a lack of critical spatial context information, which restricts our in-depth understanding of the fibrotic microenvironment.

In this study, Zhang and colleagues[4] used high-resolution spatial transcriptomics technology to overcome the limitations of traditional techniques, providing strong evidence for the characteristic fibrotic microenvironment in CD-associated strictures. The study employed multiple approaches, including histological analysis, scRNA-seq datasets, immunofluorescence, primary pericyte cultures, and quantitative polymerase chain reaction, to deeply investigate the cellular composition and molecular interaction mechanisms during intestinal fibrosis. By examining the spatial distribution of stromal and immune cells, the authors identified ECM-high myofibroblasts and reprogrammed pericytes as the core drivers of fibrotic strictures, laying the groundwork for the development of new therapeutic targets.

Zhang and colleagues[4] first confirmed that submucosal thickening caused by myofibroblast proliferation and ECM deposition is the main cause of intestinal stricture in patients with CD.[5,6] The authors conducted spatial transcriptomic analysis on fibrotic and non-fibrotic ileal specimens, finding that the submucosal myoid cells are essentially a pathogenic myofibroblast subpopulation characterized by co-expression of smooth muscle cell (SMC) markers and ECM-related genes. Combined with research data, it was confirmed that they originate from SMCs and submucosal vascular SMCs and contribute to intestinal wall thickening through both cell proliferation and ECM secretion mechanisms. Spatial transcriptomics successfully captured ECM-enriched cell populations that were missed by traditional techniques.

Mechanistically, this study confirmed multidimensional cell interactions within the fibrotic microenvironment. The research found a significant increase in pericytes within inflamed tissue, which underwent transcriptional reprogramming to acquire a myofibroblast-like phenotype. In vitro experiments also showed that transforming growth factor-β1 stimulation could induce this transformation. Clustering analysis of fibroblast subpopulations revealed that these cells exhibited pronounced spatial heterogeneity, with FAP^+ fibroblasts (marked by MMP3 and MMP1) specifically abundant in fibrotic regions and showing high ECM-producing capacity. In this study, co-localization results of inflammatory monocytes and stromal cells indicated a clear ligand-receptor interaction between them; it is thus speculated that inflammatory monocytes may act as upstream effector cells regulating ECM-producing cells through cytokine signaling.

An important value of this study lies in its shift of the traditional research focus on CD, moving from the conventional emphasis on dysfunctions of epithelial or immune cells to the role of stromal cells in driving the pathogenesis of intestinal fibrotic strictures. The authors clarified the characteristics and origins of pro-fibrotic myofibroblasts, mapped the reprogramming process of pericytes, and constructed an immune-stromal cell interaction network, providing an overall framework for analyzing the fibrotic microenvironment. Myofibroblasts and pericytes are promising new therapeutic targets, and spatial transcriptomics offers a new tool for identifying fibrosis-specific biomarkers. These findings have significant clinical implications.

These findings provide several key insights. The authors used spatial transcriptomics to identify subpopulations of high ECM-producing myofibroblasts that were missed by scRNA-seq, filling critical gaps in CD fibrosis research; they also reduced excessive ECM deposition and intestinal wall thickening by targeting the conversion of SMCs/pericytes into myofibroblasts or by blocking immune–stromal cell interactions; FAP^+ fibroblasts and inflammatory monocytes can serve as auxiliary targets to inhibit the progression of fibrotic strictures.

Naturally, the characteristics of this fibrotic microenvironment still need to be validated in larger clinical stratification cohorts, and the precise molecular pathways driving stromal cell activation need to be elucidated. In addition, in vivo models are needed to assess the efficacy of targeted anti-fibrotic strategies. It is worth noting that this study still represents an important advance in understanding the role of

stromal cells in the pathogenesis of CD, fully demonstrating the powerful capability of high-resolution spatial transcriptomics in dissecting complex tissue microenvironments.

Zhang and colleagues[4] conveyed an important message: to overcome CD-related fibrotic strictures, we must move beyond focusing solely on epithelial and immune cells and shift our targets to the supportive stroma. Through this study, the authors clarified the spatial organization of the fibrotic microenvironment and identified myofibroblasts and pericytes as central players in the CD fibrotic process—bringing new hope for the urgent development of anti-fibrotic therapies.

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References

1. Solitano V, Dal Buono A, Gabbiadini R, et al. Fibrostenosing Crohn's disease: what is new and what is next. J Clin Med 2023;12:3052.
2. Yoo JH, Holubar S, Rieder F. Fibrostenotic strictures in Crohn's disease. Intest Res 2020;18:379–401.
3. Wang J, Lin S, Brown JM, van Wagoner D, Fiocchi C, Rieder F. Novel mechanisms and clinical trial endpoints in intestinal fibrosis. Immunol Rev 2021;302:211–227.
4. Zhang D, Zou X, He M, et al. Elucidating a myofibroblast-dominated fibrotic niche in Crohn's disease-associated fibrostenosis through high-resolution spatial transcriptomics. Cell Mol Gastroenterol Hepatol 2026;20:101701.
5. Issa MT, Zaman S, Mohamedahmed AY, et al. Management of ileocolic anastomotic strictures in Crohn's disease: endoscopic or surgical intervention? A systematic review and meta-analysis. Int J Colorectal Dis 2025;40:162.
6. Veisman I, Massey WJ, Goren I, Liu W, Chauhan G, Rieder F. Muscular hyperplasia in Crohn's disease strictures: through thick and thin. Am J Physiol Cell Physiol 2024;327:C671–C683.

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