

Intestinal strictures in Crohn's disease: a 2021 update

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Abstract: Intestinal strictures remain one of the most intractable and common complications of Crohn's disease (CD). Approximately 70% of CD patients will develop fibrotic strictures after 10 years of CD diagnosis. Since specific antifibrotic therapies are unavailable, endoscopic balloon dilation and surgery remain the mainstay treatments despite a high recurrence rate. Besides, there are no reliable methods for accurately evaluating intestinal fibrosis. This is largely due to the fact that the mechanisms of initiation and propagation of intestinal fibrosis are poorly understood. There is growing evidence implying that the pathogenesis of stricturing CD involves the intricate interplay of factors including aberrant immune and nonimmune responses, host-microbiome dysbiosis, and genetic susceptibility. Currently, the progress on intestinal strictures has been fueled by the advent of novel techniques, such as single-cell sequencing, multi-omics, and artificial intelligence. Here, we perform a timely and comprehensive review of the substantial advances in intestinal strictures in 2021, aiming to provide prompt information regarding fibrosis and set the stage for the improvement of diagnosis, treatment, and prognosis of intestinal strictures.

Keywords: Crohn's disease, diagnosis, fibrosis, intestinal strictures, pathogenesis, treatment

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Introduction

Crohn's disease (CD) is a chronic relapsing and remitting inflammatory disorder involving the whole gastrointestinal tract.¹ Approximately 70% of CD patients will develop stricturing or penetrating complications after 10 years of CD diagnosis.² A real-world study found that CD patients with fibrostenosis were at significantly higher risk for hospitalization, steroid dependency, repeated endoscopy, and surgery, as well as higher health-care costs, compared with CD patients without fibrostenosis.³ Therefore, intestinal strictures are becoming one of the most vexing and complex complications of CD.

Although anti-inflammatory therapies can alleviate inflammation and improve histological healing, they fall far short of a resolution for strictures.⁴ For CD patients with complex complications, endoscopic balloon dilation (EBD) and surgery

are currently available treatment options.⁵ However, they are not ideal due to a high rate of postoperative recurrence and complications.⁶ To date, there are still no licensed antifibrotic agents,⁷ partly due to the poor understanding of the mechanisms of initiation and propagation of intestinal fibrosis. Specific predictors that are capable of identifying CD patients at a high risk of developing strictures are also lacking, which may account for the lack of timely treatment.⁷ Given the large degree of overlap between the two types, distinguishing fibrosis-predominant strictures from inflammatory-predominant ones is also difficult using tools such as ultrasonic (US) examination, computed tomography, and magnetic resonance imaging (MRI) in clinical practice,⁸ making the choice of treatment options difficult.^{5,9} Since intestinal strictures are a hot topic in both clinical research and basic science research, numerous studies have been designed to address these

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hurdles, and substantial progress has been achieved within 2021.

Here, we summarize a curated set of articles within the year 2021 that highlight cutting-edge advances in relation to the underlying mechanisms, diagnostic methods, as well as evolving therapeutic options for intestinal strictures, aiming to give researchers and clinicians more insight into the trend of intestinal strictures.

Search strategy

A literature review was conducted on the database of PubMed, Web of Science, and Embase for all relevant literatures published in the year 2021, supplemented by manually reviewing the references of the included studies and relevant review articles. The following search terms were used (all fields): ('stenotic' OR 'stenosis' OR 'fibrosis' OR 'fibrotic' OR 'fibrostenotic' OR 'fibrostenosis' OR 'stricture' OR 'strictures' OR 'stricturing' OR 'strictured' OR 'constriction' OR 'constrictions') AND ('Crohn's disease' OR 'inflammatory bowel disease' OR 'CD' OR 'IBD') AND (Filters: from 1 January 2021 to 31 December 2021). References to the identified articles were also examined for additional studies meeting these criteria.

Mechanism of intestinal strictures

The pathogenesis of CD fibrosis is not completely understood, which is largely due to the lack of human-specific intestinal fibrosis models. Excitingly, in 2021, Estrada *et al.*¹⁰ generated human intestinal organoids (HIOs) using induced pluripotent stem cells from CD patients with strictures, and epithelial and mesenchymal cells derived from HIOs under the stimulation of transforming growth factor beta (TGF- β) were able to replicate intestinal fibrotic responses. This model shed new insight on the exploration of mechanisms underlying intestinal fibrosis. Several novel findings are discussed in the following section, which is shown in Figure 1.

Immune and nonimmune cells. The complex interplay between immune cells and nonimmune stromal cells is a major driver of intestinal fibrosis.¹¹ In 2021, novel mechanisms related to mast cells (MCs), macrophages, and circulating bone marrow-derived fibrocytes in CD fibrosis have been unveiled.

MCs, mostly located at host–environment interfaces (e.g. gastrointestinal tract), are the first defense cells to interact with allergens, invading pathogens and other dangerous antigens.^{12,13} Substantial evidence showed that MCs played a crucial role in fibrotic diseases.¹⁴ However, their explicit effects on CD fibrosis remain unknown. Liu *et al.*¹⁵ first found that MCs increasingly infiltrated fibrotic intestines of both CD patients and colitis mice compared to the corresponding controls. MCs were able to activate fibroblasts through releasing tryptase and then facilitate fibroblasts to differentiate into myofibroblasts *via* PAR-2/Akt/mTOR pathway.¹⁵ *In vivo*, the authors further reported that the deficiency of MCs in mice could significantly alleviate dextran sulfate sodium (DSS)-induced intestinal fibrosis, while once MCs were reconstructed in MC-deficient mice, the degree of intestinal fibrosis tended to reappear.¹⁵ Furthermore, inhibiting tryptase released from MCs conferred resistance to intestinal fibrosis, which was accompanied by decreased expression and deposition of extracellular matrix (ECM) proteins.¹⁵ Therefore, targeting MCs may represent a potential target for intestinal fibrosis.

Macrophages, especially tissue-resident macrophages, are actively involved in intestinal fibrosis.¹⁶ Dharmasiri *et al.*¹⁷ analyzed the whole transcriptome of macrophages purified from the intestines of CD, ulcerative colitis (UC), and healthy individuals *via* RNA sequencing technology, and found that fibrotic-related genes were significantly upregulated in CD patients compared with UC patients and healthy controls. Interestingly, the expression of M2 signature genes, fibrotic genes, and TGF- β 1 were enriched in macrophages from CD rather than from UC, which indicated that subsets of intestinal macrophages might be associated with CD fibrosis.¹⁷

Circulating fibrocytes are bone marrow-derived cells characterized by carrying both hematopoietic markers (CD34) and fibroblastic markers (collagen1), which can be recruited into injured tissue and involved in fibrosis formation.^{18,19} In line with this, Ueno *et al.*²⁰ demonstrated that the number of fibrocytes was significantly increased in plasma and fibrostenotic small bowel (SB) of CD patients, compared with that of non-fibrostenotic CD patients. Meanwhile, 10 plasma proteins, associated with fibrogenesis or fibrocyte development, were significantly increased in

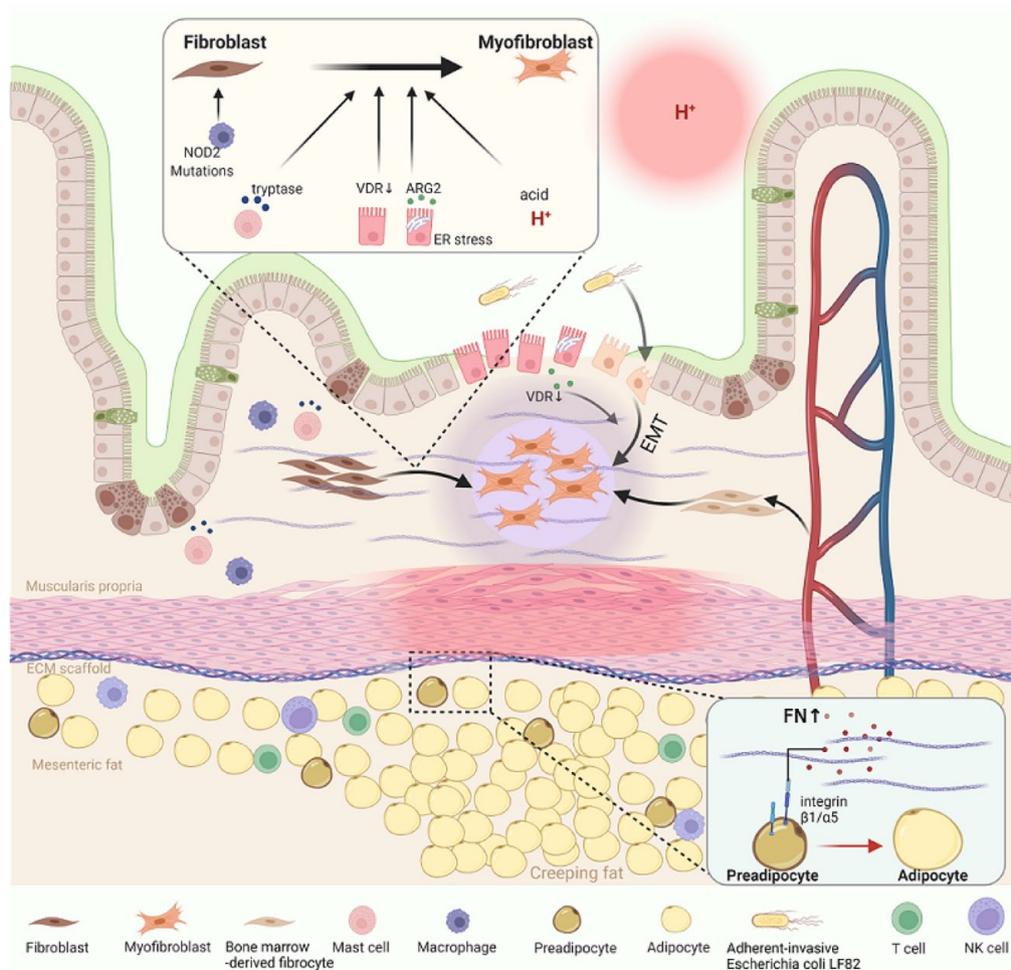


Figure 1. Schematic diagram of novel mechanisms of intestinal stricture in 2021. NOD2 mutations caused dysregulated homeostasis of activated fibroblasts and macrophages. Tryptase released from MCs, VDR deficiency in epithelial cells, AGR2 secreted by epithelial cells under ER stress, and acidic pH facilitated differentiation of fibroblasts into myofibroblasts. VDR deficiency in epithelial cells also contributed to EMT. Bacteroides fragilis colonization and the increase of circulating bone marrow-derived fibrocytes were correlated with fibrosis formation. FN which is secreted by HIMC mediated the migration of preadipocytes via the FN/ $\alpha 5\beta 1$ integrin signaling pathway, thus contributing to the formation of CrF. AGR2, anterior gradient protein 2 homolog; CrF, creeping fat; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ER stress, endoplasmic reticulum stress; FN, fibronectin; HIMC, human intestinal muscle cells; MCs, mast cells; NOD2, nucleotide-binding oligomerization domain 2; VDR, vitamin D receptor.

fibrostenotic CD patients.²⁰ It was assumed that the unique plasma protein profile from fibrostenotic CD patients might predispose human peripheral blood mononuclear cells to transform into fibrocyte-like cells.²⁰ Besides, within a 30-month follow-up, the increment of circulating fibrocytes was correlated with the subsequent escalation of medical therapy, endoscopic dilation, or surgery. These results suggest that circulating fibrocytes might serve as a disease predictor and provide a new route toward intestinal fibrostenosis.²⁰

Molecules and signaling pathways. Molecules act as the mediators of cells and play a key role in intestinal fibrosis.²¹ In the year 2021, several novel molecules have been discovered and are considered as new therapeutic targets for intestinal fibrosis, including Yes-associated protein and transcriptional coactivator with PDZ-binding motif (YAP/TAZ),²² tumor necrosis factor-like ligand 1A (TL1A),²³ anterior gradient protein 2 homolog (AGR2),²⁴ pH-sensing G protein-coupled receptor 4 (GPR4),²⁵ miR-155,²⁶ human

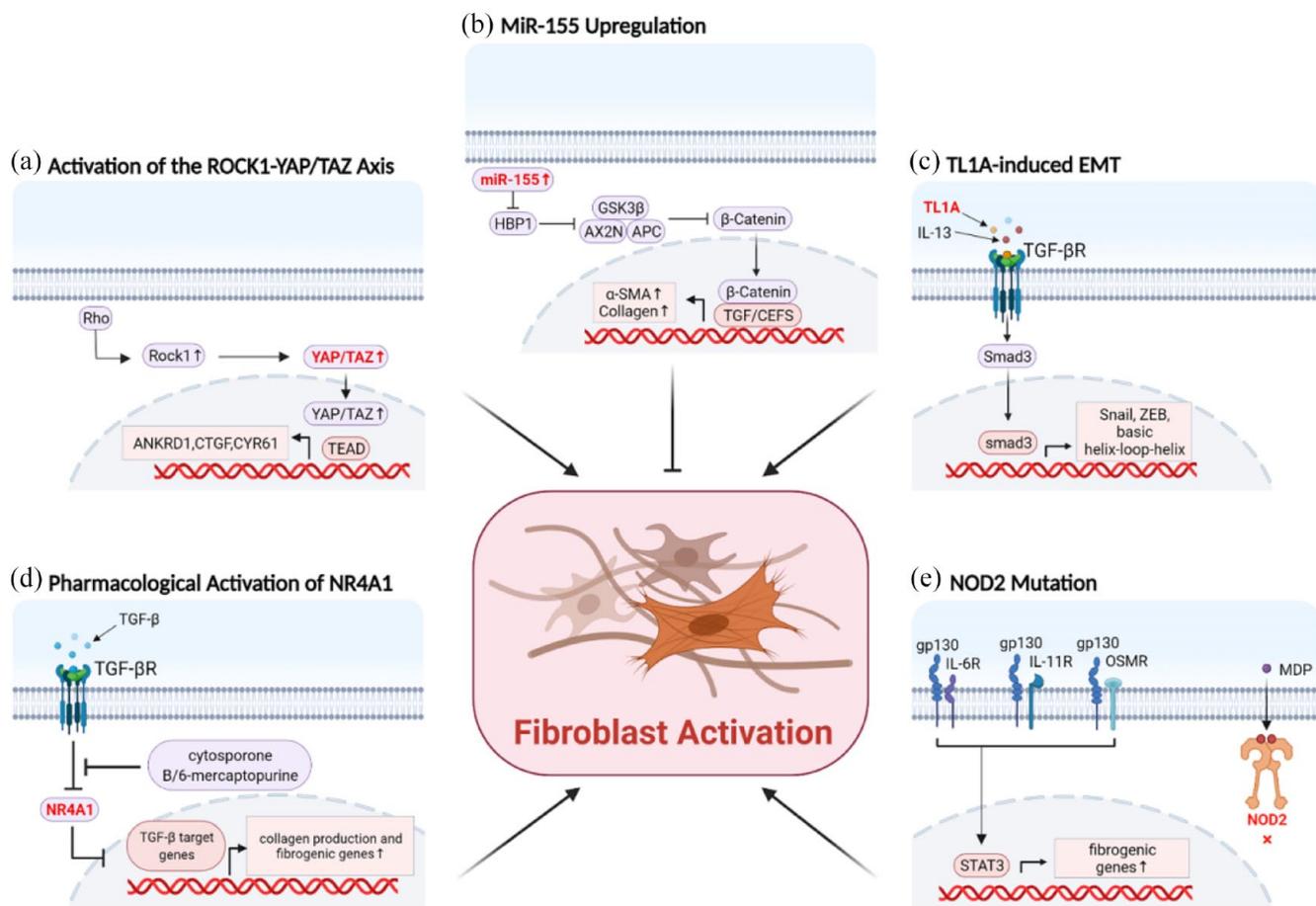


Figure 2. Novel molecules are involved in activation of intestinal fibroblasts. (a) YAP/TAZ activation was dependent on Rho/ROCK signaling pathway, and increased the expression of profibrotic-related genes and proliferation of fibroblasts. (b) The upregulation of miR-155 targeted HBP1 and then activated the Wnt/ β catenin signaling pathway, leading to the activation of fibroblasts. (c) TL1A accompanied with IL-13 induced EMT and activated fibroblasts via TGF- β 1/Smad3 pathway. (d) The pharmacological activation of NR4A1 with cytosporone B or 6-mercaptopurine attenuated TGF- β 1-induced fibrosis in myofibroblasts. (e) Gp130 family- and STAT3-related genes were highly enriched in NOD2-mutated fibroblasts and macrophages, which led to the differentiation of macrophages into activated fibroblasts.

EMT, epithelial-to-mesenchymal transition; HBP1, HMG-box transcription factor 1; IL, interleukin; NOD2, nucleotide-binding oligomerization domain 2; NR4A1, nuclear receptor 4 A1; ROCK, Rho-associated coiled-coil-containing protein kinase; STAT3, signal transducer and activator of transcription 3; TAZ, transcriptional coactivator with PDZ-binding motif; TGF- β 1, transforming growth factor beta 1; TL1A, tumor necrosis factor-like ligand 1A; YAP, Yes-associated protein; α -SMA, α -smooth muscle actin.

nuclear receptor 4A 1 (NR4A1),²⁷ and vitamin D receptor (VDR).²⁸

The activation and proliferation of intestinal fibroblasts is the hallmark of fibrosis, although its mechanism has not been fully elucidated. YAP/TAZ, transcription coactivators and effectors of Hippo pathway,²⁹ were found to be highly expressed and activated in fibroblasts isolated from stenotic intestines of CD patients and DSS-induced chronic colitis murine models.²⁴ In addition, the YAP/TAZ activation was associated with fibroblast activation and a high risk of intestinal

obstruction of CD.²² Knockdown of YAP/TAZ in fibroblasts isolated from the fibrostenotic intestines resulted in decreased expression of profibrotic-related genes and proliferation of fibroblasts, indicating that YAP/TAZ were critical activators of intestinal fibroblasts.²² It is known that YAP/TAZ activation is dependent on Rho/Rho-associated coiled-coil-containing protein kinase (ROCK) signaling pathway.²² *In vivo*, silencing of YAP/TAZ with ROCK1 inhibitor alleviated intestinal fibrosis, revealing the profibrotic effect of ROCK1-YAP/TAZ axis in intestinal fibroblasts [Figure 2(a)].²² Thus, YAP/TAZ

in fibroblasts may offer potential therapeutic strategies for intestinal fibrosis. Other promising molecules that target fibroblasts or myofibroblasts include GPR4 and miR-155.^{25,26} GPR4/ $G\alpha_{12/13}$ signaling was involved in the initiation of myofibroblast activation, and this effect could be reversed by the inhibition of GPR4.²⁵ MiR-155 was demonstrated to directly target HMG-box transcription factor 1 and then activate Wnt/ β -catenin signaling pathway, leading to intestinal fibrosis [Figure 2(b)].²⁶ Amamou *et al.*³⁰ reported that a high-salt diet also contributed to the activation of colon fibroblasts and intestinal fibrosis. The authors observed a significantly increased expression of fibrosis markers (e.g. colon MMP-9, plasmatic MMP-9, and MMP-2) in 2,4,6-trinitrobenzene sulfonic acid-induced colitis mice with a high-salt diet as well as ECM-associated proteins [e.g. α -smooth muscle actin (α -SMA), CTGF, Colla1, Col3a1] and MMP-2 in fibroblasts treated with NaCl.³⁰

Other molecules that should be mentioned here are TL1A and AGR2. TL1A has been previously reported to participate in intestinal inflammation and fibrosis, but the underlying mechanism remains unclear.²³ A study in 2021 found that the expression of TL1A in intestines of CD patients was almost twice as high as that in healthy individuals.³¹ The expression of TL1A was negatively associated with E-cadherin expression, whereas positively associated with β -catenin and α -SMA expression, implying that TL1A might be involved in the process of epithelial-to-mesenchymal transition (EMT).³¹ Indeed, evidence from both CD patients and a DSS-induced murine model indicated that TL1A could induce EMT through interleukin (IL)-13 and TGF- β 1/Smad3 pathway [Figure 2(c)].³¹ Another interesting molecule AGR2 was identified *via* secretome profile of epithelium in ileal CD strictures.²⁴ AGR2 and binding immunoglobulin protein were found to be increasingly expressed in the epithelium, especially under endoplasmic reticulum stress.²⁴ The enhanced expression of AGR2 was capable to trigger the differentiation of fibroblasts into myofibroblasts, thus promoting intestinal fibrosis.²⁴

In contrast to the aforementioned molecules that have profibrotic property, NR4A1 can dampen fibrogenic signaling in nonintestinal systems, and protect against fibrosis.³² Pulakazhi Venu *et al.*²⁷ added new evidence to support the antifibrotic

effect of NR4A1 in intestine system using a Crohn's-like ileitis murine model. They demonstrated that pharmacological activation of NR4A1 with cytosporone B or 6-mercaptopurine could decrease the deposition of ECM and proliferation of myofibroblasts, ultimately preventing fibrosis. Besides, NR4A1 activation was found to be able to attenuate TGF- β 1-induced proliferation, collagen production, and fibrogenic gene expression in human intestinal fibroblasts [Figure 2(d)].²⁷ Similarly, VDR activation or VD supplement also contributed to alleviating intestinal fibrosis.²⁸

Gut microbiota. Gut microbiota is an indispensable driver in intestinal fibrogenesis.^{1,33,34} Becker *et al.*³⁵ found that *Bacteroides fragilis*, a gram-negative commensal of the phylum *Bacteroidetes*, was associated with stricturing disease behavior and severe disease activity in CD patients. However, a deeper understanding of *B. fragilis* in CD fibrosis needs to be clarified in further investigations. Another gram-negative proteobacterium called *Adherent-invasive Escherichia coli* (AIEC) has been observed abundantly in CD patients and has been proved to cause intestinal fibrosis in a murine model.^{36,37} Using a DSS-induced murine model, Chokr *et al.*³⁸ found that LF82, the prototype AIEC strain, was capable to enhance the deposition of collagen and mRNA expression of profibrotic-related genes (e.g. Colla1, Col3a1, and Fn1), thus exacerbating intestinal fibrosis. *In vitro*, LF82 was able to induce intestinal epithelial cells to undergo EMT in response to TGF- β 1 stimulation.³⁸

Creeping fat. Creeping fat (CrF) is referred to as the characteristic expansion of mesenteric tissue at the inflamed intestinal sites in CD patients, which was originally described by Burril B. Crohn in 1932.³⁹ However, there is a paucity of information on the relationship between CrF and intestinal fibrosis. Ha *et al.*⁴⁰ reported a gut microbiota-dependent mechanism that drove the formation of CrF in CD in 2020. In 2021, our team revealed another novel mechanism of CrF formation.⁴¹ We first observed an inflammatory ECM scaffold produced by muscularis propria (MP) cells, which was positioned between CrF and MP exclusively in strictured intestines resected from CD patients.⁴¹ Under the speculation that the source of ECM scaffold was MP cells rather than CrF, human intestinal muscle cells (HIMCs) isolated from MP tissue pretreated with TGF- β 1 were further studied.⁴¹ The results

showed that only fibronectin (FN) and decorin changed significantly among proteins secreted from HIMC, which was in line with the immunofluorescence staining result of ECM scaffold in stricturing CD.⁴¹ We further identified that FN mediated the migration of preadipocytes *via* FN/ α 5 β 1 integrin signaling pathway, thus contributing to the formation of CrF.^{41,42}

One big obstacle to studying CrF is the lack of ideal animal models to mimic intestinal CrF. Remarkably, a new animal model *via* repeated colonic biopsy was established in 2021.⁴³ After four cycles of biopsy injuries (once per week), the penetrating fibrosis involving all layers of the murine colon and the expansion of mesenteric fat appeared, which was morphologically similar to CD patients with strictures.⁴³ Additionally, transcriptomic analysis revealed that gene expression in repeated colonic biopsy could recapitulate human CD.⁴³ The novel animal model thus paves a new avenue to study CrF in the future.

Host genetic susceptibility. Nucleotide-binding oligomerization domain 2 (NOD2) is the first identified gene conferring susceptibility to ileal CD, and its mutation is related to the increased risk of intestinal strictures.⁴⁴ However, the underlying mechanisms through which NOD2 drives fibrosis formation remain elusive.⁶ Nayar *et al.*⁴⁵ first unveiled how NOD2 deficiencies predisposed CD patients to develop a stricturing phenotype [Figure 2(e)]. They defined a unique activated fibroblast population characterized by CD14 and PDGFRA expression *via* single-cell RNA sequencing of inflamed ileum from patients with CD.⁴⁵ Loss of NOD2 was found to lead to dysregulated homeostasis of activated fibroblasts and macrophages.⁴⁵ Especially, Gp130 family (e.g. IL-6, IL-11, and OSM) and signal transducer and activator of transcription 3 regulation were demonstrated to be highly enriched in these activated fibroblasts and macrophages.⁴⁵ Blocking gp130 was then found to ameliorate the activated myeloid-stromal niche, which might benefit CD patients refractory to antitumor necrosis factors (TNF) therapy.⁴⁵ This study sheds insight on NOD2-driven fibrosis in CD, and highlights that gp130 blockade may be an alternative for CD patients with anti-TNF treatment failure.

Assessment of intestinal strictures

Identification and quantification of intestinal strictures is critical to accurate the diagnosis of patients

with CD and to tailor the individualized treatment strategies. Histologically, it has been well documented that CD strictures are characterized by the hypertrophy and hyperplasia of intestinal smooth muscle.^{46,47} However, a recent study has identified a novel histopathological phenotype in a subset of CD patients with ileal strictures, in which part of strictures were due to mural constriction rather than due to fibromuscular hypertrophy.⁴⁸ CD patients who presented with constrictive ileal strictures are featured by earlier onset, frequent multiplicity, and little fibromuscular mural expansion, which are pathologically and clinically distinct from those with hypertrophic strictures.⁴⁸ In addition, patients with constrictive strictures manifest as multiple strictures, and have significantly shorter surgery-free intervals than those with hypertrophic strictures.⁴⁸ This study provides evidence that intestinal strictures are truly heterogeneous entities. Thus, establishing a detailed diagnosis and treatment criteria for intestinal fibrosis is an urgent requirement. In 2021, several novel assessment and prediction models for intestinal fibrosis have been proposed and some key information is displayed in Table 1. Based on the characteristics of the above models and the area under the receiver operating characteristic curve (AUC) value, radiomic model (RM) and deep learning network displayed excellent diagnostic performances for the identification and quantification of intestinal stenosis, while blood protein and serologic markers showed a fair predictive ability.

Cross-sectional imaging modality. Cross-sectional imaging modalities, including magnetic resonance enterography, computed tomography enterography (CTE), and US, are widely used to evaluate transmural fibrosis.¹¹ However, currently, there are no reliable and widely accepted methods for determining intestinal fibrosis in CD.⁴⁹ Small-bowel stenosis (SBS) in CD was usually defined as luminal narrowing with upstream bowel dilation on cross-sectional imaging modalities.⁵² However, Stocker *et al.*⁵³ argued that luminal stenosis was sufficient for diagnosing SBS, because it had higher accuracy and sensitivity compared with the combination of luminal stenosis and upstream dilation. In the 2021 international consensus, the value of upstream dilation in histopathologically diagnosing strictures remained an unsolved issue.⁵⁴

Recently, US has gained much attention in distinguishing fibrosis because of its noninvasive and

Table 1. Novel assessment and prediction models for intestinal strictures in CD.

Model	Equipment	Parameters	Functions	AUC value	Accuracy	Sensitivity	Specificity	Limitations	References
RM	CTE	Busyness _{original} , busyness _{col3r05} , busyness _{dbir05} , busyness _{dbir15}	Differentiate moderate-severe from none-mild intestinal fibrosis	0.888	0.857	0.815	0.939	Relatively small sample sizes; time-consuming for manual volume of interest segmentation; not suitable for intestinal strictures with blurred contour	Li <i>et al.</i> ⁴⁹
State-of-the-art deep learning network	CE	Strictures images, normal mucosa images, and ulcer images	Identify intestinal strictures	0.989	0.935	0.92	0.89	A retrospective analysis; lack of strictures that were failed to pass CE or visible on cross-sectional images; lack of dynamic time-lapse movement images	Klang <i>et al.</i> ⁵⁰
Blood protein and serologic markers	-	Four plasma proteins (IL7, MMP10, IL12B, and CCL11) and two serologic markers (LnASCA IgA and LnCbir)	Predict the risk of stricturing complications	0.68	-	-	-	Relatively small sample sizes; no specific timepoints to diagnosis complications; no comparable external validation cohort	Ungaro <i>et al.</i> ⁵¹

The accuracy, sensitivity, and specificity were calculated from the receiver operating characteristic curve according to the Youden index. AUC, area under the receiver operating characteristic curve; CD, Crohn's disease; CTE, capsule endoscopy; CE, capsule endoscopy; RM, radiomic model.

nonradiating nature.⁵⁵ Bhatnagar *et al.*⁵⁶ examined the association between sonographic features and histopathological scores, and revealed that submucosal layer echogenicity, clarity, and mucosal layer thickness were associated with intestinal fibrosis. Besides, the changes in intestinal tissue stiffness were positively correlated with the severity of fibrosis, with a correlation coefficient of 0.73.⁵⁷ A systematic review including 11 studies showed that intestinal ultrasound elastography (UE) was able to evaluate intestinal strictures and differentiate inflammation from fibrosis phenotype in CD patients.⁵⁸ UE is emerging as a feasible technique to estimate tissue stiffness.⁵⁹

Magnetic resonance elastography (MRE) is also a technique to evaluate tissue stiffness.⁶⁰ In 2021, the ability of MRE to detect intestinal fibrosis in CD patients was first evaluated. Results from a pilot study showed that the intestinal stiffness value measured by MRE was proportional to the degree of fibrosis in CD patients.⁶¹ The value of bowel stiffness over 3.57 kPa achieved a good prediction for hospitalization and surgical resection, with AUC of 0.82.⁶¹ MRE may act as a predictor to estimate the risk and severity of intestinal fibrosis in CD patients. In addition, MR enterography was first used to measure terminal ileum motility in pediatric CD patients with standard free-breathing techniques in 2021.⁶² Terminal ileum motility was found to be negatively associated with CD activity, which might be a candidate biomarker for monitoring disease progression and treatment efficacy.^{62,63}

Radiomics is a popular form of radiologic imaging analysis aiming to extract high-dimensional imaging features to reveal subtle disease characteristics.⁶⁴ Li *et al.*⁴⁹ developed a novel CTE-based RM to assess intestinal fibrosis in CD patients, which substantially improved the quantitation of CTE in intestinal fibrosis. Results showed that RM had an excellent discriminatory ability for identifying moderate–severe and none–mild intestinal fibrosis with the AUC value of 0.888.⁴⁹ Subsequently validated in three different centers, RM achieved consistently high AUC values ranging from 0.724 to 0.816,⁴⁹ superior to even experienced radiologists in terms of the predictive ability for intestinal fibrosis.⁴⁹

Endoscopy. Endoscopy is an invasive method that allows direct visualization of the surface of the affected intestine; however, it fails to evaluate

transmural fibrosis.⁶⁵ A multicenter study in 2021 showed that the frequency of endoscopic diagnosis was significantly increased in CD patients with SB strictures, but its diagnostic yield did not change over time.⁶⁶ Integrating artificial intelligence (AI) technology with endoscopy may be a solution to this problem. Studies showed that AI was faster and more accurate when detecting crucial subtle lesions compared with an endoscopist, although they had a comparable diagnostic performance to some extent.⁶⁷ In addition, the application of AI to capsule endoscopy (CE) provides a new means for assessment of SB and colonic lesions,⁶⁸ especially for non-obstructed patients with SBS.⁵⁰ Notably, a state-of-the-art deep learning network had a high accuracy (93.5%) in detecting stenosis and an excellent discrimination between strictures and ulcers (AUC=0.942) on CE images.⁵⁰

Biomarkers. Up till now, specific or reliable markers to predict CD strictures are still unavailable.^{69,70} Prentice *et al.*⁷¹ first investigated a novel approach to diagnose and manage CD patients with strictures. They found that fecal calprotectin, together with US, was able to assess strictures as well as monitor treatment response in pregnant CD patients.⁷¹ Additionally, Ungaro *et al.*⁵¹ performed a prospective inception cohort with 265 pediatric CD patients to assess the association between novel blood protein biomarkers and stricturing complication. Four plasma proteins (IL7, MMP10, IL12B, and CCL11) and two serologic markers (LnASCA IgA and LnCbir) were identified, and then were pooled to predict the risk of stricturing complication with the AUC value of 0.68.⁵¹ However, there is still a long distance to go in identifying validated and accurate predictive biomarkers for intestinal strictures.

Treatment of intestinal strictures

The common methods to relieve symptoms related to intestinal strictures include drug therapy, endoscopic therapy, and surgical treatment. In 2021, several studies were put forward to evaluate the efficiency of available management strategies and to explore potential novel antifibrotic therapies.

Medical therapy. Alleviating or even reversing intestinal fibrosis is a tough challenge in the management of intestinal strictures.⁷² Immunosuppressants and biological agents have no direct

effect on fibrosis, although these are associated with a 96% and 94% reduction of stricture development, respectively.^{1,73}

Anti-TNF therapy still remains the backbone of treatment in fibrostenotic CD,⁷⁴ of which effect on strictures has been further investigated in 2021. A real-world study including 59 patients with stricturing CD showed that 88% of patients achieved clinical improvement when receiving TNF induction therapy with a median duration of 14 months.⁷⁵ Among them, 69% of patients at 1 year, 51% at 2 years, and 28% at 5 years had reached an overall cumulative treatment success, defined as no escalation or withdrawal of medical therapy, endoscopic dilation, or surgery.⁷⁵ The short- and long-term results of this real-world study were similar to a multicenter, prospective, and observational cohort (CREOLE) study.⁷⁶ However, 97 CD patients with SB strictures in the CREOLE study exclusively received adalimumab, whereas 59 CD patients with SB and large bowel strictures in the real-world study received either infliximab or adalimumab.^{75,76} Besides, 64.4% of patients in the real-world study had multiple strictures, whereas 71% of patients in the CREOLE study had a single stricture, which may be one potential reason for the lower surgery rate in the former study (11.8% within 5 years *versus* 49.3% within 4 years).^{75,76} A systematic review including 25 studies also demonstrated that anti-TNF therapy was effective, with 50% of patients free from surgery within 4 years of follow-up.⁷⁷ These results suggest that anti-TNF therapy is at least beneficial to stricturing CD in the short term.

Schulberg *et al.*⁷⁸ first performed a randomized controlled trial evaluating anti-TNF treatment in 123 CD patients with strictures. The results showed that patients receiving intensive high-dose adalimumab with later dose escalation plus thiopurine had slight improvements in obstructive symptom score, morphological stricture changes (such as bowel wall thickness in US), and higher reduction of inflammatory index (such as Crohn's Disease Activity Index, MRI Index of Activity score, fecal calprotectin, and C-reactive protein), compared with standard adalimumab monotherapy.⁷⁸ However, there were no statistically significant differences between the two groups.⁷⁸ Thus, well-designed studies are needed to support the utilization of anti-TNF escalation plus immunosuppressives in CD strictures.

In addition to novel biologics, a number of new potential antifibrosis agents have been proven to be feasible in fibroblasts and intestinal fibrosis murine models. For example, ABT-263, a mimic of B-cell lymphoma-2 homology 3, was able to reduce the expression of fibrotic-related genes and proteins.⁷⁹ Both *in vivo* and *in vitro* experiments showed that ABT-263 increased the susceptibility of myofibroblasts to apoptosis.⁷⁹ Another study showed that oral administration of hydroxamate of betulinic acid (HBA), an inhibitor of hypoxia-inducing factor, displayed a significant reduction of fibrotic and inflammatory-related markers in colitis murine.⁸⁰ HBA could improve the integrity of epithelial barrier and promote the process of wound healing, leading to alleviation of colonic inflammation and fibrosis.⁸⁰

Endoscopic management. EBD is a safe and effective therapy for CD patients with *de novo* or anastomotic strictures.^{77,81,82} Takeda *et al.*⁸³ suggested that for patients with stenotic CD who received anti-TNF as maintenance therapy, EBD was also effective and safe, with surgery-free rates of 81.1% and 73.5% after 3-year and 5-year follow-up, respectively. Several risk factors for patients who are prone to undergo surgery after EBD were identified in recent studies including age less than 50 years, SB lesions, obstructive symptoms or biologic treatment at the time of EBD, or no history of perianal involvement.^{84,85} As for duodenal CD-associated strictures, serial dilations have much longer surgery-free time and recurrence-free survival than nonserial dilation.⁸¹ Another study reported that CD patients with SBS who underwent double-balloon endoscopy had an 80% surgery-free rate within 25 months after initial dilation.⁸⁶ Of note, the mean intervention-free period can extend to 54 months for CD patients with asymptomatic SBS who had strictures in ileocecal valve or had no elemental diets.⁸⁷

Since the recurrence rate of EBD is high up to 50% during follow-up,⁸⁸ a self-expandable metal stent with antimigration and removable features may be an alternative option.^{89,90} A nationwide cohort study included 46 CD patients with partially covered self-expandable stents and found an obstruction-free rate of 58.7%, and a low migration rate of 6.5% with no adverse events could be achieved at 26 months.⁹¹ However, given the small sample size, further studies are needed to investigate its effectiveness.

Surgical management. CD patients refractory to medical or endoscopic treatment, or with complex complications (strictures, abscesses, and fistulae), would eventually need surgical interventions such as stricturoplasty (SXP) and bowel resection.^{1,92} Bislenghi *et al.*⁹³ conducted a meta-analysis including 26 studies aiming to explore the efficacy of conventional (short and intermediate procedures such as Heineke–Mikulicz and Finney) and nonconventional (long entero-enterostomies such as Michelassi) SXP. Results showed a comparatively low rate of post-operative complications (15.5% *versus* 19.2%) and surgical recurrence (26.9% *versus* 18.2%) for the two types of surgical therapies during median follow-up periods of 65.3 and 96.3 months, respectively, suggesting that both techniques were feasible.⁹³ Considering the significant heterogeneity among the included studies, the conclusion should however be further verified. For the first time, a prospective cohort study investigated the safety and feasibility of conventional or nonconventional SXP in combination with laparoscopy for complicated CD.⁹⁴ They reported that both conventional and nonconventional SXP were safe and feasible by laparoscopy with low morbidity rates.⁹⁴ Of note, SXP is not recommended for patients with dysplasia or cancer, or colonic strictures.⁹⁵ On these occasions, bowel resection is an alternative option. Recently, a study recruited 5158 patients with CD to compare the safety of open surgery with laparoscopic and robotic-assisted ileocecal resection.⁹⁶ Results showed that laparoscopic and robotic-assisted surgery displayed lower incidences of reoperation, wound infection, and anastomotic leaks than open surgery.

Future outlook

In 2021, a remarkable progress has been achieved in CD-related intestinal strictures in the fields of mechanism, disease assessment, and therapeutic management. However, there are still many issues needed to be addressed. First, the pathogenesis of stricturing CD has not been fully understood yet. Novel techniques such as multi-omics and single-cell sequencing may open up a new research direction for in-depth study on the pathogenesis of fibrosis, which may fuel the exploration of fibrosis mechanisms. Besides, novel animal models that mimic molecular features of intestinal fibrosis in CD have been successfully established,

which allow for investigating the pathogenesis of intestinal strictures in more detail. Second, there is a dire need for the development of specific predictors and diagnostic approaches to identifying strictures. Medical imaging combined with AI may provide a more precise approach for assessing CD fibrosis. More studies are needed to investigate the efficiency of AI-assisted medical imaging in the future. Lastly, in parallel with our increased understanding of the underlying mechanisms of intestinal strictures, growing potential antifibrotic agents have been developed and investigated in experimental models. However, none of them have been investigated in clinical trials, partly due to the lack of definitive clinical endpoints that are of pivotal importance to guide clinical trials. Excitingly, the Stenosis Therapy and Anti-Fibrotic Research consortium is concentrating on establishing the standardized definitions of endpoints for management of stricturing CD and has achieved some progress. All progress described above in intestinal strictures will be gradually carried forward, and will be put into use from bench to bedside in the not too distant future.

Author contributions

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