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Review Article

Cellular and Molecular Mechanisms of Intestinal Fibrosis

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Intestinal fibrosis associated stricture is a common complication of inflammatory bowel disease usually requiring endoscopic or surgical intervention. Effective anti-fibrotic agents aiming to control or reverse intestinal fibrosis are still unavailable. Thus, clarifying the mechanism underpinning intestinal fibrosis is imperative. Fibrosis is characterized by an excessive accumulation of extracellular matrix (ECM) proteins at the injured sites. Multiple cellular types are implicated in fibrosis development. Among these cells, mesenchymal cells are major compartments that are activated and then enhance the production of ECM. Additionally, immune cells contribute to the persistent activation of mesenchymal cells and perpetuation of inflammation. Molecules are messengers of crosstalk between these cellular compartments. Although inflammation is necessary for fibrosis development, purely controlling intestinal inflammation cannot halt the development of fibrosis, suggesting that chronic inflammation is not the unique contributor to fibrogenesis. Several inflammation-independent mechanisms including gut microbiota, creeping fat, ECM interaction, and metabolic reprogramming are involved in the pathogenesis of fibrosis. In the past decades, substantial progress has been made in elucidating the cellular and molecular mechanisms of intestinal fibrosis. Here, we summarized new discoveries and advances of cellular components and major molecular mediators that are associated with intestinal fibrosis, aiming to provide a basis for exploring effective anti-fibrotic therapies in this field. **(Gut Liver 2023;17:360-374)**

Key Words: Inflammatory bowel diseases; Intestinal fibrosis; Immune system; Creeping fat; Gastrointestinal microbiota

INTRODUCTION

Fibrosis is a dysregulated outcome of wound healing, especially during chronic inflammatory disorders.[1] When inflammation is persistent, the severity of the damage may exceed the ability of the affected tissue to completely heal, which then initiates fibrotic response that eventually results in fibrosis.[2,3] The gastrointestinal tract is a tubular structure and therefore fibrosis is presented with the narrowing of lumen and intestinal stricture.[4]

Intestinal stricture is a common complication of inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC).[5,6] CD is a transmural disease that can affect the entire gastrointestinal tract, while UC is a superficial inflammatory disease, restricted to the colonic mucosa and submucosa layer.[7] At initial diagnosis, at least 10% of CD patients are presented with a fibrostenosis phenotype.[8] However, up to 50% of CD patients ultimately progress to stricturing or penetrating complications and 70% of patients require surgery within their life time.[5,9] Even though stricture formation is rather infrequent in UC, recent evidence suggested fibrosis occurs in both acute and chronic UC.[10] In the past decades, despite the availability and efficacy of biological therapies in IBD, the incidence of intestinal stricture does not achieve a significant reduction.[11] This implies that pure anti-inflammatory treatments do not necessarily alleviate the associated fibrosis.

The review would provide a cellular and molecular biology of intestinal fibrosis (Fig. 1). Considering the close association between intestinal fibrosis and stricturing complications, understanding the pathogenesis of intestinal

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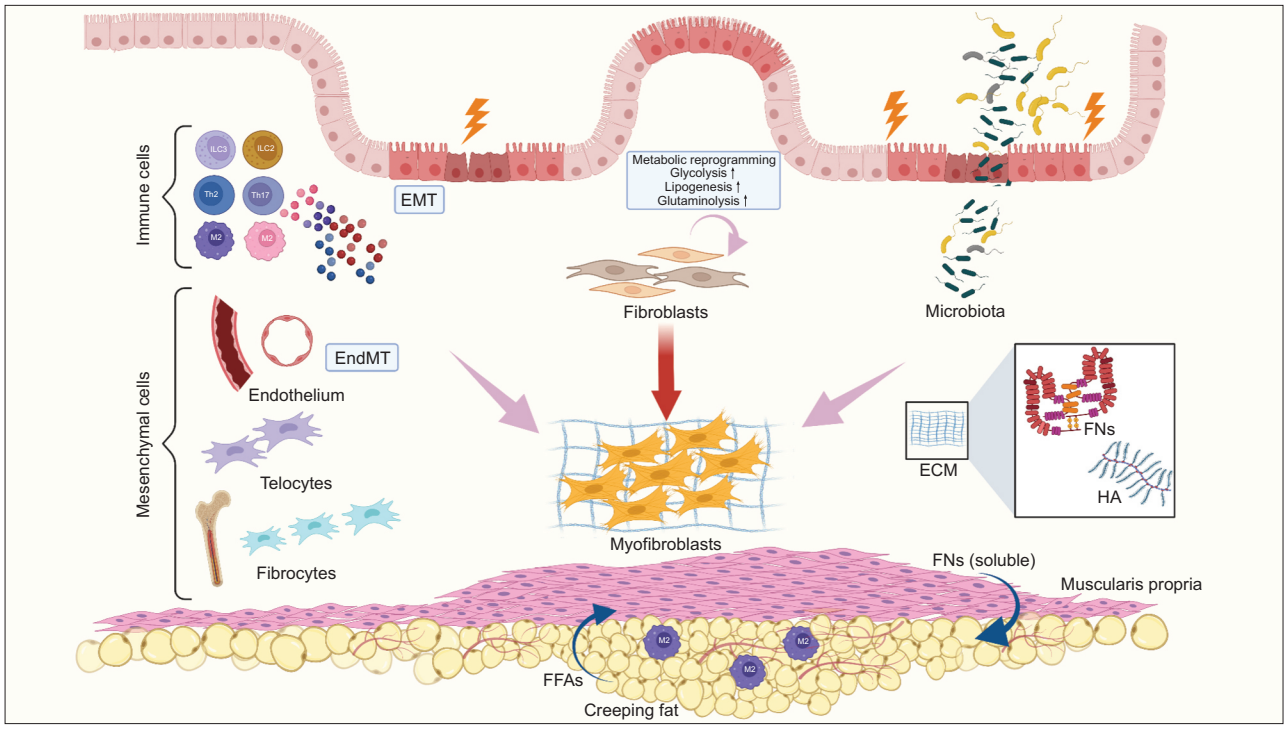

Fig. 1. Cellular and molecular components implicated in intestinal fibrosis. Intestinal strictures are characterized by extracellular matrix (ECM) accumulation, intestinal muscularis propria thickening, and mesenteric fat wrapping. Myofibroblasts, the major source of ECM production, can originate from various types of mesenchymal cells. Immune cells contribute to persistent myofibroblasts proliferation and activation by secreting abundant cytokines. In addition, inflammatory-independent factors including gut microbiota, ECM interaction, creeping fat and metabolic reprogramming are involved in fibrosis formation.
EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition; FFAs, free fatty acids; FNs, fibronectins; HA, hyaluronan.

fibrosis is crucial to identify new anti-fibrotic targets for patients with intestinal strictures.

CELLULAR MECHANISMS OF FIBROSIS

Intestinal fibrosis is driven by multiple cellular compartments including mesenchymal cells and immune cells.[12] The histological feature of intestinal stricture is thickening of the muscularis mucosa and muscularis propria owing to the activation and proliferation of mesenchymal cells. Activated mesenchymal cells not only produce matrix components, but also secrete chemokines to recruit cells from the immune system (e.g., macrophages and T cells), thus perpetuating chronic inflammation. Reciprocal interaction between mesenchymal and immune cell populations in the intestine create a unique pro-fibrotic microenvironment, eventually resulting in fibrosis formation.[13]

1. Mesenchymal cells and mesenchymal progenitors

Intestinal fibrosis results from sustained activation and proliferation of myofibroblasts.[14] The activated myofibroblasts, as the final effector cells, can produce extracellular matrix (ECM) proteins and secrete cytokines such as interleukin (IL)-6 and IL-11, which facilitates formation of a fibrogenic milieu.[15-17] The majority of myofibroblasts derive from resident fibroblasts and smooth muscle cells (SMCs). However, they can also originate from other cell types like epithelial and endothelial cells, pericytes, bone marrow stem cells and bone marrow-derived circulating fibrocytes.[18,19] The various types of cells weave together in the inflamed intestine and contribute to the development of intestinal fibrosis.[20]

1) Fibroblasts

Fibroblasts are characterized by an elongated or spindle-shaped morphology, which are the most abundant cell type in connective tissue. Their main function is to maintain tissue integrity.[21] Fibroblasts can be activated and multiply in response to pro-inflammatory mediators, such as insulin-like growth factor (IGF)-I, fibroblast growth factor, and IL-1β.[22] The growth of fibroblasts can also be induced by immune cells or inflammatory cells through a cell-to-cell contact mechanism.[23,24] In addition, fibroblasts can migrate to the site of inflammation foci along the concentration gradient of pro-inflammatory cytokines via activation of

NF-κB and JAK-STAT signaling pathways.[16,25,26] A previous study reported that fibroblasts isolated from inflamed or fibrotic CD tissue, or inflamed UC mucosa exhibited an increased proliferation, when compared with normal tissue.[27] Recently, Wohlfahrt *et al.*[28] found that activated fibroblasts could be reprogrammed into resting fibroblasts by pharmacological and genetic inactivation of PU.1, leading to fibrosis regression. In recent years, the advent of single-cell RNA sequencing (scRNA-seq) technology may assist to reveal the heterogeneous functionality of fibroblast populations, which may shed some insights on the fibrotic pathogenesis of fibroblasts.[29]

2) Myofibroblasts

Myofibroblasts are characterized by the expression of α-smooth muscle actin (α-SMA), with enhanced production of collagen and increased capacity of contraction.[30] Although the exact molecular mechanism of myofibroblasts in fibrosis remains incompletely understood, mediators acting on myofibroblasts are clearly demonstrated, including pro-inflammatory cytokines, paracrine and autocrine factors (e.g., IGF-1), and pathogen or damage-associated molecular patterns.[31] The activated myofibroblasts initiate fibrotic process in the following ways. Firstly, myofibroblasts secrete ECM components, as well as various cytokines and chemokines, directly or indirectly contributing to the thickening of mesenchymal cell layer.[32,33] Secondly, myofibroblasts participate in tissue remodeling through mechanical contractions.[34,35] Thirdly, the mechanic contraction of myofibroblasts can activate latent transforming growth factor-β1 (TGF-β1) released from ECM.[36] TGF-β1 and its related pathways are major drivers in the process of fibrosis.[37] Recently, de Bruyn *et al.*[38] using specimens from the same CD patients has firstly found that primary myofibroblasts isolated from stenotic ileum were phenotypically and functionally (e.g., ECM organization and collagen production) distinct from myofibroblasts isolated from normal and inflamed areas. Specifically, stenotic myofibroblasts can increase tissue stiffness, while suppress the expression of matrix metalloproteinase (MMP)-3 activity, to facilitate fibrosis development.[38]

3) Smooth muscle cells

SMCs are one of the three interrelated cell phenotypes (the other two being fibroblasts and myofibroblasts).[33] SMCs and fibroblasts are derived from the same primitive mesenchymal cells.[39] SMCs are regarded as the progenitors of myofibroblasts.[39] A dynamic equilibrium exists between SMCs and myofibroblasts phenotypes.[39] SMCs can change their phenotypes in response to environmental stimulation.[40] A previous study found that SMCs isolated from CD ileum presented alterations in morphology and contractile activity.[41] It was demonstrated that SMCs isolated from CD ileum had an overexpression of platelet-derived growth factor (PDGF)-β, which drove the myogenic phenotype switch to synthetic one. The effect of PDGF-β was paralleled to a reduced encoding of contractile genes that were responsible for quiescent smooth muscle.[41] SMCs are also able to release significant amounts of IL-6, contributing to inflammatory process.[42] Besides, these cells actively contribute to the development of intestinal fibrosis by inducing the production of collagens and MMPs.[41] These evidences suggested that the phenomenon of smooth muscle hyperplasia/hypertrophy in CD may be a driving force, rather than simply a passive increase of stricture formation.

4) Epithelial or endothelial-mesenchymal transition

Epithelial or endothelial-mesenchymal transition (EMT or EndMT) represents a dynamic entity where epithelial or endothelial cells transform to mesenchymal cells in response to inflammatory cytokines, oxidative stress and hypoxia.[43-45] EMT is implicated in CD-associated fistulas and intestinal fibrosis.[46,47] During formation of CD-associated fistulas, intestinal epithelial cells start with the dissociation from the base membrane and then migrate to the lining of the fistula tracts, where they convert to mesenchymal cells.[47] In CD-associated intestinal fibrosis, EMT serves as a reservoir that can generate new fibroblasts and consequently result in fibrosis formation.[46,48] Results from Iwano *et al.*[49] study found that approximately 36% of new fibroblast specific protein-1 positive fibroblast cells originated from local EMT in mouse models of liver and renal fibrosis. Frid *et al.*[50] previously demonstrated that endothelial cells could differentiate into SMCs *in vitro*. Zhang *et al.*[51] reported that 17% of fibroblasts/myofibroblasts in the fibrotic myocardium were EndMT-derived. Evidence of EndMT can be also detected in colonic tissues from IBD patients as well as patients with radiation-induced proctitis.[52] Multiple targeted therapies aiming to inhibit EMT in cancer are already undergoing clinical evaluation.[53] Targeting EMT or EndMT may hold therapeutic promise for fibrotic disorders.

5) Telocytes

Telocytes (TCs) are a novel type of interstitial cells characterized by CD34/PDGFRα, and have been demonstrated to be involved in several disorders including CD.[54-56] The function of TCs is widely linked with other cells including mast cells, macrophages, myofibroblasts, and fibroblasts.[57] Milia *et al.*[55] firstly identified that TCs were distributed in all layers of ileum, from mucosa to subserosa. Comparing normal with fibrotic resected ileal specimens from human,

they found that TCs were nearly disappeared in the fibrotic ileum. A previous study showed that disappearance of TCs was accompanied by an increasement of myofibroblasts in UC, suggesting that TCs loss might be associated with the aberrant differentiation of fibroblasts into myofibroblasts.[58] However, further studies are needed to elucidate the casual relationship of TC and fibrosis.

6) Fibrocytes

Fibrocytes are bone marrow-derived mesenchymal progenitors, with the features of both hematopoietic (CD34) and fibroblast markers (collagen-I). Fibrocytes play a critical role in fibrotic diseases.[59] Previous studies revealed that fibrocytes could be triggered by several inflammatory cytokines.[59] Specifically, within four-day following injury, activated fibrocytes typically migrate into injured sites and then participate in fibrotic reactions through a direct way by production of ECM proteins and fibrogenic cytokines, or an indirect way by differentiation into myofibroblasts.[60-62] Sazuka *et al.*[61] found that bone marrow-derived fibrocytes were associated with intestinal fibrosis, which was consistent with another study that the frequency of circulating fibrocytes was increased in fibrostenotic CD patients, compared with healthy individuals.[63] A recent study has revealed that fibrocytes deposited in inflamed colon can produced tissue inhibitor of metalloproteinase to inhibit degradation of collagen.[64] Therefore, circulating fibrocytes may be a therapeutic target of intestinal fibrosis.[63]

2. Immune cells

A variety of key innate (macrophages) and adaptive (T cell subsets) immune cell types have been well-established in orchestrating the fibrotic microenvironment in intestine. The immune cell skewing in fibrosis niche probably perpetuates inflammation and exacerbates the process of wound healing.[65] Here, we will discuss several immune cell subsets, pointing toward novel immune-based therapeutic strategies in fibrosis.

1) Th2 cells

T helper 2 (Th2) cells are hallmarked by the secretion of cytokines IL-4, IL-5, and IL-13, which are responsible for type 2 immune responses.[66] The type 2-associated cytokines are actively engaged in wound healing and fibrosis.[65] At inflammatory sites, activated innate immune cells, such as group 2 innate lymphoid cells (ILC2) and basophils, are usually the early sources of local cytokines IL-4, IL-5, and IL-13, which trigger the activation and accumulation of Th2 cells.[67,68] Th2 cells-derived IL-4 and IL-13 further promote the accumulation and proliferation of ILC2, thus creating a vicious cycle.[69] Activated Th2 cells orchestrate the process of tissue fibrosis directly and indirectly by acting on immune or non-immune cells including local M2 macrophages, fibroblasts, endothelial cells and epithelial cells.[70,71] Besides, as a well-known opponent of Th1 cells, Th2 cells can reverse the expression levels of Th1-associated antifibrotic cytokines such as interferon γ (IFN-γ).[72] However, randomized controlled trials showed that blockade of IL-13 to target Th2 responses while administration of IFN-γ to stimulate Th1 responses failed to attenuate pulmonary fibrosis.[73-75] Conversely, in a phase II trial, neutralization of IL-4/IL-13 effectively improved early skin fibrosis.[76] The inconsistent results suggested targeting Th2 response as a therapeutic strategy for fibrosis requires further investigation.

2) Macrophages

Macrophages are highly heterogeneous and plastic cell populations, and are key regulators of tissue fibrosis in several organs.[66,77] Generally, macrophages are classified into two subtypes: M1 macrophages with pro-inflammatory roles, and M2 macrophages with pro-fibrotic properties. The latter is activated by IL-4 and IL-13, and characterized by effects of inflammation resolution and tissue restoration.[66] In intestine, STAT6-dependent M2 macrophages promote mucosal repair through activating Wnt signaling pathway.[78] Moreover, macrophages from CD patients showed a significant enrichment in the expressions of M2-related as well as fibrotic-related genes, implying that M2 macrophages potentially exacerbated fibrosis formation.[79] Results from STAT6 deficient colitis mice showed that the frequency of CD16+ macrophages was enhanced in the damaged mucosa of CD patients with stenotic or penetrating complications, and were also associated with the expression of fibrotic-related markers.[80] Blockade of the interactions between inflamed macrophages and stromal cells has been proven to potentially ameliorate aberrant wound repair in zebrafish IBD model.[81] Recently, the advanced scRNA-seq has revealed a novel macrophage subgroup, named with $CX3CR1^{+}SiglecF^{+}$ transitional macrophages, which are abundant in fibrotic niche and exhibit a pro-fibrotic effect in bleomycin-induced lung fibrosis.[82] ScRNA-seq will be a promising technique to reveal the cellular heterogeneity of macrophages in fibrosis.

3) Th17 cells

T helper 17 (Th17) cells are characterized by RAR-related orphan receptor γt (ROR-γt) expression and signatured by producing IL-17, IL-21, and IL-22 cytokines,[83,84] which have fibrogenic properties. IL-17A, the predominant Th17-assciated cytokines, exerts its fibrotic effects via acting on myofibroblasts and regulating EMT.[85-87] In gut,

elevated levels of tissue Th17 cells and IL-17 production are observed in patients with intestinal stenosis.[87] Recently, Paul *et al.*[88] has showed that IL-17-driven fibrosis is negatively regulated by Itch, whereas Itch deficiency leads to increased expression of collagen-I and α-SMA in response to IL-17 in myofibroblasts. *In vitro*, IL-17A can dose-dependently induce EMT in intestinal epithelial cells.[89] *In vivo*, IL-17A blockade significantly ameliorates TNBS-induced intestinal fibrosis through enhancing ECM degradation and decreasing pro-fibrotic cytokines production.[89,90] Of note, in clinical trials, administration with neither anti-IL-17A monoclonal antibody (secukinumab) nor its receptor monoclonal antibody (brodalumab) is effective in CD patients with stenosis.[91,92] Th17 cells expressing IL-22 are also implicated in fibroblast activation, myofibroblast differentiation and ECM gene expression in skin fibrosis.[93,94] The fibrotic effects of Th17 cells-derived cytokines are still largely unknown.

4) Innate lymphoid cells

ILCs are a functionally diverse but developmentally related family of innate lymphocytes, with phenotypes and functions having striking similarities to T helper (Th) cells.[95] According to cytokine signatures and transcription factors expression, ILCs are divided into three groups.[96] Group 1 ILCs (ILC1) subsets share common properties with Th1 cells and express the transcription factor T-bet.[97] Group 2 ILCs (ILC2) express the transcription factors RORα and GATA-3, which resembles Th2 cells functionally.[98] Group 3 ILCs (ILC3), expressing transcription factor RORγt, are analogous to Th17 cells.[99,100] ILC2 can respond rapidly to tissue damage, followed by an increase of Th2-like cytokines.[101] An increased frequency of ILC2 has been detected in intestinal tissues from CD patients.[102] Lo *et al.*[103] reported that Rora$^{sg/sg}$ bone marrow transplant (BMT) chimeric mice which was a model of ILC2 deficiency was resistant to salmonella-induced intestinal fibrosis, with reduced collagens deposition and fibroblasts accumulation in infected intestinal tissues. Furthermore, restoring ILC3 function in Rora$^{sg/sg}$ BMT mice was able to reestablish the susceptibility to intestinal fibrosis.[103] Although the effect of ILCs in intestinal inflammation is explicit, their roles in fibrotic process still require more investigation.

MOLECULAR MECHANISMS OF FIBROSIS

Molecules are messengers of crosstalk between immune and non-immune cells and actively contribute to persistent inflammation.[13] Although inflammation is a prerequisite

Table 1. Cytokine and Chemokine Profiles Involved in Intestinal Fibrosis

Cytokine	Pro- or anti-fibrosis	Effects on intestinal fibrosis	References
IL-1	Pro	Induce fibroblasts activation; enhance pro-fibrotic cytokines production; inhibit ECM degradation; enhance collagens expression	104-106
IL-4	Pro	Promote myofibroblasts activation; promote type 2 immunity-induced fibrosis	107,108
IL-6	Pro	Promote SMCs activation; promote fibroblasts activation and proliferation; enhance ECM production	109-111
IL-10	Uncertain	Inhibit collagens deposition; no effects on fibroblasts and myofibroblasts	112,113
IL-11	Pro	Enhance collagens expression; may promote SMCs hyperplasia	114
IL-12	Pro	Promote inflammation	115,116
IL-13	Pro	Promote TGF-β1 production; initiate fibrosis	117,118
IL-17	Pro	Stimulate myofibroblasts activation; enhance collagens expression; decrease ECM degradation; induce EMT	85,89,119
IL-21	Uncertain	Facilitate Th2 and Th17 development; enhance MMPs secretion	120,121
IL-22	Pro	Inhibit inflammation; enhance MMPs secretion; promote myofibroblasts differentiation	122-124
IL-23	Pro	Promote inflammation; promote fibrotic responses	115,116,124
IL-25	Non	IL-13 production depends on IL-25; induce type 2 immunity; promote inflammation	125,126
IL-33	Pro	Promote pro-fibrotic type 2 immunity	127,128
IL-34	Pro	Enhance collagens expression; promote fibroblasts activation	129
IL-36	Pro	Enhance collagens expression; promote fibroblasts activation	130
TL1A	Pro	Enhance collagens expression and pro-fibrotic molecules production; promote fibroblasts activation; induce EMT	131,132
IFN-γ	Anti	Inhibit TGF-ß signaling; inhibit fibroblasts migration and myofibroblasts differentiation	133-135
TGF-ß	Pro	Enhance pro-fibrotic molecules production; promote fibroblasts activation; induce EMT	43,136-138
CXCR4	Pro	Mediate pro-fibrotic effects of PDGF-C	139
CCL11	Pro	Induce eosinophils recruitment and in turn promote fibroblasts activation	140
CXCL8	Pro	Promote pro-fibrotic growth factors production; enhance MMPs secretion	141

IL, interleukin; ECM, extracellular matrix; SMCs, smooth muscle cells; TGF, transforming growth factor; EMT, epithelial-mesenchymal transition; Th, T helper; MMPs, matrix metalloproteinases; TL1A, tumor necrosis factor-like ligand 1A; IFN, interferon; CXCR4, C-X-C motif chemokine receptor 4; PDGF-C, platelet-derived growth factor-C; CCL11, C-C motif chemokine ligand 11; CXCL8, C-X-C motif chemokine ligand 8.

of fibrosis, purely controlling intestinal inflammation cannot hold back the progression of fibrosis.[8] This implies that inflammation is not the exclusive driver of fibrosis. In the following section, a detailed discussion concerning inflammation-dependent, but with a focus on inflammation-independent factors of fibrosis, will be reported.

1. Inflammation-dependent molecular mechanisms

Cytokines and chemokines secreted by immune and non-immune cells are orchestrators of sustained inflammatory microenvironment, and are also observed to possess pro-fibrotic effects, which lay foundations for uncovering novel therapeutic targets in fibrotic disorders.[142] Several novel cytokines involved in fibrogenesis will be detailly described in this part, and the elaborate profile of cytokines and chemokines are shown in Table 1.

1) Interleukin-11

IL-11, a member of IL-6 family, is recognized as a pro-fibrotic cytokine secreted by stromal cells, as well as epithelial cells during tissue injuries.[143] IL-11 is upregulated in various fibro-inflammation disorders.[143] Ng *et al.*[144] reported that IL-11 was increasingly expressed in invasive lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis. They demonstrated that IL-11 exerted pro-fibrotic effects by driving fibroblasts activation, while anti-IL-11 treatment reversed lung fibrosis in mice.[144] Recently, Schafer *et al.*[145] has showed that fibroblast-specific IL-11 transgene expression or administration with IL-11 in mice resulted in heart and kidney fibrosis, whereas genetic deletion of IL-11 receptor alpha chain 1 (IL-11ra1) protected against fibrosis. scRNA-seq has revealed that the expression of IL-11 is enhanced in activated fibroblasts from CD inflamed segments.[146] Lim *et al.*[114] has found that SMC-specific IL-11 transgenic expression can induce inflamed, thickened and fibrotic bowel in mice. This is in line with another animal model with fibroblast-specific expression of IL-11.[114] The emerging data prioritize IL-11 as a drug target for fibrotic diseases.

2) Interleukin-33

IL-33, a member of IL-1 superfamily, is passively released upon cellular damage and necrosis and is thus considered as an alert of inflammation.[147] IL-33 is also involved in the process of fibrogenesis.[148] Binding of IL-33 to its receptor ST2 triggers activation of Th2 cells to produce amphiregulin, which then drove osteopontin production by eosinophils, thus forming IL-33-amphiregulin-osteopontin axis. The axis conferred to fibrotic responses in eosinophilic airway inflammation.[149] With regard to intestine, the expression of IL-33 and ST2 were upregulated in mucosa from UC patients and dextran sulfate sodium (DSS) colitis model.[136,137] In particular, elevated epithelial expression of IL-33 was strongly associated with fibrosis progression in pediatric Crohn's ileitis.[138] A recent study by Imai *et al.*[127] has unveiled a novel relationship between IL-33/ST2 signaling and gut dysbiosis in intestinal fibrosis. They reported that adherent-invasive *Escherichia coli* (AIEC) colonization elicited ST2 expression in intestinal epithelium, which in turn augmented the sensing of IL-33/ST2 signaling and ultimately promoted intestinal fibrosis. Alternatively, targeting IL-33/ST2 signaling with a neutralizing anti-ST2 antibody attenuated fibrotic effects of AIEC.[127]

3) Interleukin-34

IL-34, a member of 4-helical cytokine family, is produced by a wide range of cells including fibroblasts, immune cells, epithelial cells, endothelial cells and adipocytes.[150] The association of aberrant high expression of IL-34 and fibrosis has been identified in several organs, including liver, kidney, and gut.[129,151,152] Production of IL-34 was enhanced in inflamed mucosa in IBD patients and in DSS-induced colitis, which was regulated by tumor necrosis factor-α (TNF-α) via NF-κB signaling.[153,154] Notably, the expression of IL-34 was elevated in fibrostrictures sites of CD.[129] It was observed that activated fibroblasts by TNF-α exhibited increased expression of IL-34.[129,155] Besides, fibroblasts stimulated with IL-34 could enhance expression of COL1A1 and COL3A1, while this effect disappeared in fibroblast-specific IL-34 knockout mice.[129] These evidences raise a possibility that fibroblast is a cellular target of IL-34.

4) Interleukin-36

IL-36, also belonging to IL-1 superfamily, consists of five isoforms: IL-36α, IL-36β, IL-36γ, IL-36Ra, and IL-38.[156,157] Among them, IL-36α, IL-36β, and IL-36γ play pro-inflammatory effects through activating IL-36 receptor (IL-36R) signaling, while IL-36Ra and IL-38 have opposing effects as they are inhibitors of IL-36R signaling.[156,158] It is demonstrated that IL-36α and IL-36γ are elevated in both CD and UC mucosa under inflammation stimuli.[158,159] Of note, IL-36α had an increased expression in tissues of CD fibrostenosis.[130] Stimulation of IL-36α and IL-36γ can induce fibroblasts activation and epithelial cells proliferation,[159,160] which is associated with an enhancement of collagen-VI secretion and ultimately fibrosis development.[130] Importantly, both IL-36R blockade and IL-36 genes knockout are sufficient to attenuate intestinal fibrosis, which highlights the therapeutic values of IL-36 in fibrosis.[130]

5) Tumor necrosis factor-like ligand 1A

Tumor necrosis factor-like ligand 1A (TL1A) is a member of TNF superfamily and interacts with death receptor-3 (DR3) to form TL1A/DR3 co-stimulatory system.[161] Aberrant TL1A/DR3 signaling is involved in chronic inflammation and fibrogenesis.[162-165] CD patients with higher expression of serum TL1A were prone to develop stricture.[166] Another study found that CD patients presenting with specific TL1A genotype rs6478108 were susceptible to forming stricturing phenotype.[167] *In vivo*, mice with constitutive TL1A expression exhibited exaggerated intestinal inflammation and fibrosis,[166,168] while neutralizing anti-TL1A antibody attenuated and even reversed the established fibrosis.[131,165,169] Additionally, pro-fibrotic effects of TL1A/DR3 may depend on the presence of microbiota, since fibrosis was resistant in transgenic TL1A mice when specific microbiota such as *Mucispirillum schaedleri* and *Ruminococcus* absented.[170] In phase 2 clinical trial (NCT02840721), treatment with anti-TL1A antibody (PF-06480605) has reduced the expressions of fibrotic-related genes and alleviated ECM remodeling.[171]

2. Inflammation-independent molecular mechanisms

Recently, several inflammation-independent mechanisms including ECM interaction, creeping fat (CrF), gut microbiota, as well as metabolic reprogramming, have attracted much attention because of their unique roles in intestinal fibrosis, which will be discussed in the following part.[14,172,173]

1) ECM-cells interactions

ECM is a highly specialized and dynamic three-dimensional scaffold in tissue, which is an active player rather than a purely passive player in fibrosis.[14] ECM comprises a variety of fibrous components such as collagens, hyaluronan (HA) and fibronectin.[174] HA exists as a high-molecular-weight polymer in normal conditions. During excessive inflammation, the polymer is cleaved to fragments of lower molecular weight, which promotes fibroblasts proliferation and myofibroblasts differentiation, thus contributing to fibrosis process. Besides, HA in low molecular weight fragments aids in recruiting immune cells to inflammatory sites, which in turn release a variety of inflammatory mediators and growth factors to initiate fibrosis.[175-177] Fibronectin can enhance the susceptibility of SMCs to proliferation through combining with αVβ3 integrin.[178] Additionally, the phenotype and function of myofibroblasts are altered along with the increased ECM stiffness. Myofibroblasts isolated from stenotic intestine display enhanced contractility of ECM and decreased activity of MMP-3, resulting in a vicious circle that further leads to tissue rigidity.[38] Increased ECM stiffness is also able to drive fibroblasts to produce more ECM proteins through the Hippo and yes-associated protein pathway.[14]

2) CrF and intestinal fibrosis

CrF indicates that mesenteric fat wrapping around more than 50% of the intestinal circumference, which is the unique hallmark of CD.[179] Although CrF was first described nearly 100 years ago, whether CrF is pathogenic or protective is still a controversy.[179] Previous studies found that CrF was associated with the severity of intestinal inflammation and strictures.[180] Inclusion mesentery in ileocolic resection achieved a reduction of stricture recurrence and reoperation.[181,182] However, Ha *et al.*[183] has reported that translocation of *Clostridium innocuum* to mesenteric adipose tissue (MAT) stimulated tissue remodeling via M2 macrophages and adipose proliferation, suggesting that CrF may restrict intestinal inflammation and bacterial dissemination in CD patients.

The relationship between CrF and intestinal fibrosis is still underexplored. Our previous study has uncovered a positive feedback loop between CrF and intestinal muscularis propria.[184] Firstly, CrF-derived long-chain free fatty acids significantly enhanced proliferation and activation of intestinal muscle cells, with increased production of ECM proteins and strictures formation subsequently.[184,185] Vise versa, hypertrophic muscularis propria triggered migration of preadipocytes out of MAT by fibronectin production, which facilitated CrF development.[186] Another study observed that adipocytes within CrF were capable to convert to fibroblasts, whereas selective ablation of CrF adipocytes attenuated collagen deposition and bowel wall thickening.[187] Noteworthily, new animal models via repeated colonic biopsy or antimesenteric enterotomy have been recently established,[188,189] which will make a big difference for uncovering the complex relationship between CrF and intestinal fibrosis in the future.

3) Gut microbiota

Accumulating evidence indicates that gut microbiota plays crucial roles in fibrosis.[8] The direct evidence was that experimental mice when reared under specific-pathogen-free conditions displayed a minimal inflammation, whereas when injected bacteria or bacterial wall components they exhibited inflammation and fibrosis.[190] The terminal ileum is the most common site of intestinal stricture, where AIEC mainly colonize, giving us a hint that AIEC may be correlated with fibrosis development.[191] Indeed, research using mice with AIEC inoculation found that flagellin of AIEC via IL-33-ST2 signaling facilitated intestinal fibrosis.[127] Intestinal fibroblasts isolated from CD

patients are observed to have an increased expression of several Toll-like receptors (TLRs) including 2, 3, 4, 6, 7.[192] It is known that TLRs can be activated by perceiving microbial components, which are called pathogen-associated molecular patterns.[172] The activated TLRs then promote the differentiation of fibroblasts into myofibroblasts.[192] For example, TLR-3 activation in fibroblasts can augment α-SMA expression and TGF-β1 production via NF-κB signaling.[193] Additionally, lipopolysaccharide activating TLR-4 can also stimulate α-SMA expression and collagen synthesis in fibroblasts.[194,195] In conclusion, when exposed to pathogen-associated molecular patterns, intestinal myofibroblasts expressed upregulated levels of α-SMA and increased production of ECM proteins, thus confirming the link between gut microbiota and intestinal fibrosis.[172,174,192]

4) Metabolic reprogramming

Metabolic reprogramming has been widely described in fibrotic diseases. Generally, increased glycolysis and decreased fatty acid metabolism in fibroblasts are the main manifestations of metabolic reprogramming,[173] Succinate is a key regulator of glycolysis.[173] A recent study has reported that the expression levels of succinate and its specific receptor SUCNR1 in both serum and intestinal tissue are significantly increased in CD patients when compared with non-CD patients. Additionally, fibroblasts isolated from damaged intestine of CD patients also displayed an enhanced expression of SUCNR1. Furtherm ore, fibroblasts treated with succinate dose-dependently increased mRNA expressions of pro-fibrotic factor (e.g., TGF-β), as well as fibrotic markers (e.g., COL1A1, α-SMA), implying that succinate may be a potential target for intestinal fibrosis.[196]

With regard to lipid metabolism, peroxisome proliferator-activated receptor-γ (PPAR-γ) is responsible for the uptake and oxidation of fatty acids and is recognized as an anti-fibrotic factor.[173,197] Results from a mice model with intestinal fibrosis showed that the expression of PPAR-γ was significantly decreased in fibrotic colon. Additionally, the administration of PPAR-γ agonist (GED-0507-34 Levo) was able to reduce the production of collagens and the expression of pro-fibrotic molecules, as well as prevent TGF-β-induced EMT, thus attenuating fibrosis.[197]

FUTURE PERSPECTIVE

Despite substantial progress have been achieved over the past decades in the understanding of cellular and molecular pathogenesis of fibrosis, ideal anti-fibrotic agents that specifically target intestinal fibrosis without significant side-effects have not been identified yet. Unravelling the inflammatory-independent mechanisms concerning pathogenesis of intestinal fibrosis, such as intestinal muscularis propria thickening, microbiota colonization and mesenteric fat hypertrophy, may open a new avenue to this perplexing issue.[172,198] In addition, emerging methodology such as scRNA-seq has brought about new discoveries. For example, a deeper understanding of cell populations like fibroblasts or macrophages may reveal novel therapeutic points towards fibrosis.[29,82] The past few years have also witnessed a rapid evolution of multi-omics analyses, which are able to integrate data across different levels of cellular organization, including genomes, epigenomes, transcriptomes, as well as proteomes. These multifaceted approaches provide an unprecedented opportunity to decode the complex mechanisms underlying intestinal fibrosis. Promising anti-fibrotic agents targeting intestine should be available in the near future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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