The Possible Pathogenic Role of IgG4-Producing Plasmablasts in Stricturing Crohn's Disease

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Key Messages

- Strictures represent a significant source of morbidity in Crohn's disease (CD).
- The pathophysiology of CD and IgG4-related diseases share a hyperactive type 17 CD4+ T-helper T-cell response, IL-21 production and converge on sustained, aberrant plasmablast activity.
- IgG4-producing plasmablasts secrete platelet-derived growth factor, which may cause intestinal fibroplasia and eventual stricture formation.

Keywords

Crohn's disease · IgG4-related disease · Strictures

Abstract

Background: Crohn's disease (CD) is a condition on the spectrum of inflammatory bowel disease that affects up to 20 people per 100,000 in the US annually, and with incidence increasing. One of the most significant sources of morbidity in CD is the formation of strictures, with resultant intestinal blockage a common indication for hospitalization and surgical intervention in these patients. The pathophysiology of stricture formation is not fully understood. However, the fibroplasia that leads to fibrostenotic stricture formation may have shared pathophysiology with IgG4-related fibrosis.

Summary: Initial intestinal inflammation recruits innate immune cells, such as neutrophils, that secrete IL-1 β and IL-23, which induces a type 17 CD4+ T-helper T-cell (Th17)-mediated adaptive immune response. These CD4+ Th17 T cells

also contribute to inflammation by secreting proinflammatory cytokines such as IL-17 and IL-21. IL-21 recruits and stimulates CD4+ T follicular helper (Tfh) cells, which secrete more IL-21. This causes ectopic germinal center formation, recruiting and stimulating naïve B cells. The IL-17 and IL-21 produced by Th17 cells and Tfh cells also induce IgG4 plasmablast differentiation. Finally, these IgG4-producing plasmablasts secrete platelet-derived growth factor (PDGF), which activates local PDGF-receptor expressing fibroblasts and myofibroblasts, resulting in uncontrolled fibroplasia.

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Introduction

Crohn's disease (CD) is a condition on the spectrum of inflammatory bowel disease (IBD) that affects up to 20 people per 100,000 in the US annually, and with incidence increasing. Although having a relapsing and remitting

course, CD is a chronic condition with significant associated morbidity and high cost-of-care. One of the most significant sources of morbidity in CD is the formation of strictures, with resultant intestinal blockage a common indication for hospitalization and surgical intervention in these patients. The pathophysiology of stricture formation is not fully understood. However, the fibroplasia that leads to fibrostenotic stricture formation may have shared pathophysiology with IgG4-related fibrosis. The goal of this review is to explore the shared pathophysiology and immunologic mediators of both fibrostenotic stricture formation in CD and IgG4-related diseases and discuss implications on patient course and potential modes of immunotherapy.

Overview on CD

CD is a condition on the spectrum of IBD that is characterized by transmural bowel inflammation that may occur in all segments of the gastrointestinal (GI) tract [1–3]. CD affects up to 20 people per 100,000 in the US annually, and the prevalence is increasing [4–6]. CD is a chronic condition that usually follows a relapsing and remitting course. However, the disease is ultimately progressive and is thus associated with significant morbidity and high cost-of-care [7, 8]. Furthermore, all-cause mortality is elevated in CD patients, underscoring the importance of further research to improve patient outcomes [9, 10].

The presentation of CD is varied but usually affects patients between the second and fourth decades, although recent studies have suggested a second age peak of presentation in older patients [11, 12]. The most common presenting symptoms of CD include fatigue, abdominal pain, diarrhea, and bloody bowel movements [7, 8, 11]. Although nonspecific, these symptoms are generally what cause patients to present to medical attention. The diagnosis of CD is made through a combination of endoscopic and imaging findings usually showing noncontiguous lesions throughout the GI tract, as well as biopsy and histopathologic evaluation with granulomas and transmural inflammation supportive of the diagnosis of CD [5, 13].

Symptoms may progress and result in complications such as GI abscesses, fistulas, and strictures [7, 8]. The underlying pathophysiology driving disease progression to these serious complications is likely multifactorial but is driven by mucosal immune dysregulation and inflammation within the bowel. Classically, CD is thought to be driven by Th1-mediated inflammation, with interferon gamma (IFN- γ), tumor necrosis factor (TNF)-alpha

(TNF- α) release sustaining inflammation and resulting in granuloma formation [14–16]. However, more recent discoveries have implicated aberrant innate immune responses to the gut microbiome as well as involvement of the type 17 CD4+ T-helper T-cell (Th17)-IL-23 axis as contributing to the pathogenesis of CD [3, 14, 17–19].

Although sharing fundamental immune mechanisms, three distinct phenotypes of CD have been described: stricturing CD, penetrating CD, and non-stricturing non-penetrating CD [20]. These distinctions describe the primary course of disease; however, there is overlap between types [21, 22].

Stricturing CD

Strictures are a significant source of morbidity, with up to 50% of all CD patients eventually developing strictures that commonly present as obstructive symptoms [8, 21–23]. Several predictors of stricturing CD have been posited, with age of onset under 40 years, perianal involvement at diagnosis, small bowel disease location, and needing steroids during the index CD flare being associated with stricture formation [23]. Furthermore, other complications such as fistula formation have been shown to predict strictures in CD, as well, suggesting advanced disease yields progressive complications [23, 24]. Although no precise definition exists, strictures are frequently diagnosed via radiographic imaging showing narrowing of the intestinal lumen [25–27]. Bowel obstruction in these patients often results in hospitalization, with a large proportion requiring surgical intervention [28, 29].

Previously, strictures have been thought to result from bowel inflammation leading to dysregulated wound healing and resultant scar and fibrosis formation [3, 28]. However, more recent research has identified two processes by which strictures may form; both wound healing secondary to inflammation and independent fibroplasia may lead to stricture formation [29, 30]. As such, strictures can be subclassified as inflammatory strictures or fibrostenotic strictures [30, 31]. Although the clinical presentations of these types of strictures are similar, the difference in underlying pathophysiology necessitates different treatment approaches that, importantly, carry different success rates.

Inflammatory strictures that are a result of dysregulated wound healing secondary to bowel inflammation and injury respond well to existing anti-inflammatory therapy [32, 33]. However, anti-inflammatory therapy in

Fig. 1. Initial intestinal inflammation recruits innate immune cells, such as neutrophils, that release pro-inflammatory cytokines such as IL-1 β and IL-23. These cytokines induce naïve CD4⁺ T lymphocytes to differentiate into Th17 helper cells. These cells then release cytokines such as IL-17 and IL-21 that in turn induce the differentiation of other naïve CD4⁺ T lymphocytes into Th17 helper cells, contributing to a self-sustaining Th17 response. The IL-21 re-

leased by these cells also recruits Tfh cells, which in turn release more IL-21. IL-17 and IL-21 also induce the formation of ectopic germinal centers, and then further induce naïve B cells within these centers to differentiate into IgG4 producing plasmablasts. Finally, these plasmablasts secrete pro-fibrotic factors such as PDGF that contribute to intestinal fibroplasia.

CD is ineffective for reducing intestinal fibrosis and is thus an ineffective modality for fibrostenotic strictures. Anti-inflammatory therapy has been shown to not reduce the need for surgery in CD patients with strictures, with fibrosis continuing even after disease remission [8, 23, 33, 34]. As such, the mainstay of treatment for fibrostenosing strictures is surgical intervention, with endoscopic balloon therapy, stricturoplasties, or resection being employed depending on the severity of symptoms and the degree of stenosis of the intestinal lumen [35–37]. With no existing effective medical therapy for fibrostenosing strictures in CD, further elucidation of the underlying etiology and pathogenesis of intestinal fibroplasia is paramount to developing effective medical treatments for this complication. This would reduce the burden of current surgical treatments placed on patients and allow for earlier initiation of treatment.

Pathophysiology of Strictures: Aberrant Immune Mechanism versus Mesenchymal Cell Activation

The current understanding of the etiology of stricture formation is multifactorial, with a role for both inflammation and fibroplasia that eventually contributes to the narrowing and stenosis of intestines. As mentioned, the inflammatory component is a result of immune dysregulation within the mucosal epithelium of the intestine. It is thought that inflammation in CD begins with an aberrant innate immune response, with a lack of tolerance to native intestinal microbial flora posited as the inciting spark for this inflammatory response [3, 4, 18, 38–40]. This results in innate immune cells, such as neutrophils, dendritic cells, and macrophages, localizing to the lamina propria of the intestine and secreting proinflammatory cytokines such as TNF- α , IFN- γ , and interleukins (IL) 1 β , 6, 12, and 23. Innate immune cells within the intestinal lumen also

produce these cytokines [1, 3, 18, 38–40] (Fig. 1). IFN- γ and IL-12 induce a Th1-mediated adaptive immune response, with Th1 helper T cells in turn producing more inflammatory cytokines such as TNF- α and IFN- γ as well as IL-2, which sustains a continued Th1 response [1, 3, 18, 38–40]. IL-1 β and IL-23 induce a type 17 CD4⁺ Th17-mediated adaptive immune response. These CD4⁺ Th17 T cells also contribute to inflammation by secreting pro-inflammatory cytokines such as IL-17 and IL-21 [14, 18, 41]. In both of these Th1 and Th17 pathways, cytokines produced sustain further differentiation of CD4⁺ T cells into Th1 and Th17 cells, respectively (Fig. 1).

This inflammation results in epithelial and endothelial injury, leading to both anti-inflammatory regulatory responses as well as dysregulated wound healing. In response to proinflammatory cytokines such as TNF- α , IL-6, IFN- γ , and TGF- β , anti-inflammatory cytokines are produced by local immune cells as well as epithelial cells, adipocytes, and fibroblasts [29, 42–44]. These anti-inflammatory cytokines include transforming growth factor β (TGF- β), which is thought to be a main effector of further anti-inflammatory responses and fibroplasia. TGF- β promotes the differentiation of naïve helper T cells into regulatory T cells (Tregs), which in turn secrete anti-inflammatory cytokines [29, 40, 42–44]. However, this response may be tempered in the presence of IL-1 β , IL-6, and IL-21, which, along with TGF- β , promote differentiation into Th17 cells [41].

TGF- β also causes the activation and proliferation of local mesenchymal effectors of fibrosis, such as fibroblasts and myofibroblasts. Similarly, it causes recruitment of extraintestinal fibroblasts and myofibroblasts [29, 42–44]. These mesenchymal cells and recruited cells produce collagen and other elements of the extracellular matrix (ECM) [29, 42–45]. Furthermore, TGF- β has been shown to cause transformation of local epithelial and endothelial cells into mesenchymal cells, further expanding the available fibroblasts and myofibroblasts to produce ECM proteins [43]. In physiologic wound healing, this fibroplasia and the production of ECM proteins would be downregulated, while in the context of constant inflammation in CD, these processes become disordered and are continually activated.

What is less clear is the underlying mechanisms that cause progression of fibrosis even in periods of disease treatment and remission of inflammation. One proposed explanation is that the ECM produced in initial stages of fibrosis is a reservoir for further fibrogenic cytokines, such as TGF- β , which may be released even after cessation of inflammation and injury [42, 43]. This release of

latent fibrogenic cytokines may contribute to increasing stiffness of the ECM and further crosslinking of existing ECM proteins [46, 47]. This increasing stiffness has been shown to independently promote fibrogenesis even without further fibrogenic stimuli [48–50].

A second proposed explanation is that initial injury and destruction of the epithelial intestinal barrier exposes mesenchymal cells to gut microbiota. These cells are not equipped with tolerance mechanisms usually found in physiologic epithelial cells, and thus are continually activated even in the absence of Th1 and Th17 mediated inflammation. As such, these mesenchymal cells may produce further ECM proteins and contribute to fibrogenesis [51, 52]. However, other reasons for the continually increasing burden of fibrosis over the course of even well-controlled CD are unclear.

IgG4 Overview

The involvement of localized IgG4-related fibroplasia may be a possible explanation for continued fibrosis in CD. IgG4-related disease is characterized by systemic fibrosis that may affect a variety of locations, with the most commonly described being autoimmune pancreatitis, cholangitis, aortitis, retroperitoneal fibrosis, and salivary gland fibrosis [53]. Although the clinical manifestations and histopathologic features of this disease are well characterized, its pathophysiology and the underlying etiology of uncontrolled fibroplasia that characterizes IgG4-related disease are not fully elucidated [53–55].

The current understanding of the pathophysiology of these IgG4-related diseases (IgG4RD) is that T-cell-mediated inflammation results in both the aberrant and extensive production of IgG4 antibodies and in systemic fibroplasia [53–55]. It has been suggested that the IgG4 antibodies have anti-inflammatory properties, suggesting that they are not pathogenic, but possibly reactive to an upstream process [56]. Characterizing the inflammation that is the nidus for this disease has proven difficult, although several mechanisms have been proposed. The first is an autoimmune response to self-antigens, although this hypothesis has not been widely confirmed across the spectrum of IgG4RD [57–59].

Although the initiation of the systemic inflammation has not been definitively found, much progress understanding the effectors of this inflammation has been made. One cell type thought to be involved with the pathogenesis of IgG4RD is the CD4⁺ cytotoxic T cell. These cells are able to secrete granzyme B and perforin,

which allows for cytotoxic activity while interacting with major histocompatibility II-expressing cells [60]. Elevations in these cells, both in lesional tissue and in peripheral blood, are found in patients with IgG4RD and are thought to contribute to disease pathogenesis by secreting IFN γ , IL-1 β , and TGF- β , all of which are known to activate fibroblasts [61]. Notably, populations of these cells have been shown to decrease in patients successfully treated with glucocorticoids, suggesting a role for this cell subtype in disease progression [62–65].

A second cell type central to the pathogenesis of IgG4RD is the CD4+ follicular helper T cell (Tfh). These cells have also been shown to be elevated in both the peripheral blood and within involved tissue in patients with IgG4RD [66, 67]. Furthermore, these cells have been shown to have a reciprocal relationship with CD4+ cytotoxic T cells. These cells both differentiate from naïve CD4+ lymphocytes, but the differentiation of each cell type is inversely proportional and dependent on local immune milieu [68]. Tfh cells have been shown to cause the formation of pseudo germinal centers within affected tissue, and their presence correlates with plasmablast class switching, proliferation, and production of IgG4 antibodies [62, 69–71].

Finally, IgG4-secreting plasmablasts are another effector cell of interest in the pathogenesis of IgG4RD. These cells may act as antigen-presenting cells, sustaining the above described population of CD4+ cytotoxic T cells and thus contributing to sustained inflammation and fibrogenesis [65, 72]. Further, these cells may directly contribute to the fibrosis seen in IgG4RD. Plasmablasts may secrete platelet-derived growth factor (PDGF), which is known to activate fibroblasts and thus significantly contribute to fibrosis [73–78]. The central role of these plasmablasts in IgG4RD is emphasized by the efficacy of rituxumab in disease treatment, and disease flares coinciding with an increase in IgG4 producing plasmablasts [72, 73, 79–84].

Although the understanding of systemic IgG4 disease is improving, there is little reported on the influence of IgG4 mechanisms of disease on localized fibroplasia. It is possible that some or all of these mechanisms may be involved in localized fibroplasia, and further research on this topic is warranted.

Known IgG4 Involvement in CD and Plausible Mechanism of Fibroplasia

The involvement of IgG4 mechanisms within the fibrosis seen in CD is currently unclear. Although there has been evidence to suggest mucosal infiltration of IgG4 plasma cells

in patients with ulcerative colitis, there is a dearth of research on a similar process in CD [13, 74–77]. Further, there is little investigation into the contribution of IgG4 mechanisms in stricturing CD. However, there are several plausible shared immunologic mechanisms that warrant future study in the context of stricture formation and fibrosis.

The first shared mechanism of interest is the interplay between initial inflammation, Th17 response, and follicular T-cell recruitment. As mentioned, initial epithelial injury and innate immune system response within intestinal mucosa results in the release of pro-inflammatory cytokines IL-1 β , IL-6, and IL-21. These cytokines, along with TGF-B, released as part of the initial anti-inflammatory response, drive naïve CD4+ T cells to differentiate into Th17 effector cells [41]. IL-21 is particularly of interest, as it is a strong inducer of this Th17 response. Th17 cells further produce IL-21, resulting in a self-sustaining immune response [78, 85–88]. The role of IL-21 in CD is established, with evidence showing IL-21 is elevated in those with CD, specifically within samples of CD lesions, and that it contributes to a sustained, aberrant inflammatory immune response in intestinal mucosa [89–92].

This Th17/IL-21 interplay is also relevant for the recruitment of follicular T cells and the formation of germinal centers, both central effectors of IgG4RD. First, IL-21 has been shown to stimulate Tfh cells, which in turn produce more IL-21 [92, 93]. This, again, further stimulates Th17 differentiation and thus IL-21 release by Th17 cells. Tfh cells and their secretion of IL-21 also promote the formation of germinal centers [94–100]. IL-17 and the Th17 mediated immune response has also been shown to promote germinal center formation, complimenting the IL-21 mediated response [101–103]. Finally, and crucially, cytokines secreted by Tfh cells, namely, IL-21, also promotes differentiation of naïve B cells within germinal centers into IgG4 producing plasmablasts. This association has been strengthened by the localization of IL-21-secreting Tfh cells within germinal centers in IgG4RD [104–107]. Similarly, hyperactive B cells that preferentially produce IgG class antibodies have been described within granulomas in CD, lending credence to plasmablasts as a final, shared result of the Th17/IL-21 axis [108, 109] (Fig. 1).

The Pathogenic Role of IgG4 Plasmablasts in Fibroplasia

Both IgG4RD and CD have shared mechanisms that converge on the formation of plasmablast-rich germinal centers. This convergence may finally relate to fibrosis through the plasmablast-mediated release of PDGF as de-

scribed above, with PDGF causing fibroblast activation and proliferation, leading to fibrosis [73, 79–84]. Fibrosis has been reported within and surrounding germinal centers containing IgG4 plasma cells in both IgG4RD and other inflammatory conditions, potentially providing evidence of plasma cell-induced fibroplasia [110–114]. PDGF receptor-positive cells have also been described within the GI tract and PDGF has also been localized to active inflammation and active fibrosis within CD, possibly explaining the widespread fibrosis seen within some CD [115–117] (Fig. 1).

These mechanisms provide a plausible role for localized IgG4-related fibrosis within CD, and may contribute to fibrostenotic stricture formation. Furthermore, these mechanisms are not dependent on targets of current CD medical management [3]. This may explain the progression of fibrosis even in well-controlled CD in which inflammation has abated. Although further research is needed to clarify this potential relationship, localized IgG4 involvement and fibrosis as a mechanism for fibrostenotic stricture formation in CD is a promising area of future investigation.

Additionally, as IgG4 plasmablasts have been identified in the intestinal epithelium in ulcerative colitis, it is plausible that they may be responsible for colorectal strictures in UC [13, 74–76]. Although less significant in UC, potentially due to the larger caliber of the colon compared to the small intestine, IgG4 fibroplasia may be at play in UC, as well [118, 119]. Future research is warranted to clarify the significance of IgG4 plasmablasts in UC.

Nonspecific Immune Involvement

Along with the above shared pathophysiology, auxiliary immunologic mechanisms likely also contribute to the formation of IgG4-secreting plasmablasts and thus the fibrosis seen in CD. The first of these mechanisms worth noting is the significance of IL-10 as a contributor to not only fibrosis but also IgG4 plasmablast differentiation. IL-10 may be secreted from several involved cellular effectors within CD. The first worth noting is Tregs, which are promoted by the secretion of TGF- β [29, 40, 42–44]. Although, as mentioned above, differentiation of naive T cells into Tregs is likely tempered by the presence of IL-1 β , IL-6, and IL-21, which shunt this differentiation towards Th17 cells rather than Tregs [41], some Tregs are likely formed. These Tregs then secrete IL-10, a strong inducer of IgG4 plasmablast differentiation, and TGF- β , which promotes local fibrosis. Tregs have been linked to IgG4RD, with underlying pathophysiology posited to be due to this IL-10 and TGF- β secretion [120–127].

Another immunologic pathway that may contribute to IgG4 mediated fibrosis is the release and downstream effects of IL-33 within the gut mucosa. IL-33, or alarmin, is found within epithelial barriers, and, when epithelium is disrupted, IL-33 is released [128]. IL-33 has been shown to be overexpressed in patients with IBD, likely as a result of continuous inflammation causing injury to gut epithelium [129–131]. IL-33 is widely known as a strong inducer of a Th2 response; however, it is critical in the activation of macrophages implicated in wound healing [132, 133]. These macrophages, known as M2 macrophages, arise in the setting of injury and secrete IL-10 and TGF- β , further contributing to Treg differentiation, IgG4 plasmablast differentiation, and fibrosis [134–136]. IL-33 has also been shown to promote Treg differentiation, again contributing to the above mechanism [137]. Although a more recent development, IL-33 has been linked to IgG4RD, strengthening the possible relationship between IL-33 release from injured gut epithelium and IgG4 mediated fibrosis [138, 139].

These mechanisms remain promising to explain how fibrosis and resultant stricture formation may be due to dysregulated wound healing. These processes are also shared by IgG4RD, lending credence to their explanation of IgG4 fibrosis in CD. However, these mechanisms would not explain why fibrosis continues even in the absence of active inflammation, which is central to the significance and morbidity of CD strictures. As such, although they may accelerate or worsen fibroplasia during periods of active disease, these mechanisms are unlikely to be primary immunologic effectors of fibrous stricture formation. Furthermore, these mechanisms are not specific to CD, and rather represent general responses to inflammation. Thus, they may be less likely culprits for the significant fibrostenotic stricture formation seen specifically in CD. For example, gut inflammation and mucosal damage seen in ulcerative colitis would yield similar anti-inflammatory IL-10 secretion and release of IL-33; however, strictures are much rarer and more benign [140]. However, their role may be as a nidus for IgG4 differentiation and fibroplasia within CD. Future research investigating the interplay of these mechanisms and fibrostenotic stricture formation in CD is warranted.

Implications for Immunotherapy

Although confirmatory research must be conducted prior to targeting Th17, Tfh, and IgG4 plasmablasts and their effector cytokines in treatments of fibrosis in CD, several salient targets for immunotherapy emerge. First,

treatments for IgG4RD, such as rituximab, may be of use. Rituximab targets CD20 on B cells and prevents their differentiation into plasmablasts, thereby preventing PDGF-mediated fibroplasia as described above. Rituximab has proven effective and safe in small trials for IgG4RD, and this may be repurposed for localized IgG4 fibrosis within stricturing CD [73, 141, 142]. Similarly, next-generation biologics that target CD20, such as ocrelizumab, obinutuzumab, and veltuzumab, may be similarly effective [143]. However, rituximab has been implicated in GI complications and reports of rituximab-induced colitis [144–146]. Further, rituximab may target follicular B cells expressing CD20 and prevent their differentiation into plasmablasts, but would not target chronically active plasmablasts already formed prior to initiation of treatment [147].

Chronically active plasmablasts express CD38, and so the anti-CD38 biologic daratumumab may be a more effective treatment target. In a study of its efficacy in treating patients with multiple myeloma, it has been shown to decrease levels of plasmablasts in healthy controls [148]. Additionally, leveraging the overproduction of IgG4 antibodies in plasmablasts within fibrostenotic strictures by utilizing a proteasome inhibitor such as bortezomib may also be promising. One case of IgG4RD has been shown to be successfully treated with bortezomib [149]. Both daratumumab and bortezomib have shown efficacy in the treatment of multiple myeloma, a plasma cell-driven disease, and so may be effective in treating plasmablast-driven intestinal fibroplasia, as well. Finally, targeting PDGF that is secreted from plasmablasts itself as a final pro-fibrotic effector may be possible. There is little evidence for PDGF as a therapeutic target, and there is no current clinical use. However, preclinical studies have shown a reduction in fibrosis [150, 151].

Blockade of the cytokines involved in the shared pathophysiology of CD and IgG4-related fibrosis also could be an effective treatment for fibrostenotic strictures. Further, anti-IL-21 or anti-17 directed medication may be efficacious in controlling fibrosis. IL-17 blockade is effective and has a favorable safety profile in the treatment of psoriasis; however it has been paradoxically

linked to worsening CD flares, and thus may not be the optimal target in this case, although the mechanisms underlying this association are not clear [152–154]. IL-21 seems a more promising target, as anti-IL-21 drugs have been shown to reduce inflammation and neutrophil infiltration in CD. Thus, it may reduce CD inflammation while also targeting a key effector in sustaining IgG4-producing plasma cells [155–157].

Conclusion

The shared pathophysiology of IgG4-related disease and CD provide a plausible mechanism by which IgG4-related fibrosis significantly contributes to fibroplasia and resultant stricture formation. As such, what is currently a progressive and significant source of morbidity in CD may be treatable with immunotherapy directed at the mediators of intestinal fibroplasia. However, although promising, further research into IgG4-related fibrosis and the formation of strictures in CD is imperative to fully elucidate its pathophysiology and facilitate the development of effective treatments.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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