Chapter 10
Fibrosis in Ulcerative Colitis

Fernando Magro and Tatiana António

Abstract Intestinal fibrosis is a classic complication in Inflammatory Bowel Diseases where chronic inflammation and abnormal tissue repair together lead to a compromised bowel function. Although fibrosis and stricture formation are acknowledged features of Crohn's disease courses, these complications remain poorly studied in ulcerative colitis (UC). The relevance of this topic has long been ignored, despite the well-known prevalence of stenosis in UC, its clinical impact in motility and the importance of assessing stricture malignancy.

Fibrosis in UC is now perceived as a dynamic and reversible process. However, still no proper antifibrotic therapy exist, mainly due to the very limited pathophysiological insights.

This chapter aims to review the current knowledge about fibrosis development in UC, outlining disease basic concepts, epidemiology, histopathologic features and clinical consequences.

Keywords Ulcerative colitis · Inflammatory bowel diseases · Fibrosis · Stenosis · Myofibroblasts · Extracellular matrix

10.1 Ulcerative Colitis

Ulcerative colitis (UC) is, along with Crohn's disease (CD), a chronic inflammatory bowel disease where the intestinal permeability is disturbed by an inappropriate immune response. Both diseases share many epidemiological and clinical features. Nevertheless, UC distinguishes itself by being less prone to complications and by its gastrointestinal distribution, which is continuous and begins in the rectum, spreading proximally, but not reaching the ileum. Therefore, inflammation is worse in the distal colon [1, 2].

Overview of fibrosis in Ulcerative colitis

F. Magro (✉) · T. António
Faculty of Medicine, University of Porto, Porto, Portugal
e-mail: fm@med.up.pt; taa@med.up.pt

F. Rieder (ed.), *Fibrostenotic Inflammatory Bowel Disease*,
https://doi.org/10.1007/978-3-319-90578-5_10

The extent of the colonic mucosal involvement can either be limited to the rectum (proctitis), which accounts for about one third of all patients [3, 4], or progress distally, called left-sided colitis where the inflammatory process reaches the splenic flexure. When disease activity goes beyond that location and is present throughout the colon, UC is classified as extensive colitis, the most common presentation at onset in children [5]. In general, the illness' natural course is mild, marked by periods of flares and spontaneous remission of variable duration and the prognosis is usually good for the first 10 years after diagnosis [6–8].

The colonoscopy of UC reveals a diffuse, uniform inflammation with loss of the visible vascular pattern and haustral folds, as well as a granular, erythematous appearance of the mucosa. Friability is also noticeable, since the mucosa bleeds either when touched or spontaneously. Pseudopolyps may be present in long-standing UC [2, 5], but fissures, granulomas and transmural lymphoid aggregates are absent from UC patient's colon [1]. Multiple endoscopic biopsies allow the understanding of disease distribution. Findings of discontinuous mucosal impairment with sparing areas and ileal involvement favor CD diagnosis, as is a cobblestone mucosal pattern and longitudinal, irregular ulcers [1, 2]. Histologically, UC usually appears to be confined to the most superficial layers of the colon. Microscopic evidences include crypt architectural distortion, atrophy and abscesses, along with infiltration of plasma cells (plasmacytosis), lymphocytes and granulocytes [1, 5, 6].

Furthermore, some clinical manifestations are the hallmark of UC: bloody diarrhea with or without mucous secretion, fecal urgency and tenesmus [2, 7, 9]. On the other hand, CD is more likely to present with frequent abdominal pain and perianal lesions [9]. The natural course of UC can also be accompanied by frequent evacuations of blood or mucus, variable abdominal pain, overall malaise, fatigue and less commonly fever and weight loss, depending on the extent and severity of the disease [2, 6, 9]. Local complications may encompass strictures, abscesses, fistulas and cancer. Additionally, colonic dilatation (toxic megacolon) and massive bleeding may occur in the most acute fulminant form of UC [5, 10].

Besides, 10–30% of patients with UC will experience extraintestinal manifestations of the disease, which comprise musculoskeletal problems such as arthritis and osteoporosis, eye pathologies, primary sclerosing cholangitis, skin conditions like erythema nodosum, pyoderma gangrenosum and aphtous stomatitis, as well as anemia and coagulation abnormalities [2, 6, 11, 12].

Ultimately, the disease progresses towards a fibrotic pathway and, consequently, colonic failure, which appears to be a self-sustaining process that can endure even in the absence of inflammation [13].

10.1.1 Epidemiology

Overall, Inflammatory Bowel Diseases (IBD) are associated with an industrialized and westernized lifestyle, being more common in Europe and North America. Their prevalence and incidence are increasing over time and geographically, becoming a global disease [14]. The fact that IBD incidence is now much higher in prior low

incidence countries such as Asia, the finding that the disease is more typical in urban areas versus rural regions and the observation that migrating from a lower prevalence area of IBD to a higher prevalence area increases a person's disease risk all suggest that environment and lifestyle have an important role in the etiology of IBD [3, 14, 15]. UC is the most prevalent form of inflammatory bowel disease and it seems to affect both men and women in an equal manner [3, 6, 14]. The highest annual incidence of UC is found in Europe, reaching 24.3 cases per 100,000 persons [14]. This idiopathic illness is mainly diagnosed in adults between 20 and 40 years of age, although it can have its onset at any age [14–16].

Chronic inflammation in these patients eventually brings about fibrosis. This process is most of the times clinically silent and only becomes symptomatic in about 5% of the individuals with UC [17]. Benign strictures, a complication for which fibrosis is believed to contribute, occur in less than 5% of UC cases [18–20].

10.1.2 Etiology

Despite the fact that UC pathophysiology is still not fully understood, today it is widely accepted that UC does not result from a single cause, but instead it is an outcome of a multifactorial mechanism involving the immune system, environmental factors, gut commensal microbiota and genetic susceptibility [5]. These factors promote an inappropriate immune response that is accompanied by adverse clinical outcomes.

Family history is a fairly important risk factor for UC development, especially with affected first-degree relatives [21]. Genome-wide association studies (GWAS) have found 163 risk loci for IBD, 23 of those being specific for UC. These polymorphisms may disturb innate and adaptive immunity and other mechanisms that assure intestinal homeostasis [22]. However, the fact that concordance rate for UC among monozygotic twins is only about 16% denotes the great impact of non-genetic aspects in disease risk [23]. This puts a spotlight on environmental factors, particularly the ones affecting bacterial colonization of the intestine. Evidence that germ-free animals do not develop UC highlights the relevance of commensal enteric microorganisms in disease pathogenesis [24, 25]. In fact, microbiota seem to play a major role in both disease onset and severity, as well as in determining disease phenotype as UC or CD [21].

Thus, the exposure of genetically susceptible individuals to antigens of the commensal microbiota leads to a persistent immuno-mediated intestinal disorder. Nonetheless, it remains undetermined what exactly triggers chronicity in UC [10].

10.2 Fibrosis in Ulcerative Colitis

Intestinal fibrosis is frequently associated with chronic intestinal inflammation in many enteropathies and it's often observed in both main forms of IBD. It is seen as a process of long-lasting illness, where persistent tissue damage and healing result in barrier dysfunction followed by scar tissue formation [19, 26].

Fibrosis is characterized by an imbalance favoring deposition of collagen-rich extracellular matrix (ECM) over breakdown of ECM components. In UC, it is usually marked by a local increase in the mesenchymal cell pool together with thickening of the muscularis mucosa [27, 28].

Since inflammation is only rarely detected in the muscularis propria and because strictures are much less frequent in UC (1–11.2%) when compared to their fairly high incidence in CD, fibrosis was thought to be limited to the mucosa and submucosa in UC subjects [18, 20, 27, 29]. These fibrotic changes have been ignored over the years, despite their clinical relevance in leading to a stiffened colon unable to perform peristalsis or resorb fluids [30, 31]. Moreover, CD is well-known for being a transmural disease where strictures may originate from the muscular layers, whereas UC was formerly believed to be confined to the inner layers [19]. This made stricture formation in UC much harder to explain and hence mechanisms other than excessive deposition of ECM have been proposed in the formation of benign strictures in UC, namely the hypertrophy and contraction of the muscularis mucosae, which was found to narrow the lumen of the large bowel [20, 32].

It was only then suggested that disease activity might not be strictly confined to the mucosa as previously thought, but instead can affect the entire thickness of the bowel wall. This is in line with the findings of an enhanced collagen deposition throughout all the layers of the colonic wall [27, 29, 30].

10.2.1 Pathogenesis

It is widely acknowledged that fibrosis is an outcome of inflammatory damage to the tissue followed by healing impairment [33]. It has been stated that inflammation is required for the initiation of fibrosis [34]. This is supported by evidence that fibrosis follows inflammation distribution and it's never found in segments apart from the ones affected by inflammation [35]. On the other hand, inflammation seem to play only a minor role in fibrosis progression [10]. In fact, there are intestinal diseases, like celiac disease, where chronic inflammation is present but fibrosis and strictures do not occur. Furthermore, anti-inflammatory therapies have failed to prevent or reverse intestinal fibrosis. These observations highlight the existence of an independent mechanism underlying fibrosis other than inflammation [36, 37] Not only it is not yet clear what drives chronicity in UC, but also it is still undefined what prompts strictures formation. Since not all individuals develop intestinal fibrosis and the ones who do, display a variable extent of it, we can postulate that there is a genetic factor that determines susceptibility [10, 38].

It is still unclear if UC and CD share the same fibrogenic pathways [28]. Yet, in both situations, an inflammatory environment seems to be a prerequisite for the intestinal fibrotic process to begin. Inflammation leads to injury of the epithelium with ECM disassembly and release of chemokines and other cytokines, which in turn determines the recruitment and activation of immune and non-immune cell

types. Immune cells migrating to the injured site include both macrophages and neutrophils as part of the immediate innate response, and T lymphocytes as part of the adaptive immune response [34, 36, 39].

Damage additionally extends to the lamina propria by local activation of ECM-degrading enzymes, like elastases and matrix metalloproteinases (MMPs) that allow further infiltration of immune cells. Moreover, collagenases reinforce destruction of the ECM by fibronectin and collagen degradation. Eventually, this continuous cycle of epithelial damage, repair, angiogenesis and lymphangiogenesis is responsible for the loss of epithelial cells and mucosal ulceration (Fig. 10.1) [19, 29, 34].

In this manner, damaged mucosa and submucosa becomes exposed to a profibrotic milieu of soluble mediators and enzymes. In UC these include proinflammatory cytokines such as IL-13 [40], IL-17 [41] and IL-33 [42] and several growth factors among which are the insulin-like growth factor-1 (IGF-1) [43–45], the transforming growth factor-β (TGF-β) [31, 46], the platelet-derived growth factor (PDGF) [47], the basic fibroblast growth factor (b-FGF) [20, 43] and the tumor necrosis factor-α (TNF-α) [31, 45].

This microenvironment encourages local mesenchymal cells to actively differentiate and dedifferentiate between three acknowledged phenotypes: fibroblasts

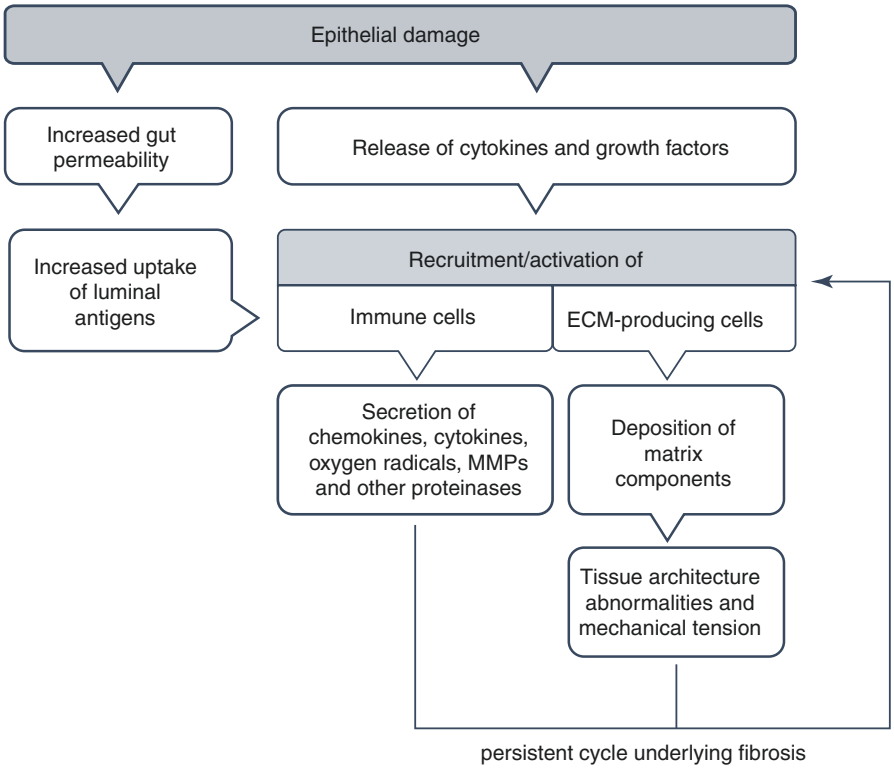

Fig. 10.1 General representation of downstream events that underscore fibrosis in UC

(α-smooth muscle actin (α-SMA) negative, vimentin positive, desmin negative), myofibroblasts (α-SMA positive, vimentin positive, desmin negative) and smooth muscle cells (α-SMA positive, vimentin positive, desmin positive) [48]. The great contractile ability of activated myofibroblasts, their capacity to migrate and secrete ECM components as well as growth factors, make them the main player in tissue remodeling and fibrosis. In the active UC mucosa, the number of α-SMA positive cells is increased, especially at the margins of deep ulcers [34, 49]. Myofibroblasts can become activated through different pathways, by means of paracrine signals from immune and nonimmune cells, as the ones mentioned above, by autocrine signaling, by pathogen-associated molecular patterns that come from the interaction of microorganisms with Toll-like and NOD-like receptors, and also by products from cell injury named damage-associated molecular patterns [17, 50]. Myofibroblast activation represents an acquisition of a pro-repair and pro-fibrogenic cell phenotype, inciting their proliferation (expansion in number) and dramatically increasing their secretion of numerous molecules, including mediators that further sustain local inflammation and ECM components deposition [43, 51].

Among these components, collagen comprises the major scar protein, with a predominance of subtypes I and III. Collagen type I provides tensile strength and mechanical stability to the tissue, whereas collagen type III is known for its elastic and flexile properties. In UC, both these subtypes of collagen together with fibronectin have been found in increased levels transmurally, i.e., not only in the mucosa and submucosa, but also in the muscularis externa [27, 29].

Normal wound healing begins with deposition of new matrix components predominantly collagen type III, which in time is replaced by collagen type I [52, 53]. Some studies also found this increased collagen type III:I ratio to exist in inflamed colonic specimens from UC patients, which relates to the initial state of fibrosis development. Moreover, the areas where this increase occurs overlap with regions of an inflammatory cell infiltrate rich in TGF-β1 and IGF-1. This ratio later changes in favor of collagen type I as the fibrotic process matures [27, 54].

Besides local proliferation, myofibroblasts may arise from a wide variety of sources: they can either migrate from neighboring tissue, be recruited from circulating precursors like fibrocytes or bone marrow stem-cells, differentiate from intestinal stellate cells and pericytes, or derive from epithelial or endothelial-to-mesenchymal transition [26, 48, 51, 55].

Under physiologic conditions, tissue repair is a self-limited controlled process. Eventually the epithelial barrier becomes fully restored, MMPs break down the fibrotic matrix and myofibroblasts become inactivated or undergo apoptosis, but still very little is known about the signals that control this process [53, 56]. In UC, however, repair mechanisms are disturbed. Instead, persistent deposition and cross-linking of matrix components modify the ECM leading to its stiffening. Since immune and nonimmune cells can sense the surrounding matrix via integrin mediated mechanisms, mechanical tension by itself can drive cells to a proliferative and activated phenotype, leading to a vicious cycle of profibrotic events (Fig. 10.1) [33, 57].

Although strictures are much less frequent in UC than in CD and often associated with longer disease duration, they can still have a significant impact on the disease course and lead to serious clinical complications. Above all, a better understanding

of stricture pathogenesis in UC is crucial when considering the risk of cancer, even though only a minority of strictures in UC are indeed malignant. It is difficult to perceive whether colonic cancer emerges from a pre-existing benign stricture or if it is in fact a malignant growth from the beginning. Benign strictures are frequently asymptomatic and associated with long-lasting disease. The time elapsed from UC diagnosis to stenosis detection is usually about 15 years [18, 20, 58].

The mechanisms for the development of benign strictures in UC remain poorly understood. Some authors believe that hyperthrophy and contraction of the muscularis mucosae is the most likely phenomenon to be responsible for the colonic narrowing related to strictures. However, the ability of the reported lesions to revert spontaneously and the inclusion of muscular hyperthrophy cases in the study suggests that these may not be in fact true strictures [18, 59]. Indeed, several inflammatory mediators are known for promoting growth and function alterations of smooth muscle cells [17]. Nevertheless, muscular thickening of the muscular layer does not seem to be the major culprit of stenosis in UC as not all stenotic specimens display a thickened muscularis propria [20]. Additionally, a more rigorous approach found stenotic cases to be linked to greater ulcer scars when comparing to nonstenotic specimens, even at segments of the colon without stenosis, denoting that stenotic subjects are more prone to fibrosis development [20]. Furthermore, b-FGF, an important proliferation factor for mesenchymal cells, was found to be highly expressed at stenotic sites, along with myeloperoxidase, in cases where neutrophils appear to be the dominant inflammatory cell type. This further supports the hypothesis that colonic stenosis in long-lasting UC is owed to fibrosis, probably by b-FGF-positive neutrophils, inducing proliferation of myofibroblasts [20]. The reason why stenosis and strictures are common complications of CD but are rather rare in UC is still uncertain. UC confinement to the most superficial layers of the colon was initially pointed out as one possible explanation, but several studies have later reported ECM deposition in all layers of the colonic wall [29, 30]. Further studies are needed to explain this observation.

10.2.2 Clinical Consequences of Fibrosis

The abnormal tissue architecture that arises from fibrosis may disturb the normal function of the epithelium and eventually trigger the development of symptoms [26]. Peristalsis and fluid reabsorption are compromised, and may lead to the abdominal pain and diarrhea often experienced by patients with UC. Fibrosis in UC has been a quite overlooked topic and therefore its serious clinical implications have been far underestimated. This is surprising as the importance of the ECM deposition in the disease course, its role in stricture formation, the ensuing obstruction and motility problems that may result and the crucial need of distinguish between benign and malignant strictures are well-known phenomena [30, 31, 33]. Clinical complications are likely related to the accumulation of scar tissue in the intestinal wall of UC subjects and therefore the smaller diameter of the colon. This comes with an increase in wall stiffness and patients with long-standing illness normally present with a

narrowed colon with diffuse loss of haustration, acquiring a “lead pipe” appearance. Clinical findings suggest that these structural alterations entail loss of colonic elastic properties and decrease of contractility and compliance. Moreover, a reduced tone of the descending colon is found in these patients after meals. Consequently, looser faeces or even diarrhea will ensue. A particularly severe form of dysmotility in UC is anorectal dysfunction, expressed by fecal urgency, incontinence and tenesmus [28, 32, 33, 60]. Generally, the clinical picture correlates with the disease extent and distal involvement, as colorectal lesions usually display more and earlier symptoms [10].

It is true that these symptoms can be more severe during the active phases of UC and indeed it is well established that inflammation itself is able to affect motor and perceptive functions of the colon [61–63]. However, even when inflammation subsides and disease is quiescent, patients’ symptoms still persist and because of that one can hypothesize that fibrosis of the large bowel wall could contribute to all of the above clinical presentations [32, 64, 65].

10.3 Conclusion and Future Questions to Be Addressed

The concept of fibrosis is now one of a dynamic and reversible process. In order to provide reliable therapeutic options to manage fibrosis in UC, some matters are yet to be addressed, as pathophysiological insights are still very limited. First, there is a need to determine the key effectors in myofibroblast activation and the markers that identify the activated form of the mesenchymal cell. Second, it would be crucial to determine which factors rule the transition from an inflammatory to a fibrostenotic phenotype, which could potentially also be used as a specific target for antifibrotic therapy.

Limitations to the study of fibrosis and stricture formation include the lack of good animal models that truly represent the chronic, polygenetic nature of the disease and the need of reliable biomarkers that would make monitoring fibrosis in clinical trials possible [22, 66].

Several compounds have been proposed as potential antifibrotic drugs [13, 67], but no specific therapy is yet available. The fibrotic mechanisms are highly complex and multifactorial and a multi-target approach would likely be the best strategy. The self-perpetuating nature in UC highlights the urge for drugs that would allow the prevention and reversal of intestinal fibrosis. As our knowledge on fibrostenotic mechanisms progresses, this target will come within reach.

References

1. Geboes K. What histologic features best differentiate Crohn’s disease from ulcerative colitis? Inflamm Bowel Dis. 2008;14(Suppl 2):S168–9.
2. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med. 2011;365(18):1713–25.
3. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol. 2015;50(8):942–51.

4. Whitlow CB. Ulcerative proctitis. Clin Colon Rectal Surg. 2004;17(1):21–7.
5. Conrad K, Roggenbuck D, Laass MW. Diagnosis and classification of ulcerative colitis. Autoimmun Rev. 2014;13(4-5):463–6.
6. Feuerstein JD, Cheifetz AS. Ulcerative colitis: epidemiology, diagnosis, and management. Mayo Clin Proc. 2014;89(11):1553–63.
7. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(3):501–23; quiz 524.
8. Cosnes J, et al. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785–94.
9. Langan RC, et al. Ulcerative colitis: diagnosis and treatment. Am Fam Physician. 2007;76(9):1323–30.
10. Latella G, et al. Can we prevent, reduce or reverse intestinal fibrosis in IBD? Eur Rev Med Pharmacol Sci. 2013;17(10):1283–304.
11. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. World J Gastroenterol. 2006;12(30):4819–31.
12. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Hepatol. 2011;7(4):235–41.
13. Johnson LA, et al. Novel Rho/MRTF/SRF inhibitors block matrix-stiffness and TGF-β–induced fibrogenesis in human colonic myofibroblasts. Inflamm Bowel Dis. 2014;20(1):154–65.
14. Molodecky NA, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54 e42; quiz e30.
15. Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clin Epidemiol. 2013;5:237–47.
16. Takahashi H, et al. Second peak in the distribution of age at onset of ulcerative colitis in relation to smoking cessation. J Gastroenterol Hepatol. 2014;29(8):1603–8.
17. Latella G, Rieder F. Intestinal fibrosis: ready to be reversed. Curr Opin Gastroenterol. 2017;33(4):239–45.
18. Gumaste V, Sachar DB, Greenstein AJ. Benign and malignant colorectal strictures in ulcerative colitis. Gut. 1992;33(7):938–41.
19. Rogler G. Pathogenesis of strictures in ulcerative colitis: a field to explore. Digestion. 2011;84(1):10–1.
20. Yamagata M, et al. Submucosal fibrosis and basic-fibroblast growth factor-positive neutrophils correlate with colonic stenosis in cases of ulcerative colitis. Digestion. 2011;84(1):12–21.
21. Ordás I, et al. Ulcerative colitis. Lancet. 2012;380(9853):1606–19.
22. Latella G, et al. Results of the 4th scientific workshop of the ECCO (I): pathophysiology of intestinal fibrosis in IBD. J Crohns Colitis. 2014;8(10):1147–65.
23. Spehlmann ME, et al. Epidemiology of inflammatory bowel disease in a German twin cohort: results of a nationwide study. Inflamm Bowel Dis. 2008;14(7):968–76.
24. Taurog JD, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. J Exp Med. 1994;180(6):2359–64.
25. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474(7351):307–17.
26. Rieder F, Fiocchi C. Intestinal fibrosis in IBD—a dynamic, multifactorial process. Nat Rev Gastroenterol Hepatol. 2009;6(4):228–35.
27. Ippolito C, et al. Fibrotic and vascular remodelling of colonic wall in patients with active ulcerative colitis. J Crohns Colitis. 2016;10(10):1194–204.
28. Latella G, Rieder F. Time to look underneath the surface: ulcerative colitis-associated fibrosis. J Crohns Colitis. 2015;9(11):941–2.
29. de Bruyn JR, et al. Development of fibrosis in acute and longstanding ulcerative colitis. J Crohns Colitis. 2015;9(11):966–72.
30. Manetti M, et al. Telocytes are reduced during fibrotic remodelling of the colonic wall in ulcerative colitis. J Cell Mol Med. 2015;19(1):62–73.

31. Maul J, Zeitz M. Ulcerative colitis: immune function, tissue fibrosis and current therapeutic considerations. Langenbeck's Arch Surg. 2012;397(1):1–10.
32. Torres J, et al. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflamm Bowel Dis. 2012;18(7):1356–63.
33. Gordon IO, et al. Fibrosis in ulcerative colitis: mechanisms, features, and consequences of a neglected problem. Inflamm Bowel Dis. 2014;20(11):2198–206.
34. Rieder F, et al. Wound healing and fibrosis in intestinal disease. Gut. 2007;56(1):130–9.
35. Bettenworth D, Rieder F. Pathogenesis of intestinal fibrosis in inflammatory bowel disease and perspectives for therapeutic implication. Dig Dis. 2017;35(1-2):25–31.
36. Speca S, et al. Cellular and molecular mechanisms of intestinal fibrosis. World J Gastroenterol. 2012;18(28):3635–61.
37. Wynn TA. Cellular and molecular mechanisms of fibrosis. J Pathol. 2008;214(2):199–210.
38. Latella G, et al. Mechanisms of initiation and progression of intestinal fibrosis in IBD. Scand J Gastroenterol. 2015;50(1):53–65.
39. Johnson LA, et al. Intestinal fibrosis is reduced by early elimination of inflammation in a mouse model of IBD: impact of a "Top-Down" approach to intestinal fibrosis in mice. Inflamm Bowel Dis. 2012;18(3):460–71.
40. Heller F, et al. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. Gastroenterology. 2005;129(2):550–64.
41. Fonseca-Camarillo G, et al. Interleukin 17 gene and protein expression are increased in patients with ulcerative colitis. Inflamm Bowel Dis. 2011;17(10):E135–6.
42. Sponheim J, et al. Inflammatory bowel disease-associated interleukin-33 is preferentially expressed in ulceration-associated myofibroblasts. Am J Pathol. 2010;177(6):2804–15.
43. Lawrance IC, Maxwell L, Doe W. Altered response of intestinal mucosal fibroblasts to profibrogenic cytokines in inflammatory bowel disease. Inflamm Bowel Dis. 2001;7(3):226–36.
44. Simmons JG, et al. IGF-I and TGF-beta1 have distinct effects on phenotype and proliferation of intestinal fibroblasts. Am J Physiol Gastrointest Liver Physiol. 2002;283(3):G809–18.
45. Theiss AL, et al. Tumor necrosis factor (TNF) alpha increases collagen accumulation and proliferation in intestinal myofibroblasts via TNF receptor 2. J Biol Chem. 2005;280(43):36099–109.
46. Hormi K, Lehy T. Transforming growth factor-alpha in vivo stimulates epithelial cell proliferation in digestive tissues of suckling rats. Gut. 1996;39(4):532–8.
47. Kumagai S, et al. Platelet-derived growth factor and its receptors are expressed in areas of both active inflammation and active fibrosis in inflammatory bowel disease. Tohoku J Exp Med. 2001;195(1):21–33.
48. Rieder F, et al. Intestinal fibrosis and liver fibrosis: consequences of chronic inflammation or independent pathophysiology? Inflamm Intest Dis. 2016;1(1):41–9.
49. Andoh A, et al. Intestinal subepithelial myofibroblasts in inflammatory bowel diseases. J Gastroenterol. 2002;37(Suppl 14):33–7.
50. Fiocchi C, Lund PK. Themes in fibrosis and gastrointestinal inflammation. Am J Physiol Gastrointest Liver Physiol. 2011;300(5):G677–83.
51. Rieder F, Fiocchi C. Intestinal fibrosis in inflammatory bowel disease - current knowledge and future perspectives. J Crohns Colitis. 2008;2(4):279–90.
52. Bainbridge P. Wound healing and the role of fibroblasts. J Wound Care. 2013;22(8):407–8, 410-12.
53. Witte MB, Barbul A. General principles of wound healing. Surg Clin North Am. 1997;77(3):509–28.
54. Lawrance IC, Maxwell L, Doe W. Inflammation location, but not type, determines the increase in TGF-β1 and IGF-1 expression and collagen deposition in IBD intestine. Inflamm Bowel Dis. 2001;7(1):16–26.
55. Leeb SN, et al. Reduced migration of fibroblasts in inflammatory bowel disease: role of inflammatory mediators and focal adhesion kinase. Gastroenterology. 2003;125(5):1341–54.

56. Lawrance IC, et al. Cellular and molecular mediators of intestinal fibrosis. J Crohns Colitis. 2015;11(12):1491–503.
57. Wells RG. The role of matrix stiffness in regulating cell behavior. Hepatology. 2008;47(4):1394–400.
58. Sonnenberg A, Genta RM. Epithelial dysplasia and cancer in IBD strictures. J Crohns Colitis. 2015;9(9):769–75.
59. Goulston SJ, McGovern VJ. The nature of benign strictures in ulcerative colitis. N Engl J Med. 1969;281(6):290–5.
60. Bassotti G, et al. Gastrointestinal motility disorders in inflammatory bowel diseases. World J Gastroenterol. 2014;20(1):37–44.
61. Fukudo S. Role of corticotropin-releasing hormone in irritable bowel syndrome and intestinal inflammation. J Gastroenterol. 2007;42(Suppl 17):48–51.
62. Neunlist M, et al. Changes in chemical coding of myenteric neurones in ulcerative colitis. Gut. 2003;52(1):84–90.
63. Vrees MD, et al. Abnormal motility in patients with ulcerative colitis: the role of inflammatory cytokines. Arch Surg. 2002;137(4):439–46.
64. Choi K, et al. Impaired integrity of DNA after recovery from inflammation causes persistent dysfunction of colonic smooth muscle. Gastroenterology. 2011;141(4):1293–301, 1301.e1-3.
65. La JH, et al. Visceral hypersensitivity and altered colonic motility after subsidence of inflammation in a rat model of colitis. World J Gastroenterol. 2003;9(12):2791–5.
66. Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases. Gastroenterology. 2017;152(2):340–350.e6.
67. Trivedi PP, Jena GB. Role of alpha-lipoic acid in dextran sulfate sodium-induced ulcerative colitis in mice: studies on inflammation, oxidative stress, DNA damage and fibrosis. Food Chem Toxicol. 2013;59:339–55.