

Intestinal fibrosis in inflammatory bowel disease: progress in basic and clinical science

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Purpose of review

Intestinal fibrosis is a potentially serious complication of inflammatory bowel disease and its pathophysiology is still unclear. This review will discuss recent developments relating to sources of fibroblasts in intestinal inflammation, mediators that modulate fibroblast activation and function, as well as new clinical, laboratory, endoscopic and radiological studies aimed at improving diagnosis and management of intestinal fibrosis in inflammatory bowel disease.

Recent findings

The fibroblast remains the central cell responsible for intestinal fibrosis in inflammatory bowel disease and transforming growth factor- β 1 is still the most potent pro-fibrogenic cytokine. Novel mediators, however, are being identified that modulate fibroblast function, such as interleukin-13, interleukin-21, galectin-3, osteopontin, Wnt and toll-like receptor ligands, and anti-tumor necrosis factor- α agents. New fibroblast sources are being identified, such as fibrocytes, and new mechanisms of fibroblast generation, like epithelial- and endothelial-to-mesenchymal transition. Animal models of intestinal fibrosis are still few, but new ways to induce gut fibrosis are being explored. Serological markers indicating a clinically complicated course that includes intestinal fibrosis are promising and are being tested in adult and pediatric populations, particularly in Crohn's disease. Video capsule endoscopy, the Given Patency capsule, double balloon enteroscopy, and computed tomographic enteroscopy are some of the new modalities being developed to assess the risk and improve the diagnosis of intestinal fibrosis. Novel therapeutic approaches include endoscopic balloon dilatation with conventional and double balloon enteroscopy, and local injection of glucocorticoids and tumor necrosis factor- α blockers, showing partial but encouraging success.

Summary

More studies are needed to improve knowledge of the pathophysiology of intestinal fibrosis if better preventive, diagnostic and therapeutic measures are to be expected in the near future.

Keywords

fibroblast, fibrosis, inflammatory bowel disease, stricture

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Introduction

Intestinal fibrosis is generally considered a common consequence of inflammatory bowel disease (IBD), but may develop into a serious complication potentially leading to bowel obstruction and surgery [1^{*}]. The lack of a better understanding of its pathophysiology is striking when compared with our continuously expanding knowledge of immunopathogenic events in IBD. This ignorance is largely responsible for our current inability to diagnose intestinal fibrosis early and accurately, treat it properly, and take measures to prevent it. This review will discuss the most recent basic and clinical science developments in IBD-associated intestinal fibrosis.

Basic science

This section presents advances made in our understanding of fibroblast function and in identifying novel mediators of tissue fibrosis, but also in detecting additional sources of intestinal fibroblasts and developing new animal models of intestinal fibrosis.

Fibroblast function and mediators of tissue fibrosis

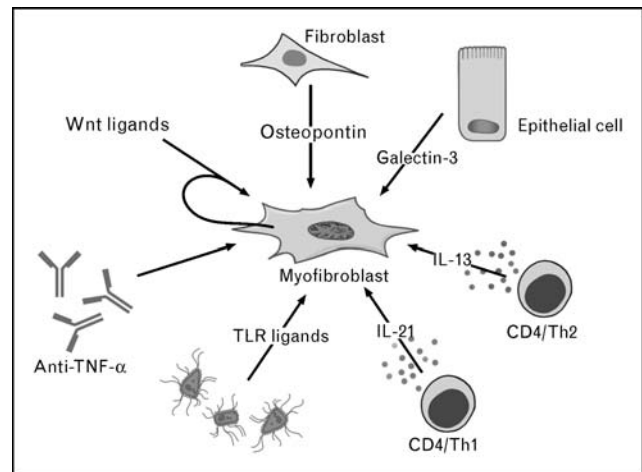
Exposure of mucosal fibroblasts (also termed myofibroblasts) to inflammatory mediators, and the subsequent collagen production and tissue remodeling are considered key events in the development of IBD-associated fibrosis [1^{*},2^{*}]. Several groups continue to probe the imbalance

between extracellular matrix (ECM) deposition and degradation in IBD. Matrix metalloproteinases (MMPs) are endopeptidases involved in ECM degradation and their activity is under the control of tissue inhibitors of matrix metalloproteinases (TIMPs). Regardless of the presence of fibrosis, in inflamed IBD tissue expression of MMP-1, 2, 3 and 9 is increased relative to that of TIMP-1 and 2 compared with noninflamed IBD and control tissue [3]. How the balance of MMPs and TIMPs is regulated is still unclear, but blocking transforming growth factor (TGF)- β 1 in cultures of intestinal biopsies seemingly upregulates the expression of MMP-3 but not of TIMP-1, suggesting a new role for TGF- β 1 in IBD tissue remodeling [4]. Single nucleotide polymorphisms (SNPs) in the genes encoding MMPs and TIMPs have been described. A SNP at the *TIMP-1* site on the X-chromosome has been associated with increased susceptibility for Crohn's disease, and a SNP at the site of *MMP-3* may increase the chance of stenotic complications [5]. Existing data do not suggest that different levels of MMPs or TIMPs are produced depending on the type of IBD or clinical phenotype, but mutation-dependent expression of MMPs or TIMPs could have an impact on disease expression.

TNF- α is considered crucial to IBD pathogenesis. Di Sabatino *et al.* [6] recently published evidence that intestinal fibroblasts express membrane-associated tumor necrosis factor (TNF)- α , and that infliximab can reduce secretion of collagen, increase expression of TIMP-1, and enhance the migratory capacity of Crohn's disease fibroblasts without inducing their apoptosis [6]. Thus, TNF- α blockade may not only promote wound healing, but also prevent intestinal fibrosis. A new cytokine that affects fibroblasts and their ability to modulate intestinal fibrosis is interleukin (IL)-21, a product of activated CD4⁺ T helper 1 cells whose level is increased in IBD mucosa. Intestinal fibroblasts express the receptor for IL-21 and its ligation stimulates MMP production contributing to tissue destruction [7]. Therefore, as for TNF- α , blockade of IL-21 may also be beneficial in preventing or reducing intestinal fibrosis (Fig. 1).

TGF- β 1 is considered the most potent mediator of fibrosis through its direct effect on fibroblasts. TGF- β 1 function is regulated at different levels, and intriguing new data suggest that the intestinal flora can modulate its profibrotic activity, as shown in a model of hepatic fibrogenesis in which toll-like receptor (TLR)-4 activation augments the TGF- β 1-mediated collagen accumulation [8^{••}]. TLRs are expressed by intestinal fibroblasts [9] and are activated by a number of specific ligands (authors' unpublished observation). This observation places TGF- β 1 under a new light, by subjecting its profibrotic activity to the control of the gut flora. IL-13

Figure 1 A variety of mediators from different cellular, bacterial and exogenous sources have the capacity to activate myofibroblasts and modulate their function



Th, T helper; TLR, toll-like receptor; TNF, tumor necrosis factor.

has also recently emerged as a profibrotic cytokine in several organs. This also appears to be true in the gut, as CD4⁺ T helper 2-derived IL-13 can cause TGF- β 1-dependent intestinal fibrosis in the trinitrobenzene sulfonic acid (TNBS) colitis model [10[•]] (Fig. 1).

In addition to classical cytokines, intestinal fibroblasts can be activated by noncytokine products, such as epithelial cell-derived galectin-3 [11[•]] (Fig. 1). Galectin-3-induced activation is mediated by nuclear factor κ B (NF- κ B), whose blockade with antisense oligonucleotides [12] or deoxyoligonucleotides [13] reduces both inflammation and fibrosis in the TNBS colitis model. A recent report by Wu and Chakravarti [14] extended these observations by showing that blocking the p65 subunit of NF- κ B with antisense oligonucleotides reduces gut inflammation-induced fibrosis.

In addition to being the target of profibrotic mediators, fibroblasts themselves can produce factors promoting fibrosis, such as osteopontin. A recent study [15[•]] shows that knockdown of the osteopontin gene in inflammation-associated skin fibrosis leads to wound healing with less scarring. If a similar response were observed in IBD it could open the door to prevention or eradication of intestinal fibrosis. Finally, the Wnt pathway is a central regulator of cell growth and differentiation, and it also appears to play a role in the pathogenesis of fibrotic diseases, as recently suggested by elevated levels of Wnt proteins in the development of age-dependent fibrosis [16^{••}]. This report suggests that investigation of the Wnt pathway in IBD could yield new insights into the mechanisms of intestinal fibrosis (Fig. 1).

New fibroblast sources

Intestinal fibrosis is characterized by fibroblast accumulation secondary to local proliferation and migration, differentiation from intestinal stellate cells, and recruitment from the bone marrow. Fibroblasts, however, can also derive from alternative sources such as circulating fibrocytes and transformation of epithelial and endothelial cells.

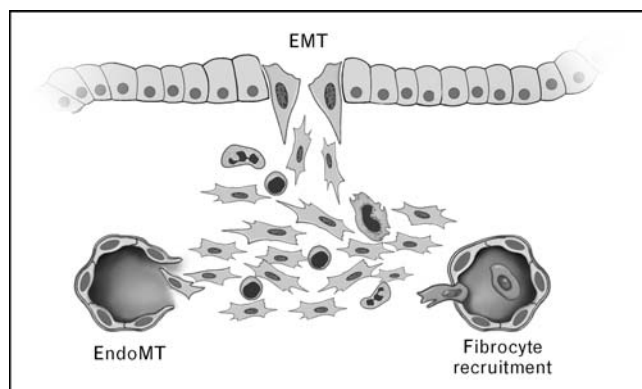
Fibrocytes

Fibrocytes are bone marrow-derived circulating mesenchymal progenitors that coexpress hematopoietic and mesenchymal cell markers and produce ECM components [17[•]]. During inflammation, fibrocytes are released from the bone marrow and migrate to affected sites, where they differentiate into epithelial, endothelial, neuronal and mesenchymal cells [17[•]]. A link between the recruitment of fibrocytes to injured sites and tissue fibrosis has been established in various animal models [18–20]. Thus, in inflammation there is not only recruitment of immune and inflammatory cells but also mesenchymal cell precursors. How much fibrocytes contribute to intestinal fibrosis should be explored in animal models of IBD (Fig. 2).

Epithelial- and endothelial-to-mesenchymal transition

Throughout the body a significant amount of fibroblasts are generated by the transformation of nonmesenchymal into mesenchymal cells. One example is epithelial-to-mesenchymal transition (EMT), which occurs in embryonal, inflammatory or neoplastic conditions, and is characterized by dramatic changes in cell phenotype and function [21]. Epithelial cells take up a spindle-shape morphology, lose classical epithelial cell markers and gain typical fibroblast markers, like fibroblast-specific protein-1, α -smooth muscle actin, vimentin, and acquire the capacity to produce interstitial collagens and fibronectin.

Figure 2 Probable new sources of fibroblasts in inflammatory bowel disease-associated intestinal fibrosis



Epithelial-to-mesenchymal transition (EMT), endothelial-to-mesenchymal transition (EndoMT) and fibrocyte recruitment.

Changes in migratory capacity and an increased resistance to apoptosis also occur [22]. EMT contributes to organ fibrosis in various tissues. In the adult liver hepatocytes can undergo EMT and transform into activated fibroblasts [23,24], an event that can be reverted by antagonizing TGF- β 1 signaling with the bone morphogenetic protein-7 (BMP-7) [23]. Endothelial-to-mesenchymal transition (EndoMT) is a similar form of cellular transformation relevant to fibrosis. Frid *et al.* [25] demonstrated that adult endothelial cells can differentiate into smooth muscle cells *in vitro*, and in a mouse model for cardiac fibrosis it has been calculated that endothelial cells contribute up to one-third of the total pool of tissue-infiltrating fibroblasts [26^{••}].

Information on the contribution of EMT and EndoMT to IBD-associated fibrosis has yet to be published. The fact that the cardiac and intestinal vascular systems bear striking developmental, functional and morphological similarities [27], and the abundant presence of soluble mediators of EndoMT in gut inflammation, however, make it likely that EndoMT occurs in IBD.

Animal models of intestinal fibrosis

Animal models are invaluable to study the pathogenesis of intestinal fibrosis and test new agents to prevent its development without impairing wound healing. As in humans, inflammation is a prerequisite for development of fibrosis in animal models of IBD, such as chronic dextran sulfate sodium colitis or peptidoglycan polysaccharide-induced small bowel inflammation [28]. Other models for intestinal fibrosis have recently been described. Adenovirus-induced overexpression of TGF- β 1 leads to colonic inflammation accompanied by differentiation of fibroblasts into smooth muscle cells, bowel wall thickening and massive ECM deposition with obstruction [29]. Using a similar adenovirus-driven system, overexpression of the chemokine MCP-1 also results in transmural gut inflammation and fibrosis [30].

Chronic TNBS administration triggers intestinal fibrosis characterized by transmural inflammation, stricture formation and proximal dilatation, resembling what occurs in Crohn's disease [12]. Further characterization of this model shows that, after stopping TNBS, the expression of genes related to inflammation, acute phase response, and cell proliferation declines [14]. This correlates with less inflammation but, interestingly, the expression of genes encoding fibrosis-related proteins remains elevated. This suggests that fibrosis-related genes remain activated after inflammation subsides, implying that fibrosis may still develop after clinical control of active IBD. Emerging evidence indicates that mesenchymal cell targeting by TNF- α is sufficient to develop Crohn's disease-like lesions in the TNF- Δ arc mouse, identifying activation of mucosal fibroblasts as a key step driving the

transition of acute-to-chronic inflammation and fibrosis [31].

Clinical science

The ultimate goal of a better understanding of the mechanisms of intestinal fibrosis is to translate discoveries from basic sciences into clinical practice. This section presents new findings in risk assessment, diagnosis, and therapy of patients with intestinal fibrosis.

Risk assessment

Identifying risk factors for fibrotic stricture formation is essential for optimal patient management. Lichtenstein *et al.* [32] investigated factors potentially predictive of stricture formation in Crohn's disease patients enrolled in the TREAT registry and ACCENT I study, identifying disease duration and clinical severity as the most important factors. A retrospective study of 432 patients [33] identified symptomatic adhesions, residual strictures, lack of effective medical therapy, and severe disease unresponsive to medical treatment as clinical indicators for rapid reoperation.

Noninvasive tests that may predict complications like fistulae or stenosis would obviously be very desirable. Antibodies against the outer membrane porin protein C of *Escherichia coli* (anti-OmpC), bacterial flagellin (CBir1) and bacterial sequence I2 (anti-I2) are common in Crohn's disease patients, and the presence of multiple seropositivities has been associated with an increased risk for fibrostenotic small bowel involvement [34]. This association has been confirmed in a large cohort of eastern European patients [35]. Anti-CBir1 antibodies are independently associated with the Crohn's disease fibrostenotic phenotype and the presence of *NOD2* variants [36]. A new association with antibodies against glycan epitopes, like laminaribioside (ALCA), chitobioside (ACCA) and mannobioside (AMCA), has been reported in a group of 1225 IBD patients [37]. Increased serum levels of these antibodies correlated with complicated disease and higher frequency of Crohn's disease-related surgery. Serum levels of the chitinase-like protein YKL-40 is also increased in Crohn's disease patients with strictures compared with those without strictures [38]. In agreement with the above retrospective studies in adults, one prospective study in children with IBD confirmed more rapid progress to complicated disease, including stricturing disease, when serum reactivity to anti-I2, anti-OMPc, anti-CBir1 or anti-*Saccharomyces cerevisiae* antibody is present [39].

Diagnosis

Current imaging techniques for identifying strictures secondary to bowel fibrosis are inadequate. The increased

utilization of videocapsule endoscopy (VCE) may help to detect small bowel strictures in Crohn's disease patients, but a suspected stricture is in itself a contraindication to its use because of possible obstruction. To obviate this complication the Given Patency capsule has been developed. This device is a radio-tagged, radio opaque sham capsule endoscope, consisting of compressed lactose, which in case of retention and obstruction disintegrates in the lumen. This system could be used to determine luminal patency even in those patients with known small bowel stenosis. Spada *et al.* [40] prospectively tested the safety of VCE in 27 patients with known or suspected intestinal stricture previously tested by the Given Patency capsule. Patients passing the lactose-covered capsule (65%) underwent subsequent VCE without any complications, including those with tight strictures, only one patient requiring hospitalization due to temporary occlusion.

Double-balloon enteroscopy (DBE) is a system consisting of a video enteroscope and a flexible overtube used for the examination of the small bowel. Sun *et al.* [41] prospectively investigated the value of DBE for the diagnosis of incomplete small bowel obstruction in patients without previous history of abdominal surgery. This technique identified the cause of obstruction in 93.1% of all patients examined, and Crohn's disease was responsible in 24.1% of cases. Similar findings were reported in a retrospective multicenter study of 179 patients [42], Crohn's disease being the most common cause of small intestinal strictures.

New radiological approaches are being increasingly explored as means to detect intestinal fibrosis and its complications. Computed tomographic enterography (CTE) has been applied to examine the transmural nature and extent of Crohn's disease. Higgins *et al.* [43] retrospectively assessed its value in clinical practice and decision-making, and concluded that clinical parameters of inflammation do not correlate with CTE findings, but CTE can detect strictures beyond those clinically suspected and exclude clinically suspected strictures. Due to its noninvasive nature, radiological modalities are highly desirable, and several are under investigation, including magnetization transfer MRI, magnetic resonance elastography, and ultrasound elastography.

Therapy

Despite major progress in the overall treatment of IBD, the incidence of stricture formation and stenosis, and the need for bowel resection have not significantly changed during the last few decades [44]. Several nonsurgical procedures are now available for the treatment of strictures, including endoscopic balloon dilation (EBD), polyvinyl over-the-guidewire dilatation, endoscopic strictureplasty using metallic stents, and local injection of

glucocorticoids [2*,45]. While these procedures offer the advantage of being less invasive and preserving intestinal length, they usually offer only short-term relief. Ajlouni *et al.* [46] summarized the outcome of a series of 37 Crohn's disease patients with small bowel stricture treated with EBD in regard to success, safety, need for surgery, and long-term outcome. The overall results were favorable, EBD being successful in 90% of patients in terms of preventing re-stenosis and safety. This favorable outcome was attributed to the experience of the endoscopist, the selection of strictures, the size of the balloon, and the use of antibiotics.

Most Crohn's disease patients with strictures treated conservatively will require repeated dilation and eventually surgery [47]. To improve long-term effectiveness, injection of anti-inflammatory or antifibrotic agents into predilated structures has been proposed as a complementary approach. East *et al.* [48**] carried out a prospective controlled trial testing local injections of triamcinolone versus placebo in the prevention of postballoon dilatation recurrent stricturing in 13 patients with Crohn's disease. Unexpectedly, the results showed a trend towards earlier need for re-intervention when triamcinolone was used, leading to an early termination of the trial. This report contrasts with more promising results of previous retrospective but uncontrolled series [49,50], leaving the clinician uncertain about optimal treatment strategies. At the moment steroid injection after dilatation should be reserved for randomized controlled clinical trials [47].

While systemic administration of anti-TNF- α is generally considered effective in patients with active Crohn's disease [51], concern has been raised about the development or worsening of strictures in some patients. Sorrentino *et al.* [52,53] recently reported the safe administration of infliximab in Crohn's disease patients with known fibrotic strictures, and another study found no association between infliximab and the development of strictures [32]. Injection of infliximab directly into a Crohn's disease stricture has been tested as a way to increase drug concentration at the site of disease. In an open-label pilot study three patients with no previous response to systemic infliximab received injections of this anti-TNF- α agent into colonic strictures. All patients showed resolution of symptoms and endoscopic improvement within 2 weeks and remained asymptomatic for 4, 6 or 7 months, respectively [54]. Based on the above reports, Crohn's disease-associated intestinal stenoses alone should no longer be regarded as an absolute contraindication to systemic or local treatment with anti-TNF- α agents.

Unlike stenosis in the ileocolic or colonic region, most small bowel strictures cannot be easily reached by an

endoscope. In addition to its diagnostic potential, DBE is now being proposed as a new therapeutic approach to small bowel strictures [55]. The use of DBE in 19 Crohn's disease patients with severe gastrointestinal stenoses showed sufficient safety and feasibility with a technical success rate of 80%, comparable to that obtained with dilatation of ileocolonic strictures. In another series DBE therapy avoided surgery in six of 13 patients with tight fibrotic small bowel strictures due to Crohn's disease [56]. Fukumoto *et al.* [42] claimed a long-term success of DBE dilatation of 74% over a period of 12 months in Crohn's disease patients without serious complications.

While the above new approaches to the management of Crohn's disease-associated strictures are encouraging, they are not danger free [57], and additional studies are necessary before indications and contraindications can be firmly defined. In the mean time, the investigation of drugs that counteract the development of fibrosis to prevent stricture formation is certainly justified. Tranilast, *N*-(3',4'-dimethoxycinnamoyl) anthranilic acid, is a substance able to inhibit the ECM remodeling enzymes MMPs and TIMP-1, and has been shown to inhibit fibrosis in some experimental models [58,59]. Oshitani *et al.* [60] administered Tranilast to 12 Crohn's disease patients with asymptomatic intestinal stenosis, and reported an increase in symptom-free time as well as the diameter of the stricture lumen compared with placebo.

Conclusion

An improved approach to prevent or reduce the complications secondary to intestinal fibrosis in IBD must rely on a greater understanding of its mechanisms of induction and persistence. Compared with the impressive advances that we have witnessed in the last decade in regard to unraveling the molecular and cellular mechanisms of mucosal inflammation, progress in both basic and clinical investigation of intestinal fibrosis has been relatively limited. Nevertheless, novel mediators of fibroblast activation and tissue remodeling, as well as novel sources for fibroblast recruitment, have been identified. Clinical, laboratory, endoscopic and radiological methods are being explored so that an early diagnosis can be made and a specific management of IBD-associated intestinal fibrosis can be developed independently of the sole control of intestinal inflammation.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 546–547).

- 1 Rieder F, Brenmoehl J, Leeb S, *et al*. Wound healing and fibrosis in intestinal disease. *Gut* 2007; 56:130–139.
Comprehensive review on the pathophysiology of intestinal wound healing and fibrosis.
- 2 Burke JP, Mulsow JJ, O'Keane C, *et al*. Fibrogenesis in Crohn's disease. *Am J Gastroenterol* 2007; 102:439–448.
Comprehensive review on the pathogenesis of stricture formation in Crohn's disease.
- 3 Meijer MJ, Mieremet-Ooms MA, van der Zon AM, *et al*. Increased mucosal matrix metalloproteinase-1, -2, -3 and -9 activity in patients with inflammatory bowel disease and the relation with Crohn's disease phenotype. *Dig Liver Dis* 2007; 39:733–739.
- 4 Di Sabatino A, Pickard KM, Rampton D, *et al*. Blockade of transforming growth factor- β up-regulates T-box transcription factor T-bet, and increases T helper cell type 1 cytokine and matrix metalloproteinase-3 production in the human gut mucosa. *Gut* 2008; 4 January [Epub ahead of print].
- 5 Meijer MJ, Mieremet-Ooms MA, van Hogezaand RA, *et al*. Role of matrix metalloproteinase, tissue inhibitor of metalloproteinase and matrix metalloproteinase-3 in Crohn's disease. *World J Gastroenterol* 2007; 13:2960–2966.
- 6 Di Sabatino A, Pender SL, Jackson CL, *et al*. Functional modulation of Crohn's disease myofibroblasts by antitumor necrosis factor antibodies. *Gastroenterology* 2007; 133:137–149.
- 7 Monteleone G, Caruso R, Fina D, *et al*. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. *Gut* 2006; 55:1774–1780.
- 8 Seki E, De Minicis S, Osterreicher CH, *et al*. TLR4 enhances TGF- β signaling and hepatic fibrosis. *Nat Med* 2007; 13:1324–1332.
Excellent investigation showing that TLR-4 is essential for hepatic fibrogenesis and augments the profibrotic activity of TGF- β 1 through MyD88 and NF- κ B signaling, supporting the new notion of fibrogenesis driven by bacterial components.
- 9 Otte JM, Rosenberg IM, Podolsky DK. Intestinal myofibroblasts in innate immune responses of the intestine. *Gastroenterology* 2003; 124:1866–1878.
- 10 Fichtner-Feigl S, Fuss IJ, Young CA, *et al*. Induction of IL-13 triggers TGF- β 1-dependent tissue fibrosis in chronic 2,4,6-trinitrobenzene sulfonic acid colitis. *J Immunol* 2007; 178:5859–5870.
First study showing the profibrotic activity of IL-13 in TNBS colitis.
- 11 Lippert E, Falk W, Bataille F, *et al*. Soluble galectin-3 is a strong, colonic epithelial-cell-derived, lamina propria fibroblast-stimulating factor. *Gut* 2007; 56:43–51.
A study showing that intestinal epithelial cell-derived galectin-3 is a potent stimulus of intestinal mesenchymal cells via NF- κ B.
- 12 Lawrance IC, Wu F, Leite AZ, *et al*. A murine model of chronic inflammation-induced intestinal fibrosis down-regulated by antisense NF- κ B. *Gastroenterology* 2003; 125:1750–1761.
- 13 Fichtner-Feigl S, Fuss IJ, Preiss JC, *et al*. Treatment of murine Th1- and Th2-mediated inflammatory bowel disease with NF- κ B decoy oligonucleotides. *J Clin Invest* 2005; 115:3057–3071.
- 14 Wu F, Chakravarti S. Differential expression of inflammatory and fibrogenic genes and their regulation by NF- κ B inhibition in a mouse model of chronic colitis. *J Immunol* 2007; 179:6988–7000.
- 15 Mori R, Shaw TJ, Martin P. Molecular mechanisms linking wound inflammation and fibrosis: knockdown of osteopontin leads to rapid repair and reduced scarring. *J Exp Med* 2008; 205:43–51.
Novel communication indicating that inflammation-triggered expression of osteopontin by mesenchymal cells hinders the rate of wound repair and promotes tissue fibrosis.
- 16 Brack AS, Conboy MJ, Roy S, *et al*. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. *Science* 2007; 317:807–810.
Excellent investigation implicating Wnt signaling in age-related muscle fibrosis, an effect reversible by Wnt inhibitors. This report points to modulation of Wnt signaling as a promising new approach to prevention or reduction of fibrosis.
- 17 Bellini A, Mattoli S. The role of the fibrocyte, a bone marrow-derived mesenchymal progenitor, in reactive and reparative fibroses. *Lab Invest* 2007; 87:858–870.
Excellent review on fibrocytes and their role in pathogenesis of fibrosis.
- 18 Pilling D, Roife D, Wang M, *et al*. Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P. *J Immunol* 2007; 179:4035–4044.
- 19 Sakai N, Wada T, Yokoyama H, *et al*. Secondary lymphoid tissue chemokine (SLC/CCL21)/CCR7 signaling regulates fibrocytes in renal fibrosis. *Proc Natl Acad Sci U S A* 2006; 103:14098–14103.
- 20 Haudek SB, Xia Y, Huebener P, *et al*. Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice. *Proc Natl Acad Sci U S A* 2006; 103:18284–18289.
- 21 Kalluri R, Neilson EG. Epithelial–mesenchymal transition and its implications for fibrosis. *J Clin Invest* 2003; 112:1776–1784.
- 22 Lee JM, Dedhar S, Kalluri R, *et al*. The epithelial–mesenchymal transition: new insights in signaling, development, and disease. *J Cell Biol* 2006; 172:973–981.
- 23 Zeisberg M, Yang C, Martino M, *et al*. Fibroblasts derive from hepatocytes in liver fibrosis via epithelial to mesenchymal transition. *J Biol Chem* 2007; 282:23337–23347.
- 24 Kaimori A, Potter J, Kaimori JY, *et al*. Transforming growth factor- β 1 induces an epithelial-to-mesenchymal transition state in mouse hepatocytes in vitro. *J Biol Chem* 2007; 282:22089–22101.
- 25 Frid MG, Kale VA, Stenmark KR. Mature vascular endothelium can give rise to smooth muscle cells via endothelial–mesenchymal transdifferentiation: in vitro analysis. *Circ Res* 2002; 90:1189–1196.
- 26 Zeisberg EM, Tavakoli O, Zeisberg M, *et al*. Endothelial-to-mesenchymal transition contributes to cardiac fibrosis. *Nat Med* 2007; 13:952–961.
Seminal study reporting that EndoMT is a significant contributor to cardiac fibrosis and showing that reversal of EndoMT by BMP-7 improves cardiac fibrosis and function. This study opens the door to new and specific antifibrotic therapies.
- 27 Wilm B, Ipenberg A, Hastie ND, *et al*. The serosal mesothelium is a major source of smooth muscle cells of the gut vasculature. *Development* 2005; 132:5317–5328.
- 28 Lund PK, Zuniga CC. Intestinal fibrosis in human and experimental inflammatory bowel disease. *Curr Opin Gastroenterol* 2001; 17:318–323.
- 29 Vallance BA, Gunawan MI, Hewlett B, *et al*. TGF- β 1 gene transfer to the mouse colon leads to intestinal fibrosis. *Am J Physiol Gastrointest Liver Physiol* 2005; 289:G116–G128.
- 30 Motomura Y, Khan WI, El-Sharkawy RT, *et al*. Induction of a fibrogenic response in mouse colon by overexpression of monocyte chemoattractant protein 1. *Gut* 2006; 55:662–670.
- 31 Armaka M, Apostolaki M, Jacques P, *et al*. Mesenchymal cell targeting by TNF as a common pathogenic principle in chronic inflammatory joint and intestinal diseases. *J Exp Med* 2008; 205:331–337.
- 32 Lichtenstein GR, Olson A, Travers S, *et al*. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. *Am J Gastroenterol* 2006; 101:1030–1038.
- 33 Binion DG, Theriot KR, Shidham S, *et al*. Clinical factors contributing to rapid reoperation for Crohn's disease patients undergoing resection and/or stricture-resection. *J Gastrointest Surg* 2007; 11:1692–1698; discussion 1698.
- 34 Mow WS, Vasiliauskas EA, Lin YC, *et al*. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology* 2004; 126:414–424.
- 35 Papp M, Altorjay I, Norman GL, *et al*. Seroreactivity to microbial components in Crohn's disease is associated with ileal involvement, noninflammatory disease behavior and NOD2/CARD15 genotype, but not with risk for surgery in a Hungarian cohort of IBD patients. *Inflamm Bowel Dis* 2007; 13:984–992.
- 36 Papadakis KA, Yang H, Ippoliti A, *et al*. Antiflagellin (CBir1) phenotypic and genetic Crohn's disease associations. *Inflamm Bowel Dis* 2007; 13:524–530.
- 37 Ferrante M, Henckaerts L, Joossens M, *et al*. New serological markers in inflammatory bowel disease are associated with complicated disease behaviour. *Gut* 2007; 56:1394–1403.
Novel antigenic antibodies are associated with complicated Crohn's disease and need for surgery.
- 38 Erzin Y, Uzun H, Karatas A, *et al*. Serum YKL-40 as a marker of disease activity and stricture formation in patients with Crohn's disease. *J Gastroenterol Hepatol* 2007; 27 August [Epub ahead of print].
- 39 Dubinsky MC, Lin YC, Dutridge D, *et al*. Serum immune responses predict rapid disease progression among children with Crohn's disease: immune responses predict disease progression. *Am J Gastroenterol* 2006; 101:360–367.
- 40 Spada C, Shah SK, Riccioni ME, *et al*. Video capsule endoscopy in patients with known or suspected small bowel stricture previously tested with the dissolving patency capsule. *J Clin Gastroenterol* 2007; 41:576–582.

- 41 Sun B, Shen R, Cheng S, *et al.* The role of double-balloon enteroscopy in diagnosis and management of incomplete small-bowel obstruction. *Endoscopy* 2007; 39:511–515.
- 42 Fukumoto A, Tanaka S, Yamamoto H, *et al.* Diagnosis and treatment of small-bowel stricture by double balloon endoscopy. *Gastrointest Endosc* 2007; 66:S108–S112.
- 43 Higgins PD, Caoili E, Zimmermann M, *et al.* Computed tomographic enterography adds information to clinical management in small bowel Crohn's disease. *Inflamm Bowel Dis* 2007; 13:262–268.
- 44 Cosnes J, Nion-Larmurier I, Beaugerie L, *et al.* Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005; 54:237–241.
- 45 Matsushashi N, Nakajima A, Suzuki A, *et al.* Long-term outcome of nonsurgical strictureplasty using metallic stents for intestinal strictures in Crohn's disease. *Gastrointest Endosc* 2000; 51:343–345.
- 46 Ajlouni Y, Iser JH, Gibson PR. Endoscopic balloon dilatation of intestinal strictures in Crohn's disease: safe alternative to surgery. *J Gastroenterol Hepatol* 2007; 22:486–490.
- 47 Van Assche G. Intramural steroid injection and endoscopic dilation for Crohn's disease. *Clin Gastroenterol Hepatol* 2007; 5:1027–1028.
- 48 East JE, Brooker JC, Rutter MD, *et al.* A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. *Clin Gastroenterol Hepatol* 2007; 5:1065–1069.
- This prospective study contradicts previous reports by showing that triamcinolone injections at stricture sites do not reduce the time to repeated dilatation or surgery.
- 49 Brooker JC, Beckett CG, Saunders BP, *et al.* Long-acting steroid injection after endoscopic dilation of anastomotic Crohn's strictures may improve the outcome: a retrospective case series. *Endoscopy* 2003; 35:333–337.
- 50 Singh VV, Draganov P, Valentine J. Efficacy and safety of endoscopic balloon dilation of symptomatic upper and lower gastrointestinal Crohn's disease strictures. *J Clin Gastroenterol* 2005; 39:284–290.
- 51 Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; 359:1541–1549.
- 52 Sorrentino D, Terrosu G, Vadala S, *et al.* Fibrotic strictures and anti-TNF-alpha therapy in Crohn's disease. *Digestion* 2007; 75:22–24.
- 53 Sorrentino D, Avellini C, Beltrami CA, *et al.* Selective effect of infliximab on the inflammatory component of a colonic stricture in Crohn's disease. *Int J Colorectal Dis* 2006; 21:276–281.
- 54 Swaminath A, Lichtiger S. Dilation of colonic strictures by intralesional injection of infliximab in patients with Crohn's colitis. *Inflamm Bowel Dis* 2008; 14:213–216.
- 55 Keuchel M. Double balloon (push-and-pull) enteroscopy: breakthrough in the management of small intestinal strictures in Crohn's disease? *Eur J Gastroenterol Hepatol* 2007; 19:523–525.
- 56 Pohl J, May A, Nachbar L, *et al.* Diagnostic and therapeutic yield of push-and-pull enteroscopy for symptomatic small bowel Crohn's disease strictures. *Eur J Gastroenterol Hepatol* 2007; 19:529–534.
- 57 Koltun WA. Dangers associated with endoscopic management of strictures in IBD. *Inflamm Bowel Dis* 2007; 13:359–361.
- 58 Kelly DJ, Zhang Y, Gow R, *et al.* Tranilast attenuates structural and functional aspects of renal injury in the remnant kidney model. *J Am Soc Nephrol* 2004; 15:2619–2629.
- 59 Martin J, Kelly DJ, Mifsud SA, *et al.* Tranilast attenuates cardiac matrix deposition in experimental diabetes: role of transforming growth factor-beta. *Cardiovasc Res* 2005; 65:694–701.
- 60 Oshitani N, Yamagami H, Watanabe K, *et al.* Long-term prospective pilot study with tranilast for the prevention of stricture progression in patients with Crohn's disease. *Gut* 2007; 56:599–600.