

## Cathelicidins: A Novel Therapy for the Treatment of Intestinal Fibrosis?



Intestinal fibrosis is an important complication of Crohn's disease (CD), often leading to stricture formation that progressively could induce intestinal obstruction. The excessive presence of fibrous connective tissue increases the thickness of the bowel wall, reducing the elasticity and the function over the affected area.

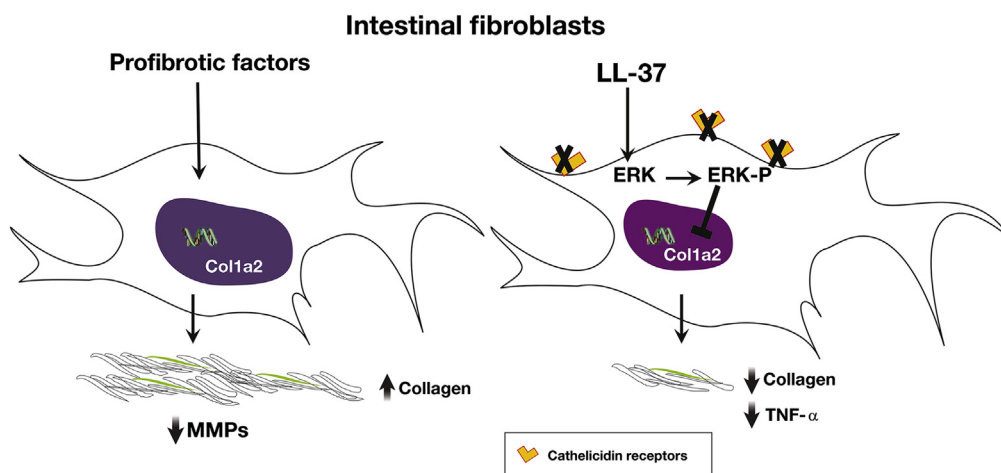
Although considerable advances have been made in the understanding of the molecular mechanisms underlying the fibrotic process, to date there are neither specific therapies nor specific markers that might be useful as accurate predictors or diagnostic tools for prevention or treatment. Surgical removal is the only means of eliminating the fibrostenosing and obstructing strictures, which can be recurrent in the same patient, significantly influencing the quality of life. Anti-inflammatory therapies are not efficient in resolving fibrosis because 20% of CD patients treated with biologics still develop strictures and associated complications. This shows that simple removal of the inflammatory trigger is not sufficient to reverse fibrosis. Nevertheless, several currently used drugs, including corticosteroids, azathioprine, and anti-tumor necrosis factor (TNF) biologics, can prevent postoperative CD recurrence. These data show that despite the incompletely defined pathogenesis of strictures in CD that remain unclear, inflammation is an essential trigger that initiates fibrosis.

Transforming growth factor- $\beta$  (TGF- $\beta$ ) is the most prominent profibrogenic factor capable of inducing extracellular matrix deposition, metalloproteinase inhibition, and

fibroblast activation. Consistent with this, TGF- $\beta$  and its receptors are up-regulated in CD strictures. Unfortunately, in a study of patients with systemic sclerosis, an anti-TGF- $\beta$ 1 monoclonal antibody was unable to reduce fibrosis.<sup>1</sup> Although mechanisms of fibrosis may differ between systemic sclerosis and CD, this reduces any hope that anti-TGF- $\beta$ 1 biologics will be of benefit to CD patients. Furthermore, TGF- $\beta$  is a pleiotropic cytokine with immunomodulatory functions that are critical to maintenance of intestinal homeostasis. Thus, despite its role as a profibrogenic factor, blockade of the TGF- $\beta$ /TGF- $\beta$ -receptor axis is unlikely to be successful as a therapeutic approach in structuring CD.

Recent work in extraintestinal organs has elucidated the involvement of cathelicidins, antimicrobial cationic peptides, in fibrosis. Cathelicidins are synthesized and secreted in large amounts by tissues exposed to bacteria, including gastrointestinal, genitourinary, respiratory tract, and skin. Remarkably, LL37, the cleaved form of the human cathelicidin hCAP18, is able to decrease TGF- $\beta$ -induced collagen synthesis in human keloid fibroblasts by a mechanism that includes activation of the extracellular signal-regulated kinase (ERK) pathway.<sup>2</sup>

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Yoo et al<sup>3</sup> aimed to determine if cathelicidins also might be able to limit intestinal fibrosis. This is an attractive hypothesis because LL-37 is expressed by many cell types, including intestinal epithelial cells and infiltrating neutrophils. By using 2 preclinical models of



**Figure 1. LL-37 involvement in intestinal fibrotic process.** Profibrotic factors such as TGF- $\beta$  promote collagen (Col1a2) synthesis and extracellular deposition by intestinal fibroblasts and matrix metalloproteinase (MMP) inhibition, both of which contribute to stricture formation in CD patients. Besides its antimicrobial properties, LL-37 ameliorates intestinal inflammation, reducing TNF- $\alpha$  expression. LL-37 exerts these antifibrotic properties via ERK-mediated signaling that is independent of cathelicidin receptors.

intestinal fibrosis, Yoo et al<sup>3</sup> showed that LL-37 not only ameliorates intestinal inflammation, as indicated by reduced TNF- $\alpha$  expression, but also prevents fibrosis. Results were similar with either intracolonic administration of recombinant LL-37 or virally mediated LL-37 expression. LL-37 also inhibited TGF- $\beta$ -induced collagen production by primary CD intestinal fibroblasts in vitro. However, in vivo LL-37 therapy did not affect TGF- $\beta$ 1 expression, suggesting that its antifibrotic properties are not a result of the modification of the TGF- $\beta$ /TGF- $\beta$  receptor axis. Furthermore, LL-37-mediated inhibition of collagen production was reversed by ERK inhibitors, implying that the same ERK signaling pathway described in dermal fibroblasts is involved in the regulation of intestinal fibroblasts and fibrosis (Figure 1).

It is widely documented that CD patients have impaired production of antimicrobial agents, including LL-37. However, it is not clear if this reduced LL-37 production is involved in the development of intestinal fibrosis. For example, despite impaired antibacterial defense, cathelicidin-deficient mice developed inflammation and fibrosis that was comparable with wild-type mice, indicating no increased predisposition to intestinal fibrosis in the absence of LL-37. However, exogenous LL-37 administration suppressed collagen synthesis and colonic TNF- $\alpha$  production in cathelicidin-deficient mice. Results were similar in a model of fibrosis inflammation-independent, suggesting that the antifibrotic activity of LL-37 is not linked to its anti-inflammatory properties.

Notwithstanding these exciting results, further studies are needed to better understand the mechanisms by which cathelicidin limits intestinal fibrosis because the data indicate that these effects were independent of putative cathelicidin receptors. Similarly, it will be interesting to assess the effects of LL-37 on the matrix metalloproteinase expression and activity. Furthermore, many questions related to the delivery route, stability, and effects of

long-term LL-37 treatment on intestinal homeostasis, including the microbiome, remain to be addressed.

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### Conflicts of interest

The authors disclose no conflicts.

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