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EDITORIAL

TRPing Up Fibrosis: A Novel Role for TRPA1 in Intestinal Myofibroblasts

Intestinal fibrosis is a common complication of the inflammatory bowel diseases (IBDs), affecting 30%–50% of patients with Crohn's disease (CD). It is thought to be a consequence of chronic inflammation, and intestinal fibrosis is characterized by myofibroblast accumulation, excessive deposition of extracellular matrix (ECM), and in some cases smooth muscle hypertrophy. The most severe phenotype, in which tissue remodeling leads to luminal narrowing, occurs in more than 30% of CD patients within 10 years of disease diagnosis,[1] with many of these patients requiring surgery and, ultimately, experiencing stricture recurrence.

The introduction of agents that modulate inflammation has improved many aspects of IBD management; however, these therapies have done relatively little to reduce pathogenic tissue remodeling. Most strikingly, despite markedly improved mucosal healing in many patients, the frequency of fibrostenotic complications in CD has not decreased significantly. This is owing, in part, to limited understanding of the mechanisms that initiate and propagate intestinal fibrosis.

Fibrosis occurs when repair responses fail to restore normal tissue architecture and, in part, reflects an imbalance between ECM production and degradation. In an otherwise healthy individual, intestinal injury (eg, after biopsy) and the resulting repair responses heal damaged tissues in a timely fashion. In this scenario, recruitment and activation of ECM-producing myofibroblasts are transient. After injury resolution, myofibroblasts undergo apoptosis and therefore cannot contribute to excessive ECM deposition. However, failure to heal damaged tissue and restore normal tissue structure leads to a chronic inflammatory response with enhanced recruitment of ECM-producing myofibroblasts that diverts resolution toward fibrosis.[1] From this model, it is apparent that targeting fibrogenic signaling within myofibroblasts might prove efficacious in treating inflammation-associated intestinal fibrosis.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Kurahara et al[2] identified the transient receptor potential ankyrin 1 (TRPA1) channel as a novel antifibrotic target in intestinal myofibroblasts. Although other investigators have reported varying roles of TRPA1 in the regulation of intestinal inflammation,[1,3,4] Kurahara et al[2] showed that TRPA1 activation in myofibroblasts attenuates transforming growth factor β1–induced fibrogenic signaling. By using an in vivo colitis model, Kurahara et al[2] showed that Trpa1 expression is increased in intestinal myofibroblasts within inflamed regions of wild-type mice, and that exaggerated tissue remodeling occurred in *Trpa1*$^{-/-}$ mice. Analysis of human CD tissues showed that TRPA1 was increased in fibrostenotic regions. Finally, Kurahara et al[2] reported that pirfenidone, an antifibrotic agent approved for the treatment of idiopathic pulmonary fibrosis, selectively activates TRPA1 in intestinal myofibroblasts, and that this is associated with reduced transforming growth factor β1–induced fibrogenic signaling.

To date, no agents for treating fibrosis and stricture formation in IBD have been evaluated in clinical trials. For new therapeutics to be conceived, there is a pressing need for greater understanding of the mechanisms that regulate the biology of the intestinal myofibroblast and fibrogenic signaling. The study by Kurahara et al[2] makes an important contribution to this field and provides translational insight into the potential efficacy of pirfenidone and other TRPA1-activating agents for the treatment of intestinal fibrosis.

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Conflicts of interest
The author discloses no conflicts.

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