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New approach to preventing fibrosing strictures in IBD

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A natural protein made by immune cells may limit fibrosis and scarring in colitis, according to research published in the inaugural issue of *Cellular and Molecular Gastroenterology and Hepatology*, the new basic science journal of the American Gastroenterological Association.

Crohn's disease—one form of inflammatory bowel disease (IBD)—is an incurable disorder that commonly presents in childhood and adolescence. Fibrosing strictures that can obstruct the intestines are a major complication of Crohn's disease. Although these obstructions can be removed surgically, disease tends to recur at those sites. As a result, patients are subjected to repeated surgeries over their lifetimes.

"We found that the antimicrobial defense protein cathelicidin can prevent such intestinal fibrosis in pre-clinical disease models," said senior study author Hon Wai Koon, PhD, from the David Geffen School of Medicine, University of California, Los Angeles. "These findings may lead to novel therapeutic approaches that prevent recurrent strictures in Crohn's disease patients."

Cathelicidin is part of a family of antimicrobial proteins produced by many cell types, including acute and chronic inflammatory and epithelial cells. Previous work has shown that cathelicidin also has anti-inflammatory properties and can suppress synthesis of collagen, the core protein of fibrotic scars, in skin.

In this study, researchers sought to determine whether cathelicidin is

effective in preventing collagen synthesis and fibrosis in intestinal disease. Success in this area could spare Crohn's disease patients the strictures that often lead to bowel obstruction and multiple surgical resections that may leave so little bowel that nutrients cannot be adequately absorbed from food and nutrition and must be provided intravenously.

Investigators studied the effect of cathelicidin in two pre-clinical models of disease and human colonic fibroblasts, the cells that synthesize collagen in scars and strictures. One model of Crohn's disease that they used involved administration of the chemical trinitrobenzenesulfonic acid, which induces chronic colitis and fibrosis over seven weeks, to mice. Instilling cathelicidin protein through the colon over the last three weeks limited weight loss and microscopic features of disease while also reducing production of pro-inflammatory cytokines, e.g. tumor necrosis factor-α. Both microscopic evidence of fibrosis and production of mRNA for synthesis of collagen were also reduced. Interestingly, expression of transforming growth factor-α, which has anti-inflammatory and pro-regenerative activities, but is also implicated in fibrosis, was not affected by cathelicidin treatment.

"While the precise mechanisms by which cathelicidin promotes healing and inhibits fibrosis remain an area of future study, the advances described in this study may make it possible to prevent recurrent strictures and spare these patients from repeated surgery," said Jerrold Turner, MD, PhD, AGAF, editor-in-chief of *Cellular and Molecular Gastroenterology and Hepatology*.

More information: Jun Hwan Yoo, et al., Antifibrogenic Effects of the Antimicrobial Peptide Cathelicidin in Murine Colitis-Associated Fibrosis, *Cellular and Molecular Gastroenterology and Hepatology* 2015: 1(1): 55-74.e1, www.cmghjournal.org/article/S2 … (14)00002-2/abstract