Letter to the Editor

Intestinal Fibrosis: Relieving the Stress. Comment on Li C. The Role of Endoplasmic Reticulum Stress in the Development of Fibrosis in Crohn's Disease

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Digestive ailments rank amongst the top three reasons to visit a physician. One common digestive malady is Crohn's disease (CD), which is a chronic, idiopathic disease characterized by abdominal cramping, pain, and diarrhea. Patients suffering from CD have limited and inconsistently effective treatment options, which contributes to their diminished quality of life. Current therapies, including steroids, broad-spectrum immunosuppressive drugs and anti-tumor necrosis factor-α, have only been effective in some patient cohorts. Moreover, although these therapies are effective in mitigating clinical symptoms, they are ineffective at reversing or slowing the development of intestinal fibrosis, a complication affecting 30–50% of CD patients.[1]

Intestinal fibrosis is a consequence of chronic inflammation, for which the disease pathology is driven by dysregulated tissue remodeling, such as increased matrix protein deposition, smooth muscle hypertrophy, and myofibroblast accumulation.[2] The severity of these structural changes contributes to tissue loss-of-function or stricture, which can be alleviated by recurrent endoscopic balloon dilation or stricturoplasty procedures.[3] The lack of antifibrotic therapeutics stems from the overall limited understanding of the cellular mechanisms of fibrosis.

In this issue of *Exploratory Research and Hypothesis in Medicine*, Dr. Chao Li reviews our current understanding of the cellular signaling mechanisms of the unfolded protein response (UPR) driven by endoplasmic reticulum (ER) stress. The UPR response encompasses many signaling pathways that regulate ER homeostasis though removal of excess unfolded proteins in the ER lumen, ultimately promoting cell survival. However, prolonged UPR responses are associated with driving mucosal barrier dysfunction and epithelial cell damage in CD. This review provides insight into the physiological consequences of prolonged UPR signaling on promoting tissue remodeling through excessive apoptosis activation, epithelial to mesenchymal transition, and sustained inflammation. Importantly, Li evaluates the cellular mechanisms of UPR signaling that may be targeted for therapeutic intervention, such as promoting increased UPR signaling resolution or inhibiting UPR-induced apoptosis signaling in the context of intestinal fibrosis. In addition to evaluating our knowledge of autophagy dysregulation in inflammatory bowel disease, Li postulates that there may be a closely-knit relationship between autophagy-driven ER stress and the proliferation of mesenchymal cells in fibrotic CD.

Reviews such as Li's, which recapitulate our current knowledge, are essential to recognizing potential novel mechanisms for expanding research. For new antifibrosis therapeutics to be discovered, these novel cellular mechanisms must be characterized in various cell types and disease states to tailor therapies to disease-specific CD phenotypes.

Conflict of interest

The author has no conflict of interests related to this publication.

Author contributions

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Abbreviations: CD, Crohn's disease; ER, endoplasmic reticulum; UPR, unfolded protein response.

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