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Pathogenesis of Strictures in Ulcerative Colitis: A Field to Explore

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Both inflammatory bowel diseases (IBD), namely ulcerative colitis (UC) and Crohn's disease (CD), are associated with chronic tissue damage and continuous tissue repair. Fibrotic disease courses still resemble a clinical challenge. In UC, intestinal fibrosis is seen frequently after long disease courses; however, the fibrosis and scar formation is usually limited to the mucosa. A stricture formation is much rarer and only found in less than 5% of UC patients. Nevertheless, strictures occur and are sometimes localized in the rectum. In those cases, the clinical management is very difficult. Whereas CD is a transmural disease which may explain the activation of mesenchymal cells and the subsequent stricture formation originating from the muscularis layers, UC is limited to the mucosa. Therefore, stricture formation is much harder to understand and different mechanisms of stricture may exist in CD and UC.

It is generally accepted that intestinal myofibroblasts play a major role in the pathophysiology of fibrosis formation. During fibrosis formation resident mesenchymal cells transform into activated, matrix-depositing myofibroblasts [1]. However, the underlying molecular mechanisms causing this mesenchymal cell activation are not yet clear [2].

Inflammation always causes damage to the tissue in which it occurs. In patients with UC, a loss of epithelial

cells with mucosal ulcerations occurs caused by enzymes and mediators mainly secreted by macrophages and granulocytes. Tissue repair has to take place involving new tissue formation and scar constitution [3]. Usually, this tissue repair is a self-limiting process requiring a well-controlled balance between pro- and anti-inflammatory signals as well as a tightly regulated matrix formation and degradation [3]. According to this view, fibrosis is an overzealous healing response to inflammation-induced injury [3]. It is still unclear what triggers increased fibrosis in some patients and not in others.

In this issue of *Digestion*, Masaru Yamagata et al. [4] screened 1,115 patients with UC that presented at Kitasato University East Hospital from 1986 to 2009. Only 15 cases of those 1,115 had a benign stricture of the colon. Of these 15 cases, 9 had to undergo surgery so that colonic tissue was available for analysis. In the stenotic areas, the authors describe a significant increase of b-FGF-positive inflammatory cells and myofibroblasts. Most b-FGF-positive cells were also found to be positively stained for myeloperoxidase. The authors further describe an association between the number of b-FGF-positive cells and total neutrophil counts.

This could indicate that neutrophils present in the inflamed mucosa of patients with UC in crypt abscesses or in the mucosa may activate mesenchymal cells via the se-

cretion of b-FGF. Unfortunately, there are no reliable animal models to test this hypothesis. Immunohistochemistry can be instructive; however, it is certainly no proof of a functional concept. In vitro studies also do not allow one to conclude on the in vivo situation. Therefore, this interesting concept cannot be challenged by respective disease models, which would be necessary to apply anti-b-FGF strategies in a therapeutic approach.

From this interesting study, it again becomes obvious what we need most in intestinal fibrosis research: similar to lung fibrosis or renal fibrosis we have to develop in vivo models for intestinal fibrosis in the near future to be able to bring new and interesting concepts on pathophysiology back to the bedside in clinical studies. Developing these models therefore is a rewarding service for all our patients suffering from stricturing IBD.

References

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