Alterations in mucin glycosylation are associated with spontaneous colitis

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Mucus covers the intestinal epithelium along the entire gastrointestinal tract and is a central part of the intestinal barrier. Enteric mucus contains goblet cellderived mucins, antimicrobial peptides and immunoglobulins and thus forms both a functional and a physical barrier that prevents the translocation of microbial organisms into the intestinal lamina propria [1]. The composition of mucus varies along the intestinal tract and increases in depth towards the distal colon, where an inner, sterile layer adjacent to the epithelium and an outer non-sterile layer can be distinguished [1, 2]. These structural features are dependent on mucins, a family of oligomerising and non-oligomerising heavily O-glycosylated glycoproteins [1, 2].

Given the central role of intestinal mucus in the prevention of uncontrolled microbial translocation into the lamina propria, it was hypothesised decades ago that inflammatory bowel diseases (IBD) are associated with alterations in the composition and structure of the intestinal mucus. Indeed, characterisation of the mucus layer in IBD revealed an inflammation-dependent decrease in mucus thickness, particularly in ulcerative colitis [3]. This is consistent with earlier reports on altered molecular mucus composition in IBD [4] and was shown to be in large part due to impaired O-glycosylation of mucins [5]. Subsequent mechanistic studies in mice indicated that altered expression of mucins might indeed play a primary, pathogenic role in IBD since genetic defects in mucin expression can lead to spontaneous intestinal inflammation [6, 7].

Fu et al. [8] have now highlighted the role of O-glycosylation of intestinal mucins in the pathogenesis of IBD. The authors generated mice with conditional, intestinal epithelial-specific deletion of core 1 β1,3-galactosyltransferase (C1galt1), an enzyme responsible for generation of the predominant form of O-glycans. Similar to previous reports on mice with mucin defects, C1galt1-deficient mice developed spontaneous colitis with histological features reminiscent of human ulcerative colitis such as epithelial ulceration and crypt abscesses. Mechanistic studies revealed that intestinal epithelial deletion of C1galt1 leads to a severely impaired mucus structure, reduced expression of mucins and unrestrained, direct contact between the intestinal epithelium and the microbiota that is associated with bacterial translocation into the lamina propria. In addition, Fu et al. demonstrated that spontaneous colitis in C1galt1-deficient mice is driven by myeloid cells in a TNF- but not toll-like receptor-dependent manner and is independent of adaptive immune cells.

Several findings suggest that these observations might be relevant to human IBD. First, the authors demonstrated that intermediates of glycan biosynthesis, normally concealed by further glycosylation, can be detected in the intestinal mucosa of patients with ulcerative colitis (UC) but not controls, which indicates incomplete glycan synthesis in UC. In addition, initial genetic analysis of UC patients exhibiting defective glycosylation of intestinal mucins revealed the presence of missense mutations in a chaperone responsible for proper function of C1galt1 (core 1 β1,3-galactosyltransferase–specific chaperone 1), which suggests that primary genetic alterations in glycan pathways might contribute to the pathogenesis of UC.

Summary: The study by Fu et al. demonstrates that alterations in glycosylation of mucins are associated with impaired mucus production, increased bacterial translocation into the intestinal lamina propria and spontaneous colitis. In addition, the authors' findings suggest that primary genetic alterations in glycan pathways might be associated with human UC. Finally, since defects in glycan biosynthesis similar to those observed in UC can also be detected in colorectal cancer, the study by Fu et al. raises the question of whether glycan alterations in UC might be related to the development of colitis-associated cancers.

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