Functional role of ST6GALNAC1-mediated sialylation of mucins in preserving intestinal barrier integrity and ameliorating inflammation.

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Abbreviations:ST6GALNAC1, ST6; mucin-2, MUC2; dextran sulfate sodium, DSS; wild-type, WT; short-chain fatty acids, SCFA.

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Keywords: epithelial barrier; MUC2; intestinal mucus; gut microbiota disruption; colitis.

Abstract

No abstract is available for this article

Main text

Sialylation is a post-translational modification, catalyzed by sialyltransferases, that consists of the addition of sialic acid to oligosaccharides, glycoproteins or glycosphingolipids. ST6GALNAC1 (ST6) is a sialyltransferase predominantly expressed in intestinal goblet cells. Goblet cells produce intestinal mucus, which has emerged as a key player in oral tolerance to food antigens[1]. The hyperglycosylated Mucin-2 (MUC2) is the major component of intestinal mucus[2] and is susceptible to undergoing post-translational modifications. Along this

line, Yao *et al.* [3] studied the contribution of ST6-mediated glycan sialylation of intestinal mucus to barrier integrity, host-commensal homeostasis and inflammation.

Certain gut bacteria, mainly pathogens, can evolve to produce a range of mucin-hydrolyzing enzymes (*i.e.* , mucinases)[4]. Yao *et al.* [3] demonstrated that ST6-mediated sialylation protects MUC2 against degradation by certain bacterial-secreted mucinases (i.e., *Escherichia coli* and *Akkermansia muciniphila* proteases), thus maintaining mucus integrity (**Figure 1**). Unraveling the stability of sialylated mucus against different gut bacteria may lead to the identification of potentially harmful species. Furthermore, it could be interesting to assess if this modification protects against mucinases secreted by pathogens such as the enterotoxigenic *Escherichia coli* or *Vibrio cholerae* .

This work also revealed that *St6-* deficient mice were more susceptible to dextran sulfate sodium (DSS)-induced colitis as compared to wild-type (WT) mice. Thickening of the mucus barrier accompanied by a marked improvement in colitis markers was observed in *St6* -deficient mice following mucin administration. Moreover, antibiotic treatment of*St6* -deficient mice prior to DSS administration eliminated the difference in disease severity between WT and *St6-* deficient mice. The authors concluded that ST6 is essential for the mucus barrier that prevents bacterial translocation and inflammation. By comparing the fecal microbiota in WT and *St6* -deficient mice, it was observed that the latter had a less diverse microbiome with increased*Akkermansiaceae* and *Ruminococcaceae* taxa (**Figure 1**). These taxa are important producers of short-chain fatty acids (SCFA) (*i.e.* , butyrate, acetate, propionate), metabolites mainly produced by bacterial fermentation of dietary fibers and resistant starch. The excess of butyrate in stool samples, as a result of the alteration of the gut microbiota, impaired intestinal stem cell proliferation delaying mucus reparation during DSS colitis in*St6-* deficient mice. Further investigation on the levels of butyrate could inform of its importance in the severity of mucus damage; however, it should bear in mind that fecal SCFA levels are not necessarily representative of intestinal luminal SCFA content.

Moreover, to investigate the role of ST6 in humans, Yao *et al*[3] examined individuals from three families with very early-onset intestinal bowel disease (*i.e* ., colitis). Remarkably, different mutations were found in all families affecting conserved amino acids in ST6 that likely compromise its activity. Additional studies with larger cohorts of autoimmune and allergic patients could shed some light on potential correlations between ST6 mutations and clinical outcome.

Due to the important role of ST6 in barrier integrity and the novel hypothesis on the epithelial barrier and type 2 responses,[5] it would be relevant to investigate the role of ST6 in allergic sensitization. A deficiency or mutation on ST6 jeopardizes mucus barrier reparation during DSS colitis, so this scenario could be prone to induce sensitization to bystander allergens (**Figure 1**). Finally, IgE sialylation has been reported as an important regulator of anaphylaxis[6,7]. Given that sialylation is a highly specific and local glycomodification, it would be interesting to investigate ST6 expression in other tissues, and its protective role in other mucosal tissues.

Figure 1 legend . ST6-mediated sialylation protects MUC2 against mucinase degradation maintaining mucus integrity. ST6-deficiency impairs the microbiome homeostasis and promotes an increase of*Akkermansiaceae* and *Ruminococcaceae* taxa, reducing the microbiome diversity. These bacteria are producers of butyrate, which delays intestinal stem cell proliferation. This also induces mucus damage which may promote a release of cytokines and alarmins. The interrogation in the label of food allergens refers to the unknown role of ST6 in allergic sensitization. Wild-type, WT; ST6GALNAC1, ST6; mucin-2, MUC-2; short-chain fatty acids, SCFAs.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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