J Gastroenterol (2016) 51:406–408
DOI 10.1007/s00535-015-1156-y

The Japanese Society of Gastroenterology

EDITORIAL

Function of the glycosyltransferase GnT-V in colitis

Motohiro Nonaka[1]

Received: 27 November 2015 / Accepted: 3 December 2015 / Published online: 24 December 2015

Inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis, are characterized by chronic inflammation in the gastrointestinal tract. Although the precise pathogenesis of IBD is not fully clarified, it is widely accepted that host genetics and intestinal microbiota collectively trigger both diseases. Among the variety of spontaneous, inducible, and genetic animal models of IBD [1–4], usage of dextran sodium sulfate (DSS) is perhaps the most common method to induce colitis in mice [5]. A possible sequence of events in DSS-driven colitis involves damage to the colonic inner mucus barrier, bacterial infiltration, and bacterial recognition by host immune cells. Given that DSS-induced colitis is reproducible even in T- and B-cell-deficient mice [6], activation of innate immune cells (e.g. macrophages) followed by secretion of a particular set of cytokines are likely critical events in disease induction.

In this issue of *Journal of Gastroenterology*, Shinzaki et al. [7] demonstrated that gene transfer and subsequent overexpression of *N*-acetylglucosaminyltransferase V (GnT-V), an enzyme that catalyzes β1,6*N*-acetylglucosamine (GlcNAc) branching on *N*-glycans, impaired macrophage function in mice. When GnT-V transgenic (Tg) mice were treated with DSS, isolated macrophages secreted lower levels of the anti-inflammatory cytokine IL-10 than did control mice, a decrease that prompted a shift in the host's immune system towards a pro-inflammatory response, and eventually caused colitis and colon cancer.

A role for IL-10 in colitis induction has been reported in IL-10- or IL-10 receptor β chain-knockout mouse models [8–10]. Mice in both models become spontaneously anemic, lose weight, and eventually develop colitis. Notably, no chemical stimulants are necessary to induce these phenotypes. Instead, IL-10-deficient mice require bacterial colonization of the intestine: mice raised in specific pathogen-free conditions did not develop colitis [9], although some showed inflammation limited to the proximal colon [8]. IL-10 receptor-deficient mice also show colitis when raised in a conventional facility where bacteria are present [10]. Collectively, these findings, together with the report from Shinzaki et al., suggest that, whether the stimulus is acute or constitutive, IL-10 production by macrophages upon bacterial recognition suppresses inflammation and induction of colitis.

Poly-*N*-acetyllactosamine is a glycan harboring type 2 LacNAc (Galβ1 → 4GlcNAcβ1 → 3) repeats, and is found on *N*-glycans, *O*-glycans, and glycolipids. Particularly in the case of *N*-glycans, β1,6 GlcNAc branching from bi-antennary core mannose by GnT-V is rate-limiting for synthesis of poly-*N*-acetyllactosamine [11, 12]. Accordingly, macrophages from GnT-V Tg mice should exhibit increased levels of linear poly-*N*-acetyllactosamine. However, Shinzaki et al. did not detect a difference in levels of linear glycans in macrophages from GnT-V-overexpressing versus wild-type mice in lectin blots using *Datura stramonium* agglutinin (DSA). Although the authors do not directly address this issue, it is possible that linear poly-*N*-acetyllactosamine structures are modified or

This comment refers to the article available at doi:10.1007/s00535-015-1119-3.

✉ Motohiro Nonaka
moto-nonaka@aist.go.jp

[1] Laboratory for Drug Discovery, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8568, Japan

branched by additional glycosyltranserases in transgenic mice and thus not reactive to DSA lectin. Indeed, enzymes associated with poly-*N*-acetyllactosamine modification, such as fucosyltransferases and sialyltransferases, are abundant in intestine and colon [13, 14]. In addition, in some cases, the non-reducing terminus of the poly-*N*-acetyllactosamine chain is replaced with a type 1 disaccharide chain (Galβ1 → 3GlcNAcβ1 → 4), generating a structure totally different from type 2 LacNAc [15, 16].

Several mechanisms could account for decreased IL-10 secretion by macrophages that highly express GnT-V. A previous study [17] reported galectin binding to increased levels of linear poly-*N*-acetyllactosamine, an outcome that facilitated intercellular communication between macrophages and B cells and subsequently stimulated IL-10 production by macrophages. In the case of GnT-V overexpression, newly modified poly-*N*-acetyllactosamine structures might interact with different lectins, such as C-type lectins and siglecs. Simultaneous recognition of pathogens by TLR4 and one of those lectins reportedly initiates crosstalk with TLR signaling and alters secretion of cytokines, including IL-10 [18]. Alternatively, an altered poly-*N*-acetyllactosamine structure could be expressed on TLR4 proteins in macrophages, which could interfere with receptor/lipopolysaccharide interaction and inhibit TLR signaling. Future studies of glycan structure as well as identification of the carrier protein of altered glycans might reveal mechanisms underlying macrophage activation and onset of DSS-colitis in GnT-V Tg mouse models.

Given phenotypes seen in IL-10-deficient mouse models [8–10], IL-10 could represent a promising novel therapeutic for IBD. IL-10 gene therapy has had a significant positive effect as treatment in IBD model mice [19, 20]. However, phase III clinical trials using recombinant IL-10 administered subcutaneously have not shown a beneficial effect in IBD patients [21, 22], possibly due to decreased bioavailability of IL-10 in the intestinal mucosa. Thus, approaches that target factors upstream of IL-10 production, such as GnT-V, are feasible. However, targeting GnT-V could impact cell types than macrophages. Since inhibition of β1,6 GlcNAc branching provides a new substrate for competing glycosyltranserases such as GnT-III, *N*-glycan structures and the function of cells expressing these glycans may be compromised. Such unwanted effects may be avoided via local drug administration (e.g. by enema). Potential obstacles notwithstanding, the present report by Shinzaki et al. highlights an important nexus of glycobiology and gastroenterology and greatly contributes to our knowledge of IBD pathogenesis.

Acknowledgments The author thanks Dr. Minoru Fukuda for the invitation to write this editorial and Dr. Elise Lamar for editing the manuscript.

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