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## Roles of galectins in inflammatory bowel disease

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### Abstract

Protein/carbohydrate interactions through specific protein families termed lectin control essential biological processes. Galectins, a family of animal lectins defined by shared amino acid sequence with affinity for  $\beta$ -galactosides, appear to be functionally polyvalent in a wide range of biological activity. Recent studies have identified immunoregulatory roles of galectins in intestinal inflammatory disorders. Galectin-1 and galectin-2 contribute to the suppression of intestinal inflammation by the induction of apoptosis of activated T cells, whereas galectin-4 is involved in the exacerbation of this inflammation by specifically stimulating intestinal CD4<sup>+</sup> T cells to produce IL-6. We review how different members of the galectins provide inhibitory or stimulatory signals to control intestinal immune response under intestinal inflammation.

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**Key words:** Galectin; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Pathogenesis; Apoptosis; Glycosylation

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### INTRODUCTION

Inflammatory bowel disease (IBD), which is characterized by two forms of intestinal inflammation, Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic, relapsing, and remitting inflammatory conditions that affect individuals throughout life<sup>[1]</sup>. Several factors such as immune imbalance, dysregulated host/microbial interaction, and genetic susceptibility are involved in the pathogenesis of IBD<sup>[2-4]</sup>. Experimental IBD models have provided a useful means to dissect the pathogenesis of this disease<sup>[2-4]</sup>. Among these models, chronic intestinal inflammation that spontaneously develops in T cell receptor  $\alpha$  knockout (TCR $\alpha$  KO) mice shares several features with human UC, e.g. marked increase in autoantibodies such as antineutrophil cytoplasmic antigens and antitropomyosin, predominant Th2 responses and negative association of colitis development with prior appendectomy (resection of cecal patch)<sup>[5-7]</sup>. Importantly, B cells and autoantibodies in TCR $\alpha$  KO mice are involved in the regulation of this inflammation<sup>[8-12]</sup>. Therefore, a screening approach utilizing autoantibodies present in TCR $\alpha$  KO mice was proposed to have an ability to provide a useful tool in the identification of molecules, which may have a role in the pathogenesis of UC<sup>[13]</sup>. Indeed, the screening approach [serological analysis of recombinant cDNA expression libraries (SEREX) for the identification of candidate molecules that are recognized by autoantibodies from TCR $\alpha$  KO mice] has provided us an unexpected opportunity to identify galectin-4 as a potential stimulator of CD4<sup>+</sup> T cells under intestinal inflammatory conditions<sup>[14,15]</sup>. Interestingly, galectin-4 was an unexpectedly discovered carbohydrate-binding protein through our screening approach, emphasizing

the importance of carbohydrate/protein interactions in the pathogenesis of intestinal inflammation. Indeed, a recent study has demonstrated that an alteration of carbohydrate composition (carboxylated glycans) on macrophages and dendritic cells contributes to the early onset of intestinal inflammation<sup>[16]</sup>. Alternatively, carbohydrate/protein interactions also play a regulatory role in the intestinal inflammation as indicated by a suppressive effect of galectin-1 and galectin-2 on this inflammation<sup>[17,18]</sup>. We, herein, review recently identified novel roles of galectins in immune responses under intestinal inflammation.

## GALECTINS

Several families of glycan-binding proteins or lectins, which include C-type lectins (such as selectin, DC-SIGN, dectin, and serum mannose binding protein)<sup>[19-23]</sup>, S-type lectins (galectins)<sup>[24-28]</sup> and siglecs<sup>[29]</sup>, have been implicated in a wide variety of immunological functions including first-line defense against pathogens, cell trafficking, cell differentiation and immune regulation. Galectins are a family of 15 members (galectin-1 to galectin-15) characterized by two properties: the ability to bind to lactosamine unit within glycans and the preserved carbohydrate recognition domains (CRD) composed of 130 amino acid residues. The 15 members of galectins are structurally classified into three groups: prototype, chimera-type, and tandem repeat type<sup>[30-32]</sup>. Prototype (galectins-1, -2, -5, -7, -10, -11, -13, -14, and -15) is non-covalent homodimers that are composed of two identical CRDs. Only galectin-3 is chimera type that is composed of a CRD linked to a proline-, glycine-, and tyrosine-rich N-terminal domain. Tandem repeat type (galectins-4, -6, -8, -9, and -12) possesses two distinct CRDs. The ability of CRDs to cross-link the lactosamine unit within surface glycoreceptors allows galectins to actively participate in several immune responses. A large body of evidence indicates important roles of galectins in the development and progression of cancer<sup>[30-33]</sup>. Recently, compelling evidence has been accumulated regarding the immunoregulatory effects of galectins in inflammatory disorders<sup>[34-36]</sup>. We focus on four members of galectins (galectins-1, -2, -3 and -4), which have been studied regarding intestinal inflammation.

### REGULATORY ROLE OF GALECTIN-1 IN INTESTINAL INFLAMMATION

Galectin-1 (prototype), which is expressed by a wide variety of cell types, is specifically upregulated on CD4+CD25+ regulatory T cells<sup>[37]</sup>. Soluble galectin-1 has been demonstrated to interact with a lactosamine unit of mature core 2 O-glycan that is assembled within some glycoreceptors including CD7, CD43, and CD45, and its cross-linking ability is crucial for the induction of T cell apoptosis<sup>[37-40]</sup>. The anti-inflammatory properties of galectin-1 have been evaluated in several models of chronic inflammation and autoimmunity including

autoimmune encephalomyelitis<sup>[41]</sup>, arthritis<sup>[42]</sup>, uveitis<sup>[43]</sup>, hepatitis<sup>[44]</sup>, and diabetes<sup>[45]</sup>. As for the colitis model, galectin-1 expression in the colon is upregulated under an intestinal inflammatory condition that is chemically induced in mouse by rectal administration of 2, 4, 6-trinitrobenzene sulfonic acid (TNBS)<sup>[17]</sup>. Administration of human recombinant galectin-1 contributes to the reduction of Th1 cytokine (TNF- $\alpha$ , IL-1 $\beta$ , IL-12 and IFN- $\gamma$ ) release and the suppression of this intestinal inflammation by specifically inducing the apoptosis of effector T cells responsible for production of IFN- $\gamma$ <sup>[17]</sup>. In addition, a recent study has demonstrated that administration of recombinant galectin-1 also contributes to increase IL-10 production in CD4+ and CD8+ T cells<sup>[46]</sup>. These data clearly address the therapeutic potential of galectin-1 to skew the balance from a Th1- toward a Th2-polarized immune response that induces a remission state in the evolution of the ongoing inflammatory disorders.

### REGULATORY ROLE OF GALECTIN-2 IN INTESTINAL INFLAMMATION

Galectin-2 (prototype) is expressed by various cells including intestinal epithelial cells. Galectin-2, structurally related to galectin-1, has been demonstrated to be an inducer of apoptosis of activated T cells, although it lacks reactivity to CD7 characteristic for galectin-1<sup>[47]</sup>. A recent study has shown that galectin-2 is constitutively expressed mainly in the epithelial compartment of the mouse intestine and binds to lamina propria mononuclear cells<sup>[18]</sup>. In acute and chronic dextran sodium sulfate (DSS)-induced colitis, and in a Th1-driven model of antigen-specific transfer colitis, galectin-2 expression was reduced, but could be restored to normal levels by immunosuppressive treatment. Administration of human recombinant galectin-2 induced apoptosis of mucosal T cells and, thus, ameliorated. Furthermore, pro-inflammatory cytokine (IL-6, IL-12p70) release was inhibited by administration of galectin-2. Their study provides evidence that galectin-2, as well as galectin-1, induces apoptosis *in vivo* and ameliorates acute and chronic murine colitis.

### ROLE OF GALECTIN-3 IN INTESTINAL INFLAMMATION

Galectin-3 (chimera type) is a multifunctional protein detected in the nucleus, cytoplasm and extracellular matrix of a wide variety of cells. Galectin-3 has the dual role of protecting T cells from apoptosis when present intracellularly while promoting apoptosis when acting on T cells from the extracellular space<sup>[30-32,36]</sup>. Regarding intestinal inflammation, a study showed that the titers of anti-galectin-3 autoantibodies were higher in CD patients with low activity index than with active disease<sup>[48]</sup>. The pathophysiological significance of the anti-galectin-3 autoantibody in Crohn's disease still remains to be elucidated. The same research group

subsequently showed that expression of galectin-3 was reduced in the intestinal epithelium of CD patients and that colonic epithelial adenocarcinoma cell line HCT-8 cells reduced galectin-3 expression by incubation with TNF- $\alpha$  but not with other cytokines<sup>[49]</sup>. It was speculated that galectin-3 was consequently downregulated by enhanced TNF- $\alpha$  production in CD. Another research group confirmed the similar findings<sup>[50]</sup>. More recently, soluble galectin-3, which is secreted by colonic epithelial cells, was identified as an activator of lamina propria fibroblasts<sup>[51,52]</sup>. The study also indicated that galectin-3 induced NF- $\kappa$ B activation and IL-8 secretion *in vitro*. Its role in pathogenesis of intestinal inflammation, especially involvement in fibrosis formation of CD, has to be clarified in further studies. In a protein expression profile study of *Enterococcus faecalis*-monoassociated IL-10 KO mice under chronic intestinal inflammation and intestinal epithelial cell lines, galectin-3 expression was reduced in association with the activation of caspase 3, a major executive caspase of apoptosis<sup>[53]</sup>. Further studies are needed to address whether galectin-3 plays a pro-inflammatory role or an anti-inflammatory role in intestinal inflammation.

## **PATHOGENIC ROLE OF GALECTIN-4 IN INTESTINAL INFLAMMATION**

Galectin-4 (tandem repeat type) is expressed only in the digestive tract<sup>[54,56]</sup> where epithelial cells are responsible for this production<sup>[14,55,56]</sup>. Galectin-4 can be secreted from both basolateral and apical sides of the intestinal epithelial cells through a nonclassical secretory pathway. In contrast to galectin-1<sup>[17]</sup>, intestinal inflammatory conditions do not enhance the galectin-4 expression: there is no significant difference in the expression level of galectin-4 in the epithelial cells from control *versus* inflamed colons<sup>[14]</sup>. Interestingly, through a combined screening approach utilizing humoral (SEREX) and cellular immune responses, we have unexpectedly identified galectin-4 as a potential stimulator of CD4+ T cells to exacerbate intestinal inflammation<sup>[14]</sup>. Neutralization of galectin-4 activity *in vivo* by administration of the specific antibody suppresses the progression of chronic colitis that spontaneously develops in B cell-deficient TCR $\alpha$  double KO mice<sup>[14]</sup>, whereas pretreatment with this antibody fails to abolish the development of colitis in these mice (A.M., unpublished observation). These data suggest that galectin-4 contributes to the exacerbation, rather than initiation, of chronic intestinal inflammation. Because it could be predicted that both acute (induction of inflammation) and healing (recovery from inflammation) processes are simultaneously involved in the chronic intestinal inflammation, galectin-4-mediated exacerbation of this inflammation may result from a suppression of the healing process. Indeed, treatment with recombinant galectin-4 delays the recovery from an acute intestinal inflammation that is induced by transient administration of DSS, whereas treatment with anti-galectin-4 antibody

enhances the recovery from this acute inflammation. In contrast, galectin-1, as mentioned above, contributes to the suppression of acute intestinal inflammation<sup>[17]</sup>. Galectin-1 (prototype) is structurally characterized by homodimers with identical CRDs, and binds to a lactosamine unit within a mature core 2 O-glycan, whereas galectin-4 (tandem repeat type) consists of two distinct CRDs and possesses a unique carbohydrate-binding specificity as indicated by the capability of interacting with an immature core 1 O-glycan with 3'-O-sulfation<sup>[57]</sup>. Therefore, it is highly likely that the binding site (lactosamine unit *versus* core 1) and the structure (prototype *versus* tandem repeat type) are an important determinants of galectin-mediated immune function<sup>[30,32,36]</sup>. Galectin-4 specifically stimulates CD4+ T cells, but not other immune cells such as B cells or macrophages to produce IL-6<sup>[14]</sup>, a well-known cytokine involved in the pathogenesis of not only intestinal inflammation, but also colon cancer<sup>[58-60]</sup>. Importantly, only CD4+ T cells that are present in the inflamed, but not non-inflamed, intestine can respond to galectin-4<sup>[14]</sup>. Splenic CD4+ T cells even from the diseased mice are unable to respond to galectin-4. These findings are consistent with the binding intensity of galectin-4 to the surface of CD4+ T cells; galectin-4 binding is significantly enhanced on the CD4+ T cells from the inflamed colon as compared to noninflamed colon and spleen. In addition, galectin-4 specifically binds to the lipid rafts on the CD4+ T cells to activate the protein kinase C  $\theta$ -associated signaling cascade<sup>[14]</sup>, a common and fundamental pathway in the different types of intestinal inflammation<sup>[61]</sup>. Notably, galectin-4 has been demonstrated to interact with lipid rafts of enterocytes as well, and subsequently stabilize the raft formation to generate "superrafts"<sup>[62]</sup>. A recent study has found that galectin-4 interacts with carcinoembryonic antigen of colon adenocarcinoma<sup>[63]</sup>. Alternatively, it remains obscure which glycosylated receptor(s) on intestinal CD4+ T cells is crosslinked by galectin-4. Production of galectin-4 by colonic epithelial cells is not enhanced under inflammatory condition, whereas the reactivity of CD4+ T cells to galectin-4 is specifically elicited under these conditions. Therefore, it is possible that a specific receptor that is selectively crosslinked by galectin-4 may be expressed on intestinal CD4+ T cells only under inflammatory conditions. However, galectin-4 can bind to the lipid rafts on both CD4+ T cells from inflamed and normal intestines although the binding intensity is much higher on diseased CD4+ T cells<sup>[14]</sup>. In addition, expression pattern of the enzymes that are involved in the glycan synthesis is altered by several inflammatory stimuli<sup>[27,34,35]</sup>. Therefore, it is more likely that an altered enzyme expression pattern by intestinal inflammatory stimuli results in the further exposure of core 1 O-glycan (a binding partner of galectin-4) on intestinal CD4+ T cells and consequently allows intensified binding of galectin-4 to them. Indeed, our recent studies have found that some glycosylation-associated enzymes, which are involved in the synthesis of core 2 from core 1, are significantly downregulated in the intestinal CD4+

T cells under inflammatory conditions as compared to a state of health (our unpublished observation). These findings provide an insight into an unexpected role of lectin/carbohydrate interaction in the pathogenesis of T cell-mediated chronic colitis.

## CONCLUSION

Glycobiology has an exiting impact to molecular biology and clinical fields, given the multifunctional activities of galectins. In this review, we provide novel insights into the role of carbohydrates crosslinked by galectins in the immune responses involved in the pathogenesis of IBD. Different members of the galectin families provide inhibitory or stimulatory signals to control intestinal immune response under intestinal inflammatory conditions. A more thorough understanding of the molecular mechanisms involved in the immunoregulatory functions of galectins is needed before galectin-based therapeutic strategies for IBD can be realized.

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