Immunologic Research 2007;37/1:47–60

Is the Sugar Always Sweet in Intestinal Inflammation?

Emiko Mizoguchi[1,2]
Atsushi Mizoguchi[1,3]

[1] Center for the Study of Inflammatory Bowel Disease, [2]Gastrointestinal Unit, Department of Medicine, and [3]Experimental Pathology Unit, Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114

Abstract

Immune responses are mediated mainly by protein/protein interactions. In addition, protein/carbohydrate (sugar) interactions through specific protein families termed lectin and chi-lectin are also involved in several immune and biological responses under not only the state of health but also inflammatory conditions. Interestingly, recent studies have identified unexpected roles of animal lectins (galectin-1 and galectin-4) and chi-lectin (chitinase 3-like-1) in intestinal inflammation. Galectin-1 contributes to the suppression of intestinal inflammation by the induction of effector T cell apoptosis. In contrast, galectin-4 is involved in the exacerbation of this inflammation by specifically stimulating intestinal $CD4^+$ T cells to produce IL-6. CHI3L1 enhances the host/microbial interaction that leads to the exacerbation of intestinal inflammation. In this review, we discuss a novel aspect of lectin/carbohydrate interactions in intestinal inflammation.

Key Words

Galectin-4
Chitinase 3-like 1
Chi-lectin
Inflammatory bowel disease
Glycans
T cells
Lipid rafts
Enteric bacteria

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 *(1)*. Several factors such as immune imbalance, dysregulated host/microbial interaction, and genetic susceptibility are involved in the pathogenesis of IBD *(2–5)*. Experimental IBD models have provided a useful means to dissect the pathogenesis of this disease *(2–6)*. Among these models, chronic intestinal inflammation that spontaneously develops in T cell receptor α knockout (TCRα KO) mice

Atsushi Mizoguchi, MD, PhD
Experimental Pathology Unit, Simches 8234,
Massachusetts General Hospital,
185 Cambridge Street, Boston, MA 02114.
E-mail: amizoguchi@partners.org

0257–277X/
(Online)1559-0755/07/
37/1:47–60/$30.00

shares several features with human UC, e.g., marked increase in autoantibodies such as antineutrophil cytoplasmic antigens (ANCA) and antitropomyosin *(3,5,6),* predominant Th2 responses *(3,5,6),* and negative association of colitis development with prior appendectomy (resection of cecal patch) *(7).* Importantly, B cells and autoantibodies in TCRα KO mice are involved in the regulation of this inflammation *(8–10).* Therefore, a screening approach utilizing autoantibodies present in TCRα 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 *(11).* Indeed, the screening approach [serological analysis of recombinant cDNA expression libraries (SEREX) for the identification of candidate molecules that are recognized by autoantibodies from TCRα KO mice] has provided us an unexpected opportunity to identify galectin-4 as a potential stimulator of $CD4^+$ T cells under intestinal inflammatory conditions *(12).* In addition, DNA microarray analysis has widely been used as a powerful approach to identify novel molecular events associated with inflammations *(13,14).* By utilizing this approach, we also have found that chitinase 3-like 1 (CHI3L1), which interacts with carbohydrate polymer (chitin), is involved in the enhancement of host/microbial interaction that contributes to the exacerbation of intestinal inflammation *(14).* Interestingly, the molecules (galectin-4 and CHI3L1) that were unexpectedly discovered through our screening approaches are both carbohydrate-binding protein, 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 *(15).* Alternatively, carbohydrate/protein interactions also play a regulatory role in the intestinal inflammation as indicated by a suppressive effect of galectin-1 on this inflammation *(16).*

The function of carbohydrates (oligosaccharides) in mucus, which forms a gel layer and serves as a semipermeable barrier between the intestinal lumen and the epithelium, has been well studied in IBD *(17).* We herein review recently identified novel roles of carbohydrates in immune responses and host/microbial interaction under intestinal inflammatory conditions.

Effects of Glycosylation on Immune Responses

The majority of surface receptors are modified by glycosylation. There are two main types of protein glycosylation: N-glycosylation (N-glycan) that is assembled on an asparagine residue and O-glycosylation (O-glycan) that is assembled on a serine or threonine residue. All mammalian N-glycans share a common trimannosyl-chitobiose core [Mannose(Man)3 N-acetyl-D-glucosamine(GlcNAc)2], which is synthesized from a biosynthetic precursor, D-Glucose (Glc)3Man9GlcNAc2 *(18–21).* In contrast, there are at least seven core structures in O-glycan, four of which are widespred in mammalian glycoprotein. After establishment of such core formation, structural diversification of glycans is induced in the Golgi compartments. The antennae stubs attached to the core are generated by the addition of a lactosamine unit [β-galactose (β-Gal) and N-acetylglucosamine (GlcNAc)]. Subsequently, the oligosaccharide antennae can be further lengthened by the sequential additions of lactosamine units, resulting in the generation of tandem repeats ("polylactosamine") of lactosamine. The addition of fucose further modifies the glycan structure.

Finally, the elongation is terminated by the addition of negatively charged sialic acid *(18–21).* Various kinds of enzymes such as sialyltransferases, N-acetylglucosaminyl transferases, galactosyltransferases, and fucosyltransferases are utilized for the elongation and modification of glycans. The expression pattern of these enzymes in cells is continuously modified through their development and activation stages and also influenced by environmental factors such as inflammation *(18,19,22–26).* Therefore, the oligosaccharide composition as well as the number and size of oligosaccharide branches (antennae) within glycoreceptors are frequently altered throughout the lives of cells *(18,19,22–26).*

The majority of key molecules that are involved in innate and acquired immune responses are glycoproteins *(27).* Recent studies have demonstrated that the glycoprotein-mediated immune responses are controlled by the glycan structures (oligosaccharide composition) *(22–25,28,29).* Glycan structure regulates major histocompatibility complexes (MHC)–associated antigen presentation by modifying the protein folding and assembly *(27).* An ability of $CD8^+$ T cells to interact with MHC class I is regulated through their glycosylation state *(25,28,30).* In addition, alteration of glycosylation has been demonstrated to affect several immune responses of T cells, e.g., their homing/adhesion, cytokine production, and TCR clustering on the immunological synapse *(23,28,29,31).* Of note, altered glycosylation state results in the development of some autoimmune diseases *(28,32,33).* Absence of β1,6-*N*-acetylglucosaminyltransferase V (Mgat5), which adds GlcNAc in β1-6 linkage to the α6-linked mannose arm of tri- and tetra-antennary complex N-glycan, leads to the development of glomerulonephritis and increases the susceptibility to experimental autoimmune encephalomyelitis *(28).* In addition, mice deficient in α-mannosidase II, which trims two mannose residues and allows the subsequent addition of multiple branches (antennae) to N-glycan by glycosyltransferases, spontaneously develop systemic lupus erythematosus-like disease *(32).* These observations emphasize an importance of normally matured glycans to prevent the development of autoimmune diseases.

Galectins

Plant-derived lectins such as concanavalin (Con) A have long been used as surrogates for authentic lymphocyte activational stimuli. Like exogenous lectins, some endogenous mammalian lectins are also actively involved in several immune responses *(22–25,28).* One of the major mammalian lectin families is C-type lectin (such as selectin, DC-SIGN, dectin, and serum mannose binding protein) that not only serves as a prototypic pattern-recognition molecule for both pathogens and self-antigens but also contributes to the tether of leukocytes to endothelium, cell/cell adhesion, and enhancement of cytokine production *(27,29,34–37).*

Another major mammalian lectin family is the galectins that are classified into 14 members (galectin-1 to galectin-14) *(38–40).* Galectins are 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 *(38–40).* The 14 members of galectins are structurally subgrouped into three groups; prototype, chimera-type, and tandem repeat type *(38–40).* Prototype (galectins-1, -2, -5, -7, -10, -11, -13, and -14) 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-

Fig. 1. Galectin-1 (prototype) with a CRD forms homodimers and binds to a lactosamine unit within mature core two-branced O-glycan. This binding induces apoptosis of thymocytes as well as activated T cells involved in the pathogenesis of intestinal inflammation. CD7 has been proposed to be responsible for the galectin-1–mediated induction of thymocyte apoptosis. In contrast, galectin-4 (tandem repeat type) with two distinct CRDs binds to an immature carbohydrate structure (core 1 O-glycan with 3′-O-sulfation). This binding stimulates the $CD4^+$ T cells in inflamed intestine to produce IL-6 through PKCθ signaling cascade. However, the glycoreceptor(s) that is specifically crosslinked by galectin-4 has not been identified.

link the lactosamine unit within surface glycoreceptors allows galectins to actively participate in several immune responses *(22,23,28,41–48).* For example, galectin-3 (chimera type) possesses abilities to dampen TCR sensitivity to antigens and induce the apoptosis of thymocytes *(28,49).* Galectin-2 (prototype) also induces the apoptosis of activated, but not resting, T cells in vitro *(50).* Galectin-8 (tandem repeat type) stimulates the proliferation of a T cell line through Rac-1 pathway *(51).* Galectin-9 (tandem repeat type) has recently been shown to interact with Tim-3 and, consequently, terminate effector Th1 response *(52).*

Regulatory Role of Galectin-1 in Intestinal Inflammation

Galectin-1 (prototype), which is expressed by a wide variety of cell types including muscles, neurons, and thymic stromal cells *(28,53),* is specifically upregulated on $CD4^+CD25^+$ regulatory T cells among T cell population *(54).* Soluble galectin-1 has been demonstrated to interact with a lactosamine unit of mature core two-branched O-glycan that is assembled within some glycoreceptors including CD7, CD43, and CD45 *(22,49,55).* Functionally, galectin-1 induces the apoptosis of thymocytes *(42,43)* and also antagonizes TCR signaling of a $CD4^+$ Th1 T cell clone specific to pigeon cytochrome c by affecting lipid-raft clustering *(44).* A recent study shows that CD7 is required for the galectin-1–induced thymocyte apoptosis *(55).* In addition, galectin-1 has more recently been shown to enhance the migration of dendritic cells through extracellular matrix *(56).* Interestingly, 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) *(16).* Administration of human recombinant galectin-1 contributes to the suppression of this intestinal inflammation by specifically inducing the apoptosis of effector T cells responsible for production of IFN-γ *(16).* In addition, a study has demonstrated that treatment with recombinant galectin-1 also contributes to the suppression of Th1-mediated retinal disease presumably by inducing $CD4^+$ regulatory T cells *(57).* These data clearly address galectin-1 as an immune regulatory molecule.

Pathogenic Role of Galectin-4 in Intestinal Inflammation

The expression of galectin-4 (tandem repeat type) is restricted to the digestive tract *(58,59)* where epithelial cells are responsible

Fig. 2. Glycosylation is controlled by a wide spectrum of glycosylation-associated enzymes. Expression pattern of these enzymes is influenced by several inflammatory stimuli. Therefore, it is possible that intestinal inflammation may suppress the expression of some glycosylation-associated enzymes that are involved in the maturation of O-glycan from immature core-1 structure. This altered enzyme expression may allow intestinal $CD4^+$ T cells to respond to galectin-4 by enhancing the exposure of core-1 O-glycan on their glycoreceptor(s).

Fig. 1.

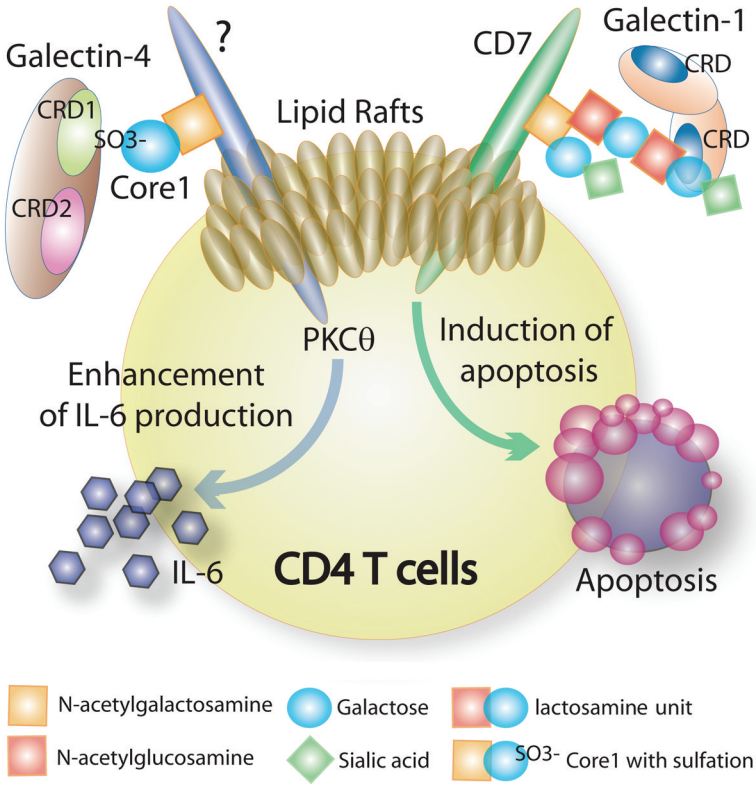
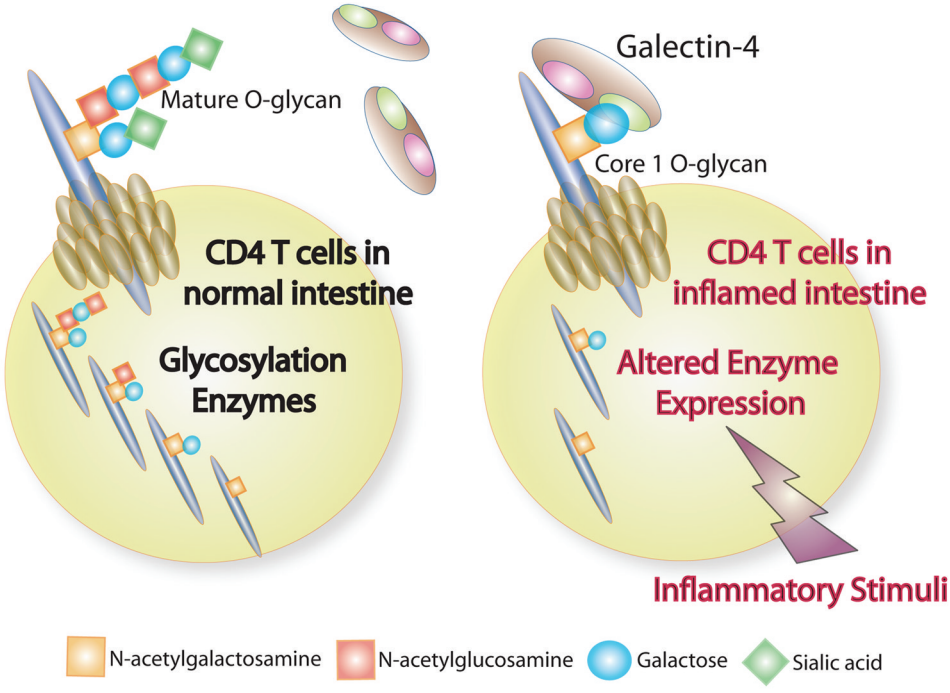

Galectin-4
?
CD7
Galectin-1
CRD
CRD1
SO3-
Core1
Lipid Rafts
CRD
CRD2
PKCθ
Induction of
apoptosis
Enhancement
of IL-6 production
IL-6
CD4 T cells
Apoptosis
N-acetylgalactosamine
Galactose
lactosamine unit
N-acetylglucosamine
Sialic acid
SO3- Core1 with sulfation

Fig. 2.


Mature O-glycan
Galectin-4
Core 1 O-glycan
CD4 T cells in
normal intestine
CD4 T cells in
inflamed intestine
Glycosylation
Enzymes
Altered Enzyme
Expression
Inflammatory Stimuli
N-acetylgalactosamine
N-acetylglucosamine
Galactose
Sialic acid

for this production *(12,59).* Galectin-4 can be secreted from both basolateral and apical sides of the intestinal epithelial cells through a nonclassical secretary pathway *(60).* In contrast to galectin-1 *(16),* 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 diseased colons *(12).* 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 *(12).* Neutralization of galectin-4 activity in vivo by administration of the specific antibody suppresses the progression of chronic intestinal inflammation that spontaneously develops in B cell–deficient TCRα double knockout (μDKO) mice *(12).* In contrast, pretreatment with this antibody fails to abolish the development of intestinal inflammation 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 dextran sulfate sodium (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 *(16).* Galectin-1 (prototype) is structurally characterized by homodimers with identical CRDs and binds to a lactosamine unit within mature core two-branched 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 *(61,62)* (Fig. 1). 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 determinant of galectin-mediated immune function *(40)* (Fig. 1).

Galectin-4 specifically stimulates $CD4^+$ T cells but not other immune cells such as B cells or macrophages to produce IL-6 *(12),* a well-known cytokine involved in the pathogenesis of intestinal inflammation *(63–65).* Importantly, only $CD4^+$ T cells that are present in the inflamed, but not non-inflamed, intestine can respond to galectin-4 *(12).* 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 intestine as compared to non-inflamed intestine and spleen. In addition, galectin-4 specifically binds to the lipid rafts on the $CD4^+$ T cells to activate the protein kinase C (PKC) θ-associated signaling cascade *(12).* Notably, galectin-4 has been demonstrated to interact with lipid rafts of enterocytes as well and subsequently stabilize the raft formation to generate "superrafts" *(66,67).* A recent study has found that galectin-4 interacts with carcinoembryonic antigen (CEA) of colon adenocarcinoma *(68).* Alternatively, it remains obscured 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 intestinal con-

ditions, 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 the inflammatory condition. However, galectin-4 can bind to the lipid rafts on both $CD4^+$ T cells from inflamed and normal intestines albeit the binding intensity is much higher on diseased $CD4^+$ T cells *(12)*. In addition, expression pattern of the enzymes that are involved in the glycan synthesis is altered by several inflammatory stimuli *(18,19,22–26)*. 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 (Fig. 2). 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 the inflammatory conditions as compared to a state of health (our unpublished observation).

Chitin, Chitinases, and Chitinase-like Molecules

Chitin, a β-1,4-linked polymer of N-acetylglucosamine, is the second most abundant carbohydrate polymer next to cellulose in nature, but entirely lacks in mammals. Viruses, fungi, insects, nematodes, and house dust mites contain chitin as a structural component of these species *(69–71)*.

Chitin is involved in some immune responses. Small size (1–10 μm), but not nonphagocytoble size (>50 μm), of chitin induces Th1 response in vitro and in vivo comparable to that induced by heat killed *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) and HK–Propionibacterum acnes suspensions *(72,73)*. In addition, oral administration of chitin significantly downregulates serum IgE level and lung eosinophilia in an experimental allergic asthma model *(71)*. Therefore, it is possible that chitin contributes to an enhancement of Th1 immune responses by dampening Th2 immune responses.

Enzymes capable of degrading chitin are classified to chitinases. Chitin-containing organisms (e.g., parasites) produce chitinases to remodel the chitin-containing structures for their morphogenesis *(71,74)*. Chitinases are also produced by bacteria and plants for their defense against chitin-containing pathogens and for the maintenance the ecological balance *(69,70)*. Therefore, chitinases have been considered to play a crucial role in innate immune responses in lower life forms to control the infection with chitin-containing pathogens *(69–71,75)*. Because chitin is not produced by mammals, chitinase expression was initially believed to be restricted to the lower life forms. However, chitinases and chitinase-like proteins (CLP) have recently been noted even in mice and humans (Table 1) *(76)*. The mammalian chitinases and CLP are grouped in "glycohydrolase family 18" that is characterized by an eightfold alpha/beta barrel structure *(76)*. Mammalian chitotriosidase and acidic mammalian chitinase (AMCase) possess chitinase (glycohydrolase) enzymatic activity, whereas other mammalian chitinases or CLP do not exhibit this activity *(77,78)*. Mammalian chitinases with enzymatic activity have a chitin-binding domain that contains six cysteine residues responsible for their binding to chitin *(79)*. In contrast, CLP does not contain such typical chitin-binding domains *(80)*. However, the CLP can still interact with chitin via van der Waals interactions between the side chains of aromatic acid residues in a binding groove of

Table 1. Members of mammalian chitinases in human and mouse

Chitinases	Synonyms	References
Human chitinases		
Acidic mammalian chitinase	CHIA, AMCase, TSA1902	*83, 100*
Chitinase 1 (chitotriosidase)	CHIT1, Chi3, MGC125322, FLJ00314	*101, 102*
Chitinase 3-like-1	CHI3L1, YKL40, HC-gp39	*88, 103*
Chitinase 3-like-2	CHI3L2, YKL39	*104*
Oviductal glycoprotein 1	OVGP1, EGP, OGP, MUC9, CHIT5	*105, 106*
Stabilin-1 interacting chitinase-like protein	SI-CLP	*80*
Mouse chitinases		
Acidic mammalian chitinase	CHIA, AMCase	*83*
Chitotriosidase	CHIT1	*107*
Chitinase 3-like-1	CHI3L1, Brp39	*108*
Chitinase 3-like-3	CHI3L3, Ym-1, ECF-L	*109*
Chitinase 3-like-4	CHI3L4, Ym-2	*110, 111*
Oviductin/ Oviductal glycoprotein	OVGP1, CHIT5, OGP	*112, 113*

CLP and GlcNAc within chitin *(78, 81)*. Based on these characteristics (ability to interact with oligomer or monomer of GlcNAc and absence of glycohydrolase activity), CLP family has been called "chi-lectins" *(82)*.

Chitinase in Th2 Inflammation

Chitotriosidase and AMCase are typical chitinases with glycohydrolase activity *(83)*. AMCase is synthesized as 50 kDa protein in both human and mouse. In contrast to chitotriosidase, AMCase is extremely acid stable and has a distinct second pH optimum around pH2 in chitinolytic enzymatic activity *(83)*. A recent study shows that AMCase expression is induced through a Th2-specific, interleukin-13 (IL-13)–mediated pathway in allergic asthma patients and the experimental model *(84)*. Bronchial epithelial cells and pulmonary macrophages are mainly responsible for the AMCase production. Neutralization of AMCase activity in vivo by administration of anti-AMCase antibody or a pan-chitinase inhibitor (allosamidine) significantly ameliorates airway inflammation as well as airway hyper responsiveness. AMCase directly stimulates the lung epithelial cells to produce monocyte chemotactic protein (MCP)-10 and eotaxin, and these induced chemokines may subsequently contribute to the pathogenesis of bronchial asthma *(84)*. Therefore, chitinases have been proposed as one of therapeutic targets in Th2-mediated inflammation *(84)*.

Chitinase 3-like-1 (CHI3L1) in Acute and Chronic Intestinal Inflammation

Through DNA microarray analysis, we have found that chitinase 3-like-1 (CHI3L1/YKL-40/HC-gp39) expression is specifically induced only under intestinal inflammatory conditions *(14)*. CHI3L1 is expressed by both lamina propria cells (mainly macrophages) and epithelial cells (CECs) in the colon of several experimental IBD models including TCRα KO and IL-10 KO mice and DSS-colitis model *(14)*. In contrast, the expression of CHI3L1 is undetectable in the normal colon of not only WT mice but also of these IBD models without colitis. In addition, like experimental IBD models, colonic CHI3L1 mRNA expression is specifically detectable in active UC and CD

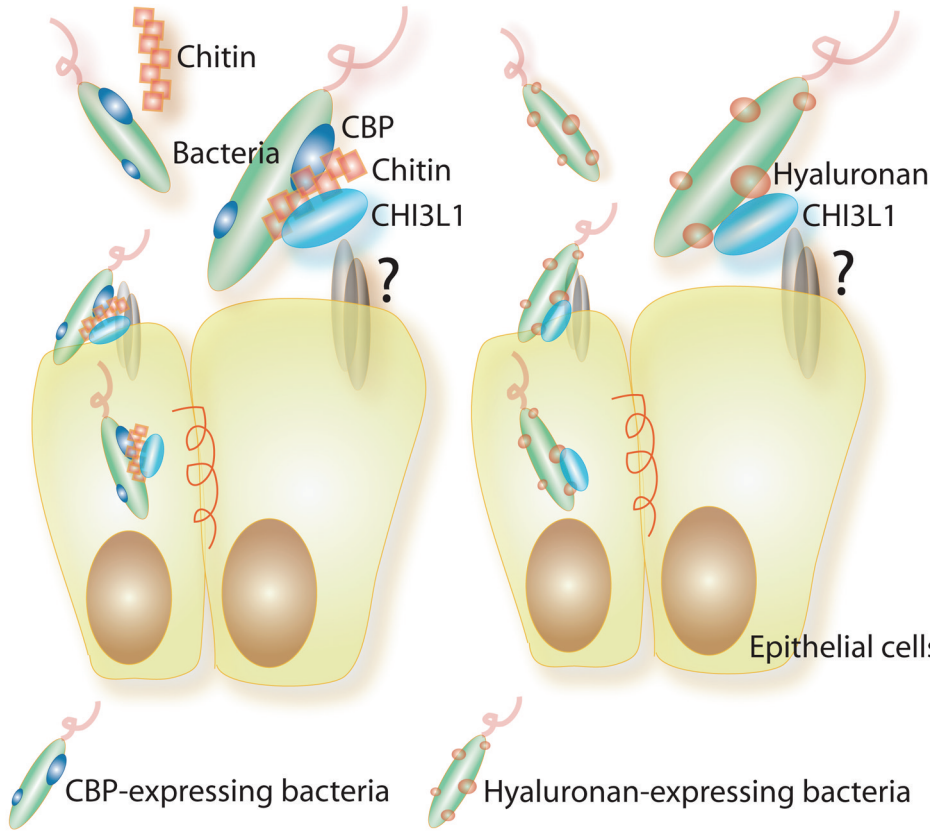


Fig. 3. CBP-expressing bacteria (left panel) may directly bind to chitin. CHI3L1 then interacts with the chitin/CBP complex on the bacteria to enhance its adhesion and invasion to CEC. Alternatively, CHI3L1 may directly bind to hyaluronan present in the capsule of bacteria (right panel). This interaction may subsequently enhance the adhesion and invasion of bacteria to CEC.

patients but not inactive UC or CD patients or control subjects *(14)*. A positive correlation between serum CHI3L1 and C-reactive protein (CRP, a marker for the severity of inflammation) levels in UC patients has been reported *(85, 86)*. Notably, neutralization of CHI3L1 activity in vivo by anti-CHI3L1 antibody administration significantly suppresses DSS-induced acute intestinal inflammation *(14)*.

CHI3L1, a member of CLP family, is N-glycosylated at Asn^{60} residue and disulfide bonds are formed between Cys^{26} and Cys^{51} and between Cys^{300} and Cys^{364}. CHI3L1 binds to long carbohydrates such as chitin and chitooligosaccharides *(87, 88)*. CHI3L1 also interacts with glycosaminoglycans such as heparin and hyaluronan *(82, 87, 88)*. Furthermore, Bigg et al. have reported an ability of CHI3L1 to bind to collagen type I, II, and III *(89)*. Unexpectedly, our study has demonstrated that CHI3L1 significantly enhances the adhesion and invasion of *Salmonella typhimurium* and adherent invasive *Escherichia coli* (AIEC) to CEC in vitro and in vivo. AIEC have been proposed as a potentially pathogenic bacteria in CD due to the ability to strongly adhere to intestinal epithelial cells and subsequently invade into macrophages *(90–92)*. In contrast,

CHI3L1 does not affect the adhesion and invasion of non-pathogenic *E. coli* such as DH10B and DH5α strains to CEC *(14)*. These in vitro data are further confirmed by in vivo experiments; anti-CHI3L1 Ab treatment significantly reduces the translocation of orally inoculated *S. typhimurium* to host peripheral tissues (e.g., spleen, mescenteric lymph nodes, liver, and colon) *(14)*. Therefore, it is possible that adhesion/invasion of pathogenic and potentially pathogenic, but not non-pathogenic, bacteria to host may be enhanced by their interaction with CHI3L1.

Bacteria do not contain chitin. However, *Serratia marcescens* expresses chitin-binding protein-21 (CBP-21) and the majority of chitinase-producing pathogenic microorganisms contain a gene encoding the homolog of CBP-21, suggesting a potential binding ability of pathogenic bacteria to chitin *(93)*. Therefore, it is possible that CHI3L1 may bind to a complex of CBP and chitin formed on bacteria and this binding may subsequently enhance the adhesion and invasion of these bacteria to CEC (Fig. 3). Alternatively, hyaluronan is present in the capsule of some bacterial strains such as *Streptococci* and CHI3L1 contains two potentially hyaluronan-binding domains *(94)*. Therefore, it is also possible that CHI3L1 may enhance the adhesion/invasion of specific enteric bacteria with hyaluronan to CEC (Fig. 3). Studies are currently being conducted to define these possibilities for bacteria/CHI3L1 interaction and to identify the specific receptor(s) of CEC to bind to CHI3L1.

CHI3L1 is produced by cartilage of rheumatoid arthritis (RA) and osteoarthritis patients, but not healthy individuals *(95–97)*, consistent with our data that CHI3L1 expression is specifically induced only under inflammatory conditions. In RA, CHI3L1 has been proposed as an autoantigen capable of inducing pathogenic T cell responses *(98)*. Alternatively, CHI3L1 also has a potentially protective effect on the destruction of chondrocytes and synovial cells by decreasing the production of metalloproteinases and chemokines *(99)*. Therefore, it is possible that CHI3L1 may play distinctly different roles depending upon the cell types under inflammatory conditions.

Conclusion

Because mucus is a source of carbohydrates in our bodies, the role of mucus-associated carbohydrates produced by intestinal epithelial cells has been well studied in IBD. In this review, we provide additional, novel insights into the role of carbohydrates crosslinked by animal lectins in the immune responses that are involved in the pathogenesis of IBD. The carbohydrate/lectin interactions are actively involved in the determination (activation versus suppression) of $CD4^+$ T cell–mediated immune responses under intestinal inflammatory conditions. In addition, we discuss an unexpected aspect of a recently identified chi-lectin that binds to carbohydrate polymers and glycosaminoglycans and contributes to the enhancement of host/microbial interactions for the exacerbation of intestinal inflammation. These findings emphasize an importance of carbohydrate/protein interactions in intestinal inflammation. Strategies targeting carbohydrates might provide a rationale to develop novel therapeutic approaches for IBD patients.

Acknowledgments

This study was supported by NIH DK064351 (AM), DK064289 (EM), DK074454 (EM), the Eli and Edythe L. Broad Medical Research Program, and the Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital.

References

1. Podolsky DK: Inflammatory bowel disease. N Engl J Med 2002;347:417–429.
2. Strober W, Fuss IJ, Blumberg RS: The immunology of mucosal models of inflammation. Annu Rev Immunol 2002;20:495–549.
3. Mizoguchi A, Mizoguchi E, Bhan AK: Immune networks in animal models of inflammatory bowel disease. *Inflamm Bowel Dis* 2003;9:246–259.
4. Wilk JN, Bilsborough J, Viney JL: The mdra–/– mouse model of spontaneous colitis: a relevant and appropriate model to study inflammatory bowel disease. Immunol Res 2005;31:151–160.
5. Mizoguchi A, Mizoguchi E, Chiba C, et al: Cytokine imbalance and autoantibody production in TCR-α mutant mice with inflammatory bowel disease. J Exp Med 1996;183:847–856.
6. Bhan AK, Mizoguchi E, Smith RN, Mizoguchi A: Colitis in transgenic and knockout animals as models of human inflammatory bowel disease. Immunol Rev 1999;169:195–207.
7. Mizoguchi A, Mizoguchi E, Chiba C, Bhan AK: Appendix lymphoid follicle plays an important role for the development of inflammatory bowel disease in TCR-α mutant mice. J Exp Med 1996;184:707–715.
8. Mizoguchi A, Mizoguchi E, Smith RN, Preffer FI, Bhan AK: Suppressive role of B cells in chronic colitis of T cell receptor α mutant mice. J Exp Med 1997;186:1749–1756.
9. Mizoguchi A, Mizoguchi E, Takedatsu H, Blumberg RS, Bhan AK: Chronic intestinal inflammatory condition generates IL-10 producing regulatory B cell subset characterized by CD1d upregulation. Immunity 2002;16:219–230.
10. Mizoguchi A, Bhan AK: A case for regulatory B cells. J Immunol 2006;176:705–710.
11. Targan SR: The search for pathogenic antigens in ulcerative colitis. Gastroenterology 1998;114:1099–1100.
12. Hokama A, Mizoguchi E, et al: Induced reactivity of intestinal $CD4^+$ T cells with an epithelial cell lectin, galectin-4, contributes to exacerbation of intestinal inflammation. Immunity 2004;20:681–693.
13. Mizoguchi E, Xavier R, Reinecker H-C, et al: Colonic epithelial functional phenotype varies with type and phase of experimental colitis. Gastroenterology 2003;125:148–161.
14. Mizoguchi E: Chitinase 3-like-1 exacerbates intestinal inflammation by enhancing bacterial adhesion and invasion in colonic epithelial cells. Gastroenterology 2006;130:398–411.
15. Srikrishna G, Turvskaya O, Shaikh R, et al: Carboxylated glycans mediate colitis through activation of NF-κB. J Immunol 2005;175:5412–5422.
16. Santucci L, Fiorucci S, Rubinstein N, et al: Galectin-1 suppresses experimental colitis in mice. Gastroenterology 2003;124:1381–1394.
17. Einerhand AW, Renes IB, Makkink MK, van der Sluis M, Buller HA, Dekker J: Role of mucins in inflammatory bowel disease: important lessons from experimental models. Eur J Gastroenterol Hepatol 2002;14: 757–765.
18. Dell A, Morris HR: Glycoprotein structure determination by mass spectrometry. Science 2001;291: 2351–2356.
19. Helenius A, Aebi M: Intracellular functions of N-linked glycans. Science 2001;291:2364–2369.
20. Wells L, Vosseller K, Hart GW: Glycosylation of nucleocytoplasmic proteins: signal transduction and O-GlcNAc. Science 2001,291:2376–2378.
21. Bertozzi CR, Kiessling LL: Chemical glycobiology. Science 2001;291:2357–2363.
22. Lowe JB: Glycosylation, immunity, and autoimmunity. Cell 2001;104:809–812.
23. Baum, LG: Developing a taste for sweets. Immunity 2002;16:5–8.
24. Moody AM, Chui D, Reche PA, Priatel JJ, Marth JD, Reinherz EL: Developmentally regulated glycosylation of the CD8ab coreceptor stalk modulates ligand binding. Cell 2001;107:501–512.
25. Daniels MA, Devine L, Miller JD, et al: CD8 binding to MHC class I molecules is influenced by T cell maturation and glycosylation. Immunity 2001;15: 1051–1061.
26. Nakamura N, Yamakawa N, Sato T, Tojo H, Tachi C, Furukawa K: Differential gene expression of β-1,4-galactosyltransferase I, II and V during mouse brain development. J Neurochem 2001;76:29–38.
27. Rudd PM, Elliott T, Cresswell P, Wilson IA, Dwek RA: Glycosylation and the immune system. Science 2001;291:2370–2376.
28. Demetriou M, Granovsky M, Quaggin S, Dennis JW: Negative regulation of T-cell activation and autoimmunity by Mgat5 N-glycosylation. Nature 2001;409: 733–739.
29. Malý P, Thall AD, Petryniak B, et al: The (1,3)fucosyltransferase Fuc-TVII controls leukocyte trafficking through an essential role in L-, E-, and P-selectin ligand biosynthesis. Cell 1996;86:643–653.
30. Priatel JJ, Chui D, Hiraoka N, et al: The ST3Gal-I sialyltransferase controls $CD8^+$ T lymphocyte homeostasis by modulating O-glycan biosynthesis. Immunity 2000;12:273–283.
31. Khan AA, Bose C, Yam LS, Soloski MJ, Rupp F: Physiological regulation of the immunological synapse by agrin. Science 2001;292:1681–1686.
32. Chui D, Sellakumar G, Green RS, et al: Genetic remodeling of protein glycosylation in vivo induces autoimmune disease. Proc Natl Acd Sci USA 2001;98: 1142–1147.
33. Cobb BA, Kasper DL: Carbohydrates and immunity. Eur J Immunol 2005;35:352–356.
34. Feinberg H, Mitchell DA, Drickamer K, Weis WI: Structural basis for selective recognition of oligosaccharides by DC-SIGN and DC-SIGNR. Science 2001; 294:2163–2166.
35. Kwon DS, Gregorio G, Bitton N, Hendrickson WA, Littman DR: DS-SIGN-mediated internalization of

HIV is required for Trans-enhancement of T cell infection. Immunity 2002, 16:135–144.
36. Rogers NC, Slack EC, Edwards AD, et al: Syk-dependent cytokine induction by dectin-1 reveals a novel pattern recognition pathway for C type lectin. Immunity 2005;22:507–517.
37. Takahashi K, Michelow IC, Ezekowitz RA: The mannose-binding lectin: a prototype pattern recognition molecule. Curr Opin Immunol 2006;18:16–23.
38. Barondes SH, Castronovo V, Cooper DN, et al: Galectins: a family of animal β-galactoside-binding lectins. Cell 1994;76:597–598.
39. Barondes SH, Cooper DNW, Gitt MA, Leffler H: Galectins. J Biol Chem 1994;269:20807–20810.
40. Rabinovich GA, Baum LG, Tinari N, et al: Galectins and their ligands: amplifiers, silencers or turners of the inflammatory response? Trend Immunol 2002;23: 313–320.
41. Perillo NJ, Pace KE, Seihamer JJ, Baum LG: Apoptosis of T cells mediated by galectin-1. Nature 1995;378:736–739.
42. Perillo NL, Uittenbogaart CH, Nguyen JT, Baum LG: Galectin-1, an endogenous lectin produced by thymic epithelial cells, induces apoptosis of human thymocytes. J Exp Med 1997;185:1851–1858.
43. Perillo NL, Marcus ME, Baum LG: Galectins: versatile modulators of cell adhesion, cell proliferation, and cell death. J Mol Med 1998;76:402–412.
44. Chung CD, Patel VP, Moran M, Lewis LA, Miceli MC: Galectin-1 induces partial TCRα-chain phosphorylation and antagonizes processive TCR signal transduction. J Immunol 2000;165:3722–3729.
45. Swarte VVR, Mebius RE, Joziasse DH, Van den Eijnden DH, Kraal G: Lymphocyte triggering via L-selectin leads to enhance galectin-3-mediated binding to dendritic cells. Eur J Immunol 1998;28:2864–2871.
46. Cortegano I, Pozo V, Cardaba B, et al: Galectin-3 down-regulates IL-5 gene expression on different cell types. J Immunol 1998:161:385–389.
47. Sato S, Ouellet N, Pelletier I, Simard M, Rancourt A, Bergeron MG: Role of galectin-3 as an adhesion molecule for neutrophil extravasation during streptococcal pneumonia. J Immunol 2002;168:1813–1822.
48. Liu FT: Regulatory roles of galectins in the immune response. Int Arch Allergy Immunol 2005;136:385–400.
49. Stillman BN, Hsu DK, Pang M, et al: Galectin-3 and galectin-1 bind distinct cell surface glycoprotein receptors to induce T cell death. J Immunol 2006;176: 778–789.
50. Sturm A, Lensch M, Andre S, et al: Human galectin-2: novel inducer of T cell apoptosis with distinct profile of caspase activation. J Immunol 2004;173:3825–3837.
51. Carcamo C, Pardo E, Oyanadel C, et al: Galectin-8 binds beta 1 integrins and induces polarized spreading highlighted by asymmetric lamellipodia in Jurkat T cells. Exp Cell Res 2006;312:374–386.
52. Zhu C, Anderson AC, Schubart A, et al: The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. Nat Immunol 2005;6:1245–1252.
53. Chiariotti L, Salvatore P, Benvenuto G, Bruni CB: Control of galectin gene expression. Biochimie 1999;81: 381–388.
54. McHugh RC, Whitters MJ, Piccirillo CA, et al: $CD4^+CD25^+$ immunoregulatory T cells: gene expression analysis reveals a functional role for the glucocorticoid-induced TNF receptor. Immunity 2002;16: 311–323.
55. Nguyen JT, Evans DP, Galvan M, et al: CD45 modulates galectin-1-induced T cell death: regulation by expression of core 2 O-glycan. J Immunol 2001;167: 5697–5707.
56. Fulcher JA, Hashimi S, Levroney EL, et al: Galectin-1-matured human monocyte-derived dendritic cells have enhanced migration through extracellular matrix. J Immunol 2006;177:216–226.
57. Toscano MA, Commodaro AG, Ilarregui JM, et al: Galectin-1 suppresses autoimmune retinal disease by promoting concomitant Th2- and T regulatory-mediated anti-inflammatory responses. J Immunol 2006; 176:6323–6332.
58. Rechreche H, Mallo GV, Montalto C, Dagorn J-C, Iovanna JL: Cloning and expression of the mRNA of human galectin-4, an S-type lectin down-regulated in colorectal cancer. Eur J Biochem 1997;248:225–230.
59. Gitt MA, Colnot C, Poirier F, Nani KJ, Barondes SH, Leffler H: Galectin-4 and galectin-6 are two closely related lectins expressed in mouse gastrointestinal tract. J Biol Chem 1998;273:2954–2960.
60. Hughes RC: Secretion of the galectin family of mammalian carbohydrate-binding proteins. Biochim Biophy Acta 1999;1473:172–185.
61. Ideo H, Seko A, Yamashita K: Galectin-4 binds to sulfated glycosphingolipids and carcinoembryonic antigen in patches on the cell surface of human colon adenocarcinoma cells. J Biol Chem 2005;280:4730–4737.
62. Blixt O, Head S, Mondala T, et al: Printed covalent glycan array for ligand profiling of diverse glycan binding proteins. Proc Nalt Acad Sci USA 2004;101: 17033–17038.
63. Atreya R, Mudter J, Finotto S, et al: Blockade if interleukin 6 *trans* signaling suppress T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn disease and experimental colitis *in vivo.* Nat Med 2000;6:583–588.
64. Yamamoto M, Yoshizaki K, Kishimoto T, Ito H: IL-6 is required for the development of Th1 cell-mediated murine colitis. J Immunol 2000;164:4878–4882.
65. Suzuki A, Hanada T, Mitsuyama K, et al: CIS/SOCS3/SSI3 plays a negative regulatory role in STAT3 activation and intestinal inflammation. J Exp Med 2001;193: 471–481.
66. Hansen GH, Immerdal L, Thorsen E, et al: Lipid rafts exist as stable cholesterol-independent microdomains in the brush border membrane of enterocytes. J Biol Chem 2001;276:32338–32344.
67. Braccia A, Villani M, Immerdal L, et al: Microvillar membrane microdomains exist at physiological temperature. J Biol Chem 2003;278:15679–15684.

68. Ideo H, Seko A, Ohkura T, Matta KL, Yamashita K: High affinity binding of recombinant human galectin-4 to SO(3)(–)→3Galbeta1→3GalNAc pyranoside. Glycobiology 2002;12:199–208.
69. Debono M, Gordee RS: Antibiotics that inhibit fungal cell wall development. Annu Rev Microbiol 1994;48: 471–497.
70. Shhabuddin M, Toyoshima T, Aikawa M, Kaslow DC: Transmission blocking activity of a chitinase inhibitor and activation of malaria paracyte chitinase by mosquito protease. Proc Natl Acad Sci USA 1993;90: 4266–4270.
71. Shibata Y, Foster LA, Bradfield JF, Myrvik QN : Oral administration of chitin downregulates serum IgE levels and lung eosinophilia in the allergic mouse. J Immunol 2000;164:1314–1321.
72. Suzuki K, Suzuki M, Taiyoji M, Nikaidou N, Watanabe T: Chitin binding protein (CBP21) in the culture supernatant of *Serratia marcescens* 2170. Biosci Biotechnol Biochem 1998;62:128–135.
73. Shibata Y, Metzger WJ, Myrvik QN: Chitin-particle-induced cell mediated immunity is inhibited by mannan: mannose receptor-mediated phagocytosis initiates interleukin-12 production. J Immunol 1997;159:2462–2467.
74. Herrera-Estrella A, Chet I: Chitinases in biological control. EXS 1999;87:171–184.
75. Dessens JT, Mendoza J, Claudianos C, et al: Knockout of the rodent malaria paracyte chitinase pbCHT1 reduces infectivity to mosquitoes. Infect Immun 2001;69:4041–4047.
76. Henrissat B, Davies G: Structural and sequence-based classification of glycoside hydrolases. Curr Opin Struct Biol 1997;7:637–644.
77. Harbord M, Novelli M, Canas B, et al: Ym1 is neutrophil granule protein that crystallizes in $p47^{phox}$-deficient mice. J Biol Chem 2002;277:5468–5475.
78. Chang NA, Hung SI, Hwa KY, et al: A macrophage protein, Ym1, transiently Expressed during inflammation is a nobel mammalian lectin. J Biol Chem 2001;276:17497–17506.
79. Tjoelker LW, Gosting L, Frey S, et al: Structural and functional definition of the human chitinase chitin-binding domain. J Biol Chem 2000;275:514–520.
80. Kzhyshkowska J, Mamidi S, Gratchev A, et al: Novel stabilin-1 interacting chitinase-like protein (SI-CLP) is up-regulated in alternatively activated macrophages and secreted via lysosomal pathway. Blood 2006;107: 3221–3228.
81. Fusetti F, Pijning T, Kalk KH, Bos E, Dijkstra BW: Crystal structure and carbohydrate-binding properties of the human cartilage glycoprotein-39. J Biol Chem 2003;278:37753–37760.
82. Houston DR, Reclie AD, Krupa JC, van Aalten DM: Structure and ligand-induced conformational change of the 39-kDa glycoprotein from human articular chondrocytes. J Biol Chem 2003;278:30206–30212.
83. Boot RG, Blommaart EFC, Swart E, et al: Identification of a novel acidic mammalian chitinase distinct from chitotriosidase. J Biol Chem 2001;276: 6770–6778.
84. Zhu Z, Zheng T, Homer RJ, et al: Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. Science 2004;304:1678–1682.
85. Vind I, Johansen JS, Price PA, Munkholm P: Serum YKL-40, a potential new marker of disease activity in patients with inflammatory boel disease. Scand J Gastroenterol 2003;38:599–605.
86. Johansen JS: Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodeling, fibrosis and cancer. Danish Med Bull 2006;53: 172–209.
87. Rejman JJ, Hurley WL: Isolation and characterization of a novel 39 kilodalton whey protein from bovine mammary secretions collected during the nonlactating period. Biohem Biophys Res Commun 1998;150: 329–334.
88. Shackelton LM, Mann DM, Millis AJT: Identification of a 38-kDa heparin-binding glycoprotein (gp38k) in differentiating vascular smooth muscle cells as a member of a group of proteins associated with tissue remodeling. J Biol Chem 1995;270:13076–13083.
89. Bigg HF, Wait R, Rowan AD, Cawston TE. The mammalian chitinase-like-lectin, YKL-40, binds specifically to type I collagen and modulates the rate of type I collagen fibril formation. J Biol Chem 2006;28:21082–21095.
90. Boudeau J, Glasser AL, Masseret E, Joly B, Darfeuille-Michaud A: Invasive ability of an *Escherichia coli* strain isolated from the ileal mucosa of a patient with Crohn's disease. Infect Immun 1999;67:4499–4509.
91. Darfeuille-Michaud A, Boudeau J, Bulois P, et al: High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in crohn's disease. Gastroenterology 2004;127:412–421.
92. Swidsinski A, Ladhoff A, Pernthaler A, et al: Mucosal flora in inflammatory bowel disease. Gastroenterology 2002;22:44–54.
93. Vaaje-Kolstad G, Horn SJ, van Aalten DNF, Synstad B, Eijsink VGH: The non-catalytic chitin-binding protein CBP21 from Serratia marcescens is essential for chitin degradation. J Biol Chem 2005;280:28492–28497.
94. Malinda KM, Ponce L, Kleinman HK, Shackelton LM, Millis AJT: Gp38k, a protein synthesized by vascular smooth muscle cells, stimulates directional migration of human umbilical vein endothelial cells. Exp Cell Res 1999;250:168–173.
95. Johansen JS, Jensen HS, Price P: A new biomedical marker for joint injury. Analysis of YKL-40 in serum and synovial fluid. Br J Rheumatol 1993;32:949–955.
96. Johansen JS, Stoltenberg M, Hansen M, et al: Seum YKL-40 concentrations in patients with rheumatoid arthritis: relation to disease activity. Rheumatology 1999;38:618–626.
97. Volck B, Johansen JS, Stoltenberg M, et al: Studies on YKL-40 in knee joints of patients with rheumatoid arthritis and osteoarthritis. Involvement of YKL-40 in the joint pathology. Osteoarthritis Cartilage 2001;9: 203–214.

98. Tsark EC, Wang W, Teng YC, Arkfeld D, Dodge GR, Kovats S: Differential MHC class II-mediated presentation of rheumatoid arthritis autoantigens by human dendritic cells and macrophages. J Immunol 2002;169: 6625–6633.
99. Ling H, Recklies AD: The chitinase 3-like protein human cartilage glycoprotein 39 inhibits cellular responses to the inflammatory cytokines interleukin-1 and tumor necrosis factor-alpha. Biochem J 2004;380:651–659.
100. Saito A, Ozaki K, Fujiwara T, Nakamura Y, Tanigami A: Isolation and mapping of a human lung-specific gene, TSA1902, encoding a novel chitinase family member. Gene 1999;239:325–331.
101. Renkema GH, Boot RG, Muijsers AO, Donker-Koopman WE, Aerts J: Purification and characterization of human chitotriosidase, a novel member of the chitinase family of proteins. J Biol Chem 1995;270:2198–2202.
102. Boot RG, Renkema GH, Strijland A, van Zonneveld AJ, Aerts JM: Cloning of a cDNA encoding chitotriosidase, a human chitinase produced by macrophages. J Biol Chem 1995;270:26252–26256.
103. Hakala BE, White C, Recklies AD: Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, as a mammalian mmber of a chitinase protein family. J Biol Chem 1993;268:25803–25810.
104. Hu B, Trinh K, Figueira WF, Price PA: Isolation and sequence of a novel human chondrocyte protein related to mammalian members of the chitinase protein family. J Biol Chem 1996;271:19415–19420.
105. Verhage HG, Fazleabas AT, Donnelly K: The in vitro synthesis and release of proteins by the human oviduct. Endocrinology 1988;122:1639–1645.
106. Arias EB, Verhage HG, Jaffe RC: Complementary deoxyribonucleic acid cloning and molecular characterization of an estrogen-dependent human oviductal glycoprotein. Biol Reprod 1994;51:685–694.
107. Zheng T, Rabach M, Chen NY, et al: Molecular cloning aqnd functional characterization of mouse chitotriosidase. Gene 2005;357:37–46.
108. Aronson NN, Blanchard CJ, Madura JD; Homology modeling of glycosyl hydrolase family 18 enzymes and proteins. J Chem Inf Comput Sci 1997;37: 999–1005.
109. Jim HM, Copeland NG, Gilbert DJ, Jenkins NA, Kirkpatrick RB, Rosenberg M. Genetic characterization of the murine Ym1 gene and identification of a cluster of highly homogenous genes. Genomics 1998;54:316–322.
110. Ward JM, Yoon M, Anver MR, et al: Hyalinosis and Ym1/Ym2 gene expression in the stomach and respiratory tract of 129S4/SvJae and wild-type and CYP1A2-null B6, 129 mice. Am J Pathol 2001;158: 323–332.
111. Webb DC, McKenzie AN, Foster PS: Expression of the Ym2 lectin-binding protein is dependent on interleukin (IL)-4 and IL-13 signal transduction: identification of a novel allergy-asociated protein. J Biol Chem 2001;276:41969–41976.
112. Sendai Y, Komiya H, Suzuki K, et al: Molecular cloning and characterization of a mouse oviduct-specific glycoprotein. Biol Reprod 1995;53:285–294.
113. Takahashi K, Sendai Y, Matsuda Y, Hoshi H, Hiroi M, Araki Y: Mouse oviduct-specific glycoprotein gene: genomic organization and structure of the 5′-flanking regulatory region. Biol Reprod 2000;62:217–226.