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Review

Galectins, Galactoside-Binding Mammalian Lectins: Clinical Application of Multi-Functional Proteins

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Galectins are β-galactoside binding mammalian lectins and they share homologous carbohydrate recognition domains. To date, 11 members of galectin family have been cloned and identified. They have been shown to play roles in diverse biological events, such as embryogenesis, oncogenesis, adhesion and proliferation of the cells, receptor for advanced glycation end products, mRNA splicing, bacterial colonization, apoptosis, and in the modulation of the immune response. The mechanisms by which galectins exert these diverse effects remain largely unknown. However, the elucidation of multi-functional proteins belong to galectin family are going to open new fields in clinical science including diagnosis and therapy of autoimmune disorders, cancers, and vascular complications in diabetes and hypertension.

Key words: galectins, β-galactoside binding lectins, apoptosis, cell adhesion and proliferation, oncogenesis, autoimmune diseases, diabetic vascular complications

Carbohydrates are present on the cell surface and within extracellular matrix, and specific oligosaccharide structures on glycoproteins play specific cellular functions. Mammalian lectins are carbohydrate binding proteins that have affinity for specific oligosaccharides, and they have been classified into four groups: C-type lectins, P-type lectins, pentraxins, and galectins; the latter are formerly known as soluble-type (S-type or S-Lac) lectins [1, 2]. Since the polysaccharide chains constitute an integral component of many plasmalemmal and of the extracellular matrix (ECM) proteins, it is conceivable that by virtue of the interaction between lectins and their putative ligands they mediate a wide variety of biological process [3]. Among the lectins, the role of Ca^{2+} -dependent (C-type) mammalian lectins have been well documented in various biological processes. For instance, the adhesion of leukocytes to the activated endothelial cells has been shown to be mediated by selectins and their ligands, *i.e.* sialylated and fucosylated oligosaccharides, such as, sialyl-Lewis^x and sialyl-Lewis^a [4].

Galectins were first recognized as galactoside-binding proteins in various vertebrate tissues derived from amphibians, birds, fish, and mammalians. The galectin family was formally defined based on homologous amino acid sequence and galactoside biding activities [1, 2]. Human galectins had been identified and discovered in various contexts under multiple names, and they were re-named as galectin-1 to galectin-4 [1]. Since the formal naming of 4 mammalian galectins, the additional 7 galectin members, galectin-5 through galectin-11 [5-13], have been identified by molecular biology technique mainly utilizing sequence similarity (Table 1, Fig. 1). The growing members of galectin family interact with glycoconjugate on cell surface and ECM (extracellular matrix) proteins and influence diverse cellular functions, such as adhesion, migration, chemotaxis, proliferation, apoptosis, and differentiation. Furthermore, novel impli-

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Table I Structure and tissue distribution of galectins

Galectin	Structure	Tissue Distribution
1	1 CRD, dimer	Skeletal/smooth muscle. Motor/sensory neurons, kidney, placenta, thymus
2	1 CRD, dimer	Hepatoma, gastrointestinal tract
3	1 CRD + N-termminal domain	Activated macrophages, eosinophils, mast cells, epithelium of gastrointestinal and respiratory tracts, kidney, sensory neurons
4	2 CRDs	Intestinal and oral epithelium
5	1 CRD, monomer	Erythrocytes and oral epithelium
6	2 CRDs	Intestinal epithelium
7	1 CRD, monomer	Keratinocytes
8	2 CRDs	Lung, liver, kidney, heart, brain
9	2 CRDs	Thymus, liver, small intestine, kidney, spleen, lung, cardiac and skeletal muscle
10	1 CRD, dimer	Eosinophils and basophils
11	1 CRD	Gastrointestinal tract

CRD, carbohydrate recognition domain; N-terminal domain, Glycine-tyrosine-glutamine-proline-rich repeat sequence of galectin-3.

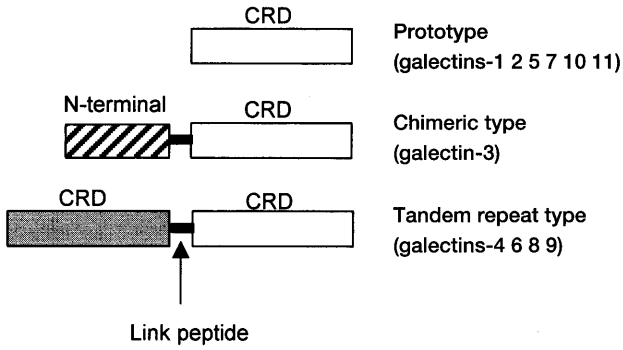

Fig. 1 Structures of galectins. The homologous carbohydrate recognition domains (CRD) are conserved in all galectins. Glycine-tyrosine-glutamine-proline-rich repeat sequence of galectin-3 (N-terminal) and link peptides of tandem repeat type is shown.

cations of galectins reveal that they play a key role in various pathological states, including autoimmune diseases, allergic reactions, inflammation, tumor spreading, atherosclerosis and diabetic complications. Although galectins share homologous carbohydrate binding domains and evolutionally conserved, the existence of dozens of galectins in a single species and their diverse tissue distribution suggests that each galectin family member participates in a variety of specific biological functions in a given cell-type or tissue. In this review article, we would like to summarize structural and functional features of galectins and possible application to clinical diagnosis and therapeutic interventions (Table 2).

Conserved structure of carbohydrate-binding domains of galectins

Galectins share characteristic carbohydrate binding domains consisting of ~130 amino acids, which are highly conserved. All the known galectins lack a signal peptide, have cytoplasmic distribution, and are also secreted as soluble proteins by a non-classical secretory pathway [14]. Structural analyses of various galectins indicate the presence of homodimers of carbohydrate-binding domains in galectin-1, -2, and 10, monomer of carbohydrate-binding domain in galectin-5 and 7 (prototype), and a single polypeptide chain with 2 carbohydrate-binding domains joined by a link peptide in galectin-4, -6, -8, and -9 (tandem repeat type). Galectin-3 has a carbohydrate-binding domain, and a short N-terminal segment, consisting of $PGAYPG(X)_{1-4}$ repeats, and an intervening stretch of amino acids, enriched with proline, glycine and tyrosine (chimeric type).

Homodimer of prototype or 2 distinct carbohydrate-binding domains in tandem-repeat type galectins can cross-link specific glycoprotein on both cell surface and ECM, activate differential signaling events, and eventually induce diverse biological response. Such multiple response may depend upon the cell types and a discrete spectrum of glycoconjugate receptors with β-galactoside sugars.

Expression Regulation of galectins

Expression analyses have revealed that certain

Table 2 Expression, function, and therapeutic application in various intractable diseases.

Galectins	Expression, function, and application in various diseases	References
Tumor invasion and metastasis		
Galectin-1, -3	Expressed in colon, thyroid and breast carcinomas	[27]
Galectin-3	Decrease metastatic potential in thyroid and breast carcinomas	[36, 37]
Galectin-3	Increase metastatic potential in melanoma and fibrosarcomas	[38]
Galectin-3	Decreased with the progression of colon, breast and thyroid carcimomas	[39]
Galectin-3	Increased with the progression of colon carcinoma	[40]
Galectin-1	Correlated with malignant potential of human gliomas	[41]
Modulation of immune system and the application to autoimmune diseases		
Galectin-1	Prevent myasthenia gravis and experimental encephalomyelitis	[42, 43]
Galectin-1	Suppress collagen-induced arthritis via T cell apoptosis	[48]
Galectin-9	Inhibit anti-GBM nephritis in WKY rats by inducing apoptosis of CD8-positive cells	[49]
Inflammation and allergic diseases		
Galectin-1, 3	Inhibit proliferation and infiltration of macrophages in the glomeruli in anti-GBM nephritis	[48]
Ecalectin (galectin-9)	A novel eosinophil chemoattractant and involved in eosinophil accumulation in various allergic diseases	[16]
Atherosclerosis and diabetic vascular complications		
Galectin-3	Expressed in carotid atherosclerotic lesions	[53]
Galectin-3	Receptor for advanced glycation end products and galectin-3 deficient mice are associated with accelerated diabetic glomerulopathy	[56]

GBM, glomerular basement membrane; WKY rats, Wistar-Kyoto rats.

galectins display restricted distribution, *e.g.*, galectin-2 in hepatoma, galectin-4 and -6 in small intestine, galectin-5 in erythrocytes, and galectin-7 in keratinocytes. Galectins with broad tissue distribution include galectin-1, expressed in cardiac, smooth and skeletal muscles, neurons, thymus, kidney, and placenta; galectin-3, present in blood cells, intestine, kidney, and neurons; and galectin-8, expressed in liver, kidney, cardiac muscle, lung, and brain [14]. We found that galectin-9 also reveals wide tissue distribution in thymus, liver, intestine, kidney, lung, cardiac and skeletal muscle. Interestingly, in addition to original form of galectin-9 with 14 amino acids link peptide, intestine isoform of 26 amino acid link peptide and ecalectin with 58 amino acids link peptide were also discovered [10, 15, 16].

Expression of galectins was found to be developmentally regulated and hallmark of specific stages in embryogenesis [17]. Galectins are present in intracellular space, as well as on cell surface and ECM. In addition, various stimuli, such as sodium butyrate [18], viral infections [19], tumor suppressor genes [20], and inflammatory agents [21], modulate expression levels and subcellular and extracelluar localizations. Thus, galectins should have distinct biological roles depending on their localization, although most reported functions are related to the process requiring the common recognition of carbohydrate on cell surface and it is also noted that most of data indicated in following sections are assigned to galectin-1 and -3, which have been extensively investigated [22].

Cell-cell and cell-matrix interactions

Adhesion and migration of cells are mediated by the interaction between cells and ECM glycoproteins and they are involved in inflammation and metastasis of cancer cells. Since galectins are secreted into extracellular space and recognize and cross-link glycoconjugates on cell surface and ECM glycoproteins, a variety of candidates of extracellular and cellular ligands were reported including laminin [23], fibronectin [24], lysosome-associated membrane proteins 1 and 2 [25] and CD45 [26]. Despite specific binding of galectins to these glycoconjugates, controversies are still remained whether galectins facilitate or inhibit cell adhesion [27]. Galectin-1 promotes the adhesion of ovarian carcinoma cells to extracellular matrix [28], whereas it inhibits the adhesion of myoblast to laminin by blocking the laminin receptor integrin $\alpha 7\beta 1$ from recognizing laminin [29]. Similarly, galectin-3 mediates adhesion of the neutrophils [30], but not of the melanoma cells to laminin [31, 32]. The binary action of galectin-1 and -3 may be related to its

concentration and expression and to the glycosylation of the counter-receptors [27]. Albeit these divergent actions, galectins seem to cross-link glycoconjugates of different cells or of cell and ECM to facilitate adhesion. However, in the presence of high concentration of galectins, it could be speculated that the cell surface glycoproteins on the same cells get cross-linked and the divalent carbohydrate-binding domains of galectins become occupied, and as a result they loose their adhesive potential [32].

Cell growth regulation

In addition to adhesion potential, the galectins also modulate cell proliferation and growth. Galectin-1 has been found to promote as well as inhibit cell proliferation. Its over-expression has been reported to induce transformation of 3T3 fibroblasts [33], while addition of galectin-1 in the culture media leads to the inhibition in the replication of mouse embryonic fibroblasts [34]. Such biphasic response in cell growth seems to be concentration dependent and galectin-1 is mitogenic at low physiological concentrations, while galectin-1 exerts growth inhibitory effect in a higher concentration range in human cells *in vitro* [35]. The effects of galectin-1 seem to be bifunctional depending upon the presense of concominant signals, dose, cell type, and expression of glycoconjugate receptors on cell surface [35].

Tumor invasion and metastasis

Since galectins are involved in cell adhesion and proliferation, tumorigenic potential of galectins and their role in tumor invasion have been extensively investigated. Galectin-1 and galectin-3 is expressed in many epithelial tumors such as colon, thyroid, and breast carcinomas [27]. However, there are still controversies whether galectin-3 promotes the metastatic potential and correlates with a poorly differentiate morphology or not. For example, the expression of galectin-3 is inversely correlated with metastatic potential in breast and thyroid carcinoma [36, 37], and in another study overexpression of galectin-3 conferred an increase metastatic potential to low metastatic cells in mouse melanoma and fibrosarcoma cells [38]. The level of galectin-3 expression decreases with the progression of colon, breast and thyroid carcimonoma [39], while it increases in and correlated with the neoplastic progression of colon carcinoma [40]. Recently, galectin-1 is found to correlate with the malignant potential of human gliomas and the expression of galectin-1 and antisense oligonucleotide of galectin-1 inhibits the growth of glioma cells [41]. As mentioned in the above sections, galectins reveal biphasic or binary effects upon cell adhesion and proliferation, the efficacy of galectins to tumor cells need to be carefully examined using different malignant cells and various concentrations of galectins.

Modulation of immune system and the application to autoimmune diseases

Among the various functions of galectins, the role in the modulation of the immune responce has been well documented. Research over the past decade indicated that the administration of galectin-1 prevented clinical and histopathological signs of myasthenia gravis and experimental encephalomyelitis, *i.e.*, T-cell-mediated antoimmune diseases [42, 43]. In line of this evidence, Perillo *et al.* introduced conceptional idea and a novel pradigm that galactoside binding lectins could affect the apoptotic threshold of T cells and they showed that galectin-1 induces apoptosis of PHA-activated peripheral T cells and of the thymocytes [26, 44]. Such an induction by the galectin seems to be specific and is conceivably mediated via its sugar-binding moiety on apoptosis-related receptors (death receptors) since apoptosis can be inhibited by lactose [26, 44]. In particular, it plays a vital role in the clonal deletion or negative selection of self-reactive T cells during thymocyte development, since the vast majority of cortical thymocytes (97%) die in thymus and only 3% are positively selected and migrate to the peripheral circulation [45]. During this clonal deletion, a number of adhesion molecules, including receptor and counter receptor pairs CD2 and LFA-3, and LFA-1 and intercellular adhesion molecule-1 (ICAM-1) that are expressed on the thymocytes and thymic epithelial cells, have been shown to participate in cell-cell interactions. In addition to cell surface protein-protein interactions, many investigators have suggested the potential role of carbohydrate-protein interactions in thymocyte-thymic epithelial (stromal) cell adhesion processes. Two subpopulations were particularly susceptible to galectin-1-induced apoptosis, *i.e.* non-selected thymocytes bearing the immature phenotype $CD3^-$ $CD4^{low}$ $CD8^{low}$ $CD69^-$ and negatively selected population of $CD3^{int}$ $CD4^{low}$ $CD8^{low}$ $CD69^-$ [44]. The potential candidate(s) for the counter receptor(s) may include leukosialin (CD43) or leukocyte common antigen

(CD45) since both bind to other galectins, *i.e.*, galectin-1 [26], and CD45 has been proposed to participate in apoptosis [46]. We also demonstrated that galectin-9 is also highly expressed on stromal cells in thymus and induce apoptosis of murine thymocytes [14, 15].

Although all members of the galectin family contain β-galactoside binding domains, they do not consistently induce apoptosis. For instance, galectin-3 does not induce apoptosis of the thymocytes. On the contrary, the galectin-3 has been reported to protect the Fas-antibody-mediated apoptosis in human T-cell leukemia cell line (Jurkat E6-1), transfected with galectin-3 cDNA [47]. Interestingly, galectin-3 and *bcl-2* share the NWGR motif that is highly conserved in *bcl-2* family. Conceivably, it is critical for the lactose-inhibitable intracellular heterodimerization of *bcl-2*/galectin-3 [47], and in negating Fas-antibody-mediated apoptosis. Homology alignment revealed that NWGR motif overlaps XWGXEER conserved sequences of the galectin family, and thus, the observed opposing biological effects of galectin-3 *vs* galectin-1 or -9 are rather intriguing. The motif in the overlapping segments of galectin-1 is AWGT, and of galectin-9 are QWGP and SWGQ in the respective N- and C-terminal domains. Therefore, the differential effects may be related to the NWGR motif, which is exclusively present in galectin-3.

Administration of galectin-1 or galectin-9 would be beneficial for the therapy of autoimmune diseases by terminating the T cell activation by inducing apoptosis. Indeed, galectin-1 is effective in experimental animal model of autoimmune encephalitis [42, 43], collagen-induced arthritis [48], and anti-glomerular basement membrane (GBM) glomerulonephritis [49]. In anti-GBM nephritis in WKY (Wistar Kyoto) rats, the administration of galectin-9 induced apoptosis of activated CD8 positive cells and ameliorated proteinuria and renal tissue injuries. Galectin-9 did not induce apoptosis of T cells in normal rats, while dexamethasone induced T cell apoptosis in both diseased and normal rats. This evidence suggested that galectin-9 is candidate for selective immunosuppresants with less chance of opportunistic infections [49].

Inflammation, atherosclerosis, and diabetic vascular complications

Galectins also play important roles in inflammation process suggested by the expression of galectin-3 on the surface of thioglycollate-elicited peritoneal macrophages [50]. In addition to galectin-3, rat macrophage galectin (RMGal) is expressed in activated macrophage and induces apoptosis of mature T cells in its carbohytrate-binding dependent manner [51]. We also demonstrated that administration of excess amount of recombinant proteins of galectin-1, -3, and -9 inhibited proliferation and infiltration of macrophages into the glomeruli in anti-GBM nephritis in WKY rats [49]. Besides macrophage activation and infiltration, gelectins are also involved in leukocyte chemotaxis and regulation of respiratory burst. Galectin-3 has been reported to activate the NADPH-oxidase and stimulate superoxide production from peripheral blood neutrophils [53]. Actually, mice lacking galectin-3 have so far been shown to have abnormalities in neutrophil accumulation during inflammation [53]. It is also interesting to note that ecalectin, a variant of human galectin-9, has been proposed as a novel eosinophil chemoattractant produced by T cells [16]. Ecalectin seems to be important for the eosinophil accumulation in various allergic diseases such as bronchial asthama, rhinitis and atopic dermatitis [16].

In atherosclerosis and diabetic nephropathy, macrophages are known to be present in atherosclerotic lesions and glomeruli in diabetes. The infiltration of macrophages in these macro- and micro-vasculatures has similarity with inflammatory response. Galectin-3 is strikingly localized in carotid atherosclerotic lesions mainly in macrophages and foam cells [54]. Furthermore, advanced glycation end-product receptor function of galectin-3 has been demonstrated in macrophages, astrocyte, and endothelilal cells by high-affinity binding for advanced glycation end products (AGEs) [55]. In diabetic condition, galectin-3 is up-regulated in mesangial cells, and galectin-3 deficiency in knockout mice are associated with accelerated diabetic glomerulopathy compared with wild-type animal [56]. These evidences suggest the possible usage of galectins in the therapy of diabetic vascular complications by modulating macrophage function and AGE clearance.

Concluding remarks

Although mammalian galectins are evolutionarily conserved and share homologous carbohydrate domains, they seem to play diverse physiological and pathological roles. Many questions are inevitably raised, however, they still remain to be answered. Why are there so many galectin members? All the redundant proteins are really

playing specific roles? Why do they exert binary actions, promoting *vs* inhibiting adhesion or proliferation of the cells? They are promoting or inhibiting the carcinogenesis? Is it possible to control the immune system by using galectins as molecular targets? Answering these questions would facilitate the discovery of novel therapeutic modalities for curing intractable diseases, such as autoimmune disorders, cancers, and vascular complications in diabetes and hypertension.

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