

Galectins

STRUCTURE AND FUNCTION OF A LARGE FAMILY OF ANIMAL LECTINS*

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Lectins are proteins that bind to specific carbohydrate structures and can thus recognize particular glycoconjugates among the vast array expressed in animal tissues. Most animal lectins can be classified into four distinct families (1): C-type lectins (including the selectins); P-type lectins; pentraxins; and galectins (2), formerly known as S-type or S-Lac lectins (1). The purpose of this short review is to provide a framework for integrating the rapid increase in knowledge of the diversity, structure, and function of the galectins. While the emphasis here is on mammalian galectins, important advances are also being made in studies of galectins in other species, including nematode (3) and sponge (4).

Structural Classification and Properties of Galectins

Members of the galectin family are defined by two properties: shared characteristic amino acid sequences and affinity for β -galactoside sugars (2). Individual mammalian galectins are named by consecutive numbering. Presently four mammalian galectins, galectin-1, -2, -3, and -4, have been well characterized. Of these, galectin-1 and galectin-3 have been rediscovered in several species and in different contexts, leading to multiple names and the potential for confusion. Fortunately, a consensus on naming has recently been reached (2) so that galectin-1 will be used for the same lectin that has been described in human, bovine, rat, and mouse tissues as L-14-I, L-14, galaptin, and BHL among other names; and galectin-3 will be used for the same lectin that has been described in human, dog, rat, and mouse tissues as Mac-2, eBP, CBP-35, CBP-30, and L-29 among other names. The general designation of the genes encoding galectins is *LGALS* (lectin, galactoside-binding, soluble), and gene numbering is being kept consistent with the numbering of the proteins, so that *LGALS1* encodes galectin-1, etc. (2). In humans, *LGALS1* and -2 have been mapped to the q12-q13 region of chromosome 22 (5), and *LGALS3* has been mapped to chromosome 1p13 (6).

The overall structures of galectin-1, -2, -3, and -4 are shown schematically in Fig. 1. Galectin-1 and -2 are homodimers composed of subunits of approximately 130 amino acids (Fig. 2). Each subunit folds as one compact globular domain (7, 8) as shown in Fig. 3. Galectin-3 and -4 include one or two such domains, as well as others (Fig. 1). The shared domain has been referred to as the carbohydrate-binding domain.

The sequence of each carbohydrate-binding domain has been shown to be mainly encoded by 3 exons (9–11) as shown in Fig. 2. Most of the residues that are conserved among galectins (marked by orange dots below sequences in Fig. 2) are found in the sequence encoded by the middle one of these three exons (*middle part* of Fig. 2). This sequence includes four contiguous β -strands and intervening loops in the structure of galectin-1 (8) and galectin-2 (7) (colored blue in Fig. 3 and marked by *blue bars* in Fig. 2) and contains all



FIG. 1. Schematic of the overall structures of galectin-1, -2, -3, and -4. The proteins are shown schematically as linear diagrams corresponding to single peptide chains (*top*) and as assembled proteins (*bottom*). The carbohydrate-binding domains of about 130 amino acid residues are *blue*, the proline-, glycine-, and tyrosine-rich repeating domain of galectin-3 (about 100 residues) and link peptide of galectin-4 (about 30 residues) are *orange*, and the N-terminal domain of galectin-3 (about 30 residues) is *green*.

residues that interact directly with a carbohydrate ligand (marked by *light blue dots* above the sequences in Fig. 2 and shown in detail in Fig. 4). The importance of some of these residues for carbohydrate binding activity is also supported by site-directed mutagenesis (12, 13). Deletion of sequences encoded by the other two exons that encode the carbohydrate-binding domain also impairs activity (12).

The amino acid identity in the carbohydrate-binding domains among different known galectins from one mammalian species ranges from about 20 to 40% (14). The identity of the same galectin from different mammalian species is 80–90%, so that it is fairly easy to identify the equivalent lectin in these different species. In contrast, it is more difficult to relate galectins from non-mammalian species to those from mammals. For example, two chicken galectins, C-16 and C-14, have been cloned and sequenced (3). Both have subunits of about 15 kDa and are 48% identical in sequence. Since each is about 50% identical to galectin-1 and 38% identical to galectin-2, it is not clear on the basis of sequence how they correspond with the mammalian galectins.

In addition to the carbohydrate-binding domain, galectin-3 has a short N-terminal domain and an intervening proline, glycine, and tyrosine-rich domain (Fig. 1). The latter domain consists of repeats of 7–10 amino acids with a consensus sequence of PGAYPG(X)_{1–4} (where X is any amino acid). The number of repeats varies with species, and hence the size of galectin-3 varies from 26.2 kDa in man to 30.3 kDa in dog (15). Neither of the additional domains is required for carbohydrate binding activity, which is preserved by the C-terminal domain generated upon proteolysis of the intact protein (16, 17). Galectin-3 is isolated as a monomer but undergoes multimerization on binding to surfaces that contain glycoconjugate ligands, and the N-terminal half of the protein is required for this property (16, 17). Galectin-4, a monomer of about 36 kDa, contains two carbohydrate-binding domains within a single peptide chain. These domains are connected by a link region that is homologous to the repeating domain of galectin-3 (14).

In addition to the four well characterized mammalian galectins already mentioned, three related mammalian proteins have been identified and tentatively called galectin-5, -6, and -7. Publications describing them are in preparation, and partial sequences are already deposited in GenBank for galectin-5 (accession number L21711) and galectin-7 (accession numbers L07769 and U06643).

A number of interesting proteins have structural similarity to galectins but do not fulfill the definition of galectins. The Charcot-Leyden protein, a major constituent of eosinophils, has been found to share significant sequence homology with galectin carbohydrate-binding domains (18) but lacks some of the critical residues that

* This minireview will be reprinted in the Minireview Compendium, which will be available in December, 1994. The molecular graphics images were produced using the MidasPlus, RibbonJr, Neon, and Ilabel programs from the Computer Graphics Laboratory, University of California, San Francisco (supported by National Institutes of Health Grant RR-01081).

	S1	F2					
Galectin-1	1 MACGLVASNLNLKPGECLRVRGEVAPDAKS	30					
Galectin-2	1 MTGELEVKNMDMKPGSTLKITGSIADGTDG	30					
Galectin-3	115 IVPYNLPLPGGVPRMLITILGTVKPNANR	144					
Galectin-4-dom-I	16 TLPYKRPIPGGLSVMMSIYIQQIAKDNMRR	45					
Galectin-4-dom-II	193 PVPYVGTIQLQGGLTARRTIIKKGYVLPTAKN	222					
	S3	S4	S5	S6a	S6b		F3
Galectin-1	FVLNLG-----KDSNNLCLHFNPRLNAHGDANTIVCNNSKDGGAWGTEQREAVF -PFQPGSVAE						
Galectin-2	FVINLG-----QGTDKLNLHFNPRLFSE-STIVCNSLDGNSNWGQEQRREDHL-CFSPGSEVK						
Galectin-3	IALDF-QRGN----D-VAFHFNPRLFEN-NRRVIVCNKLDNNWGREERQSVF-PFESGKPKF						
Galectin-4-dom-I	FHVNF-AVGQDEGAD-IAFHFNPRFDGW-D-KVVFNTMQSGQWGKEEKKKS-MPFQKGHHFE						
Galectin-4-dom-II	LIINF-KVGS-TG-D-IAFHMNPRI-G--D--CVVRNSYMGNSWGEERKIPYNPFGAGQFFD						
	F3	F4	F5	S2	F1		
Galectin-1	88 VCITFDQADLTIKLPDGYEFKFPNRNLNEAINYMAADGDFKIKCVAFE	135					
Galectin-2	84 FTVTFESDKFKVLPDGHELTFPNRNLGHSHLSYLSVRGGFMSSFKLKE	132					
Galectin-3	200 IQVLVEPDHFKVAVNDAHLLQYNHRVKKNLEISKLGISGDIDLTSASYTMI	250					
Galectin-4-dom-I	103 LVFMVMSEHYKVVVNGTPFYEHGHL-PLQMVTIQLQVDGDLEL--QSINFL	150					
Galectin-4-dom-II	277 LSIRCGTDRFKVFANGQHLFDFSHRFQAFQRVDMLEIKGDTL---SYVQI	324					

FIG. 2. Sequence of the carbohydrate-binding domains of galectin-1, -2, -3, and -4. The sequences are presented in three parts reflecting the genomic organization of galectin-1, -2, and -3, with the middle part corresponding to the exon encoding the carbohydrate-binding site (exon III for galectin-1 and -2 (9), and exon V for galectin-3 (10, 11)). The symbols above the sequences refer to structural features of galectin-2 (7) and are colored as in Fig. 3. The bars indicate sequences in the different β -strands (S1–5, S6a, S6b, and F1–5) in galectin-2 (as labeled in the right subunit in Fig. 3) and are colored blue (if encoded by exon III) or white. The residues indicated with dots above the sequences directly interact with the carbohydrate (light blue) or contribute to the dimer interface (purple). Residues that are identical in all five of the carbohydrate-binding domains shown (and most other galectins (14)) are indicated by orange dots below the sequences. The sequences are for human galectin-1 (9), galectin-2 (41), galectin-3 (79), and rat galectin-4 carbohydrate-binding domains I and II (14).

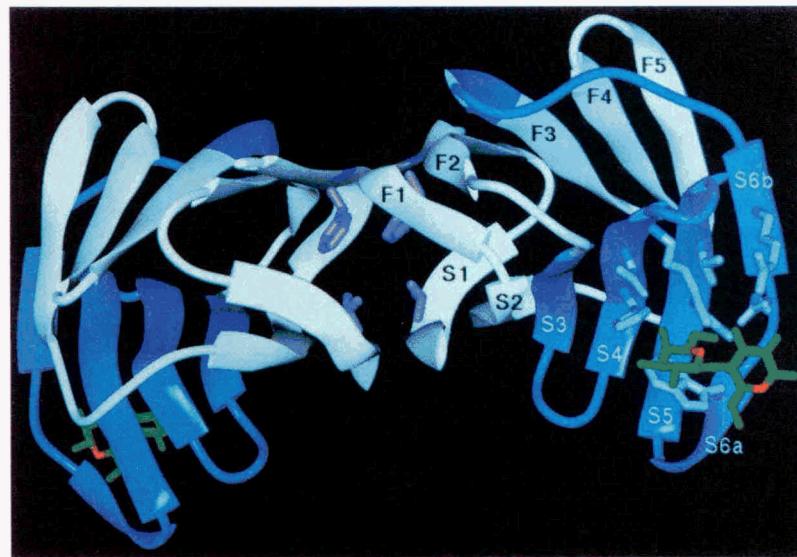
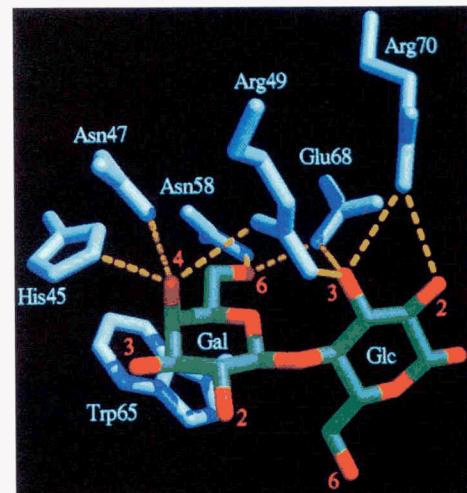


FIG. 3 (left). X-ray crystal structure of human galectin-2 (7). The figure shows a dimer of two globular carbohydrate-binding domains (blue and white ribbon diagram) with bound lactose (green stick representation with red ring oxygens). The part of each domain (subunit) encoded by exon III (middle part of Fig. 2) is shown in blue and the other parts in white. The dimer interface is in the middle and is highlighted by purple coloring of the major contributing residues (Val and Ile). Each subunit consists of a sandwich of two β -sheets of 6 and 5 strands. In the subunit to the right the strands of each sheet are labeled S1–5, S6a, and S6b (strand 6 is interrupted by a β -bulge), and F1–5. The amino acid side chains interacting with the carbohydrate are displayed as light blue stick figures. In the right subunit the carbohydrate-binding site is facing toward the viewer, whereas in the left subunit the carbohydrate-binding site is facing away from the viewer.

FIG. 4 (right). Fine structure of interaction between galectin-2 and lactose (7). The sugar residues are shown in green with red oxygen atoms and position numbers. The amino acid side chains interacting with the saccharide are shown in light blue. The principal hydrogen bonds between the amino acid side chains and the sugar residues are shown as yellow dotted lines. Figs. 3 and 4 were generated using UCSF MidasPlus (80).



may be required for sugar binding and has no known carbohydrate binding activity. Subunits of the legume lectins (19) and serum amyloid P-component (a pentraxin with lectin activity) (20) have the same topology and very similar tertiary structure as the galectin carbohydrate-binding domains but show no significant sequence homology. This suggests that galectins are a subset of a larger group of proteins sharing conserved folding motifs. Members of this group may include other pentraxins, as well as recently

discovered membrane proteins in the endoplasmic reticulum-Golgi that show sequence homology to the legume lectins (21).

Carbohydrate Binding Specificity of Galectins

All mammalian galectins whose carbohydrate binding specificity has been examined in detail recognize the same structural determinant on lactose and related β -galactosides (14, 22–26). X-ray crystallography confirms this interaction in the case of galectin-1

(8) and galectin-2 (7) (Fig. 4). The major interaction is with the galactose residue in lactose. However, interaction with the glucose residue in lactose is also significant, as reflected in the 100-fold higher affinity for lactose compared with galactose (22).

Further substitutions on the β -galactose residue differentially affect interaction with specific galectins, presumably reflecting differences in β -strands S2–4 (Figs. 2 and 3) which may contribute to an extended binding site (22, 26, 27). Such an extended site might explain the much higher affinity of galectin-3 for blood group A saccharides that are substituted with GalNAc 1–3 (22). It might also accommodate consecutive *N*-acetyllactosamine residues as found in polylactosaminoglycans, which are particularly good ligands for many galectins (22, 27).

Major Known Sites of Expression of Mammalian Galectins

Galectins are expressed with distinct but overlapping distributions in mammalian tissues. Although there has been a history of immunohistochemical localization of galectins, the recent discovery of potentially cross-reactive galectins complicates the interpretation of these results. Nevertheless, based on studies that have identified specific galectins by protein or nucleic acid sequence, it is clear that galectin-1 is abundant in skeletal, smooth, and cardiac muscle (28), motor and sensory neurons (29, 30), thymus, kidney, and placenta (28). In contrast, expression of galectin-3 is highest in activated macrophages, basophils, and mast cells (31, 32), some epithelial cells (*e.g.* intestine and kidney) (33–35), and in some sensory neurons (30, 36). In many tissues galectin synthesis is activated only during particular developmental or physiological stages (3, 28, 37–39), and low levels have been found for additional cell types, such as fibroblasts (40). Much less is known about the distribution of galectin-2, which is expressed in hepatomas (41), or galectin-4, which is expressed in intestinal epithelium (14).

Non-classical Secretion of Galectins

Although some galectins clearly are secreted, no galectins (mammalian or other) show any evidence of a typical secretion signal peptide (3, 4, 42, 43). This would normally imply that galectins are confined to the cytoplasm. However, galectin-1 and -3 are abundant not only in the cytosol but also extracellularly (37, 39, 44); and there is direct evidence that these galectins are externalized by non-classical secretory mechanisms (31, 33, 44, 45). Non-classical secretion of cytosolic proteins that play extracellular roles has also been demonstrated for interleukin-1 β , basic fibroblast growth factor, and other proteins (46, 47).

Non-classical secretion of galectin-1 has been best studied in skeletal muscle, where the protein moves from a diffusely intracellular to an extracellular location during *in vivo* development (38, 44, 49). In cultured myoblasts, galectin-1 remains in the cytosol until it is externalized during differentiation, apparently by membrane evagination (44, 48). The lectin can then interact with oligosaccharides on laminin (50) and perhaps other extracellular glycoproteins (51).

Secretion of galectin-3 by macrophages was first inferred when this protein was identified as a major macrophage cell surface antigen, Mac-2 (39). In kidney and polarized intestinal epithelial cells, there is direct evidence for its secretion, again by a non-classical pathway, in this case specifically to the apical surface (33, 45). Secretion increases strikingly in response to stress, such as inflammation (31) or heat shock (33).

There is also evidence for secretion of other galectins. For example, a 14-kDa chicken galectin has been found in intestinal epithelial cells and directly shown to be secreted into the intestinal lumen (52). A galectin in *Xenopus* skin (42) has been shown to be secreted by a specialized holocrine mechanism (53). In this case the cytosolic lectin and some other cytosolic constituents are released by rupture of glandular cells in the skin.

The reason galectins are secreted by non-classical pathways is not known. One possibility is to segregate them from complementary glycoconjugate ligands (externalized by the classical pathway) so that galectins and their ligands interact only after externalization. Another possibility is that, in contrast with the single classical secretion pathway, there may be multiple non-classical secretory mechanisms so that different galectins in a cell might be selectively secreted in response to specific signals, as suggested for other pro-

teins (54). Such specific secretion is known in bacteria where different cytosolic proteins are exported by specific transporters (55).

Ligands for Galectins

Despite the large number of β -galactoside-containing glycoconjugates present in the cellular milieu, few glycoproteins from cell extracts bind to particular galectins *in vitro* (50, 56–61), suggesting that these may be the interactions that are physiologically significant. It is not unreasonable to expect that there will be more than one significant ligand for each galectin, as for other molecules such as neurotransmitters that have many different receptors.

Among naturally occurring glycoconjugates, glycoproteins that contain polylactosamines are especially good ligands for galectins (22, 27). Of these, laminin, a glycoprotein with many polylactosamine chains, has been implicated as a natural ligand for galectin-1 (50, 62, 63) and is also bound by galectin-3 (25, 64). Galectin-1 has also been shown to bind to other glycoconjugates including polylactosamine-rich lysosome-associated membrane proteins (LAMPs) (56, 60) that are sometimes found on the cell surface, a lactosamine-containing glycolipid on olfactory neurons (65), and integrin $\alpha_7\beta_1$ on skeletal muscle cells (51). Galectin-3 is also known to interact with immunoglobulin E (32) and its receptor (66) and to copurify with a 90-kDa secreted glycoprotein (57, 58) found in epithelial cells. Other putative ligands from macrophages have been detected by chemical cross-linking (31).

Biological Functions of Galectins

Given their evolutionary conservation, wide tissue distribution, marked developmental regulation, and abundance in particular tissues, the galectins have been presumed to function in important biological processes. The fact that galectin-1, -2, and -4 are divalent and galectin-3 can form multivalent aggregates suggests that they act by cross-linking carbohydrate chains on cell surfaces and/or in the extracellular matrix. However, direct evidence for particular functions has only recently begun to accumulate even for the best studied galectins, galectin-1 and -3.

The general idea that animal lectins might function in modulating cell-cell and cell-matrix interactions has a long history (37) and has been well demonstrated for some members of a different lectin family, the selectin subgroup (1, 67) of C-type lectins. Recent studies suggest that galectins, too, participate in modulating cell adhesion but in novel ways that promise to open an entirely new area in cell biology. In addition, there is mounting evidence that galectins also participate in a number of other biological processes and that the function of a given galectin can vary from site to site depending on the nature of available ligands.

Galectin-1 has been shown to either promote or inhibit cell adhesion. In skeletal muscle, where galectin-1 is secreted during differentiation and binds to laminin (50), it inhibits cell-matrix interaction. This is presumably the result of binding of galectin-1 to polylactosamine chains on laminin, which interferes with laminin recognition by the major laminin receptor on myoblasts, integrin $\alpha_7\beta_1$ (51). Consequent inhibition of cell-matrix adhesion has been proposed to have a role in muscle development (50, 51). In contrast, galectin-1 can promote cell-matrix adhesion for other cell types, apparently by cross-linking cell surface and substrate glycoconjugates (27, 60, 65). In addition, there is evidence that galectin-1 might participate in regulating cell proliferation (68–70) and some immune functions (71, 72). However, mice lacking galectin-1 have been engineered, and thus far, no phenotype has been detected (73). Absence of a phenotype is frequently seen with gene knockout experiments and has been attributed to alternative proteins and biological mechanisms that compensate for the missing protein.

Galectin-3 might also play a role in multiple biological processes through interaction with specific ligands. As with galectin-1, binding of galectin-3 to polylactosamine chains on laminin can inhibit cell adhesion (25). On the other hand, affinity of galectin-3 for both IgE and an IgE receptor can trigger activation of mast cells and basophils (66) and play a role in inflammation (32). Upon secretion from intestinal epithelial cells galectin-3 has been postulated to play a role in bacterial colonization through its ability to bind both to mucins and bacteria in the intestinal lumen (33, 74). Galectin-3 might also perform intracellular functions, because it has been identified as a component of ribonucleoprotein particles (75) and is

concentrated in the nucleus during proliferation of some cell types (34, 75). Elevated expression of galectin-3 in tumors has been proposed to play a role in metastasis (76). Overexpression of recombinant galectin-3 in a weakly metastatic fibrosarcoma line resulted in a large increase in metastatic potential (77).

While galectin-1 is not believed to undergo any post-translational modification other than N-terminal methionine cleavage and acetylation, several post-translational modifications of galectin-3 might influence its function. Ser-6 is phosphorylated by casein kinase I (78), and the proline-, glycine-, and tyrosine-rich domain can be degraded by tissue collagenases (15), which would prevent galectin-3 self-aggregation (16, 17).

Future Directions

In the past few years, there has been progress in identifying new galectins in mammals and other species, cloning them, and ascertaining the structural features that determine carbohydrate binding. This work has provided new reagents and opportunities to answer the following questions. How large is the galectin gene family? What are the relevant glycoconjugate ligands for each of these lectins, and what are the physiological functions of galectin binding? What is the significance of the unusual manner of galectin secretion and how is it accomplished? Answering these questions should greatly advance our limited understanding not only of galectins but also of a larger issue, the significance of the complex glycoconjugates that surround all cells.

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