N-Tailed Monomeric Proto-Type-like Galectin

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Galectins are multi-purpose effectors acting via interactions with distinct counterreceptors based on proteinglycan/protein recognition. These processes are emerging to involve several regions on the protein so that the availability of a detailed structural characterization of a full-length galectin is essential.

β-hairpin β-sandwich blood group B

1. Introduction

Storage of biological information involves more than nucleic acids and proteins. The ubiquity of occurrence, the enormous diversity already at the level of oligomers and the fine-tuned spatiotemporal regulation of the appearance of distinct structures are solid arguments for a fundamental functional meaning of the glycan part of cellular glycoconjugates [1][2][3][4][5][6]. Indeed, by molecular complementarity of oligosaccharides with a contact region in the carbohydrate recognition domains (CRDs) of sugar-binding proteins (lectins), glycan-encoded messages are 'read' and 'translated' into cellular effects [6][7][8]. Toward this end, triggering specific bioeffects, not only the selection of the binding partner(s), appears to matter. Furthermore, the lectin's design, modularity and quaternary structure are first revealed in the case of the tetrameric leguminous lectin concanavalin A by a lower extent of crosslinking of certain cell surface receptors ^{[2][10]}. Fittingly, the context of presentation of the CRD shows a wide range of variability within lectin families. When considering the emerging multifunctionality of lectins, regions not involved in glycan binding can also affect their mode of action. Variability in design and the potential of regions beyond the glycan-binding site to be a physiologically relevant call for a detailed structural analysis within the lectin families in all their naturally occurring forms.

Focusing on the adhesion/growth-regulatory ga(lactose-binding) lectins, their common CRD is presented in three types of protein architecture, i.e., as (non)covalently associated homo/heterodimers (proto or tandem-repeat types) or as the chimera-type galectin-3 (Gal-3) with its N-terminal stalk attached to the CRD ^{[11][12][13][14]}. This highly dynamic, over 100-amino-acid-long sequence is composed of sections of known functionality; i.e., non-triple helical collagen-like repeats (for self-association) and an N-terminal peptide with two sites for serine phosphorylation (for intracellular compartmentalization) ^{[12][15][16][17]}. Two members of this lectin family are peculiar: galectin-related protein (GRP) and rat galectin-5 (rGal-5) present a short N-terminal extension (of up to 37 amino acids) of the canonical CRD of unknown function, which is clearly a challenge to study. Their special status as N-tailed proto-type-like proteins thus prompted to accomplish structural characterization of the full-length protein. In particular, it is of interest to define the structural features of the N-terminal extension, if adopted. Since respective attempts had so

far been unsuccessful in the cases of human and chicken GRP, which had been crystallized as a truncated version ^{[18][19]}, rGal-5 is the remaining target protein to try a full characterization of an N-tailed proto-type-like galectin.

This lectin was first purified from rat lung (denoted as RL-18) ^[20]. Sequencing of the cDNA from a rat reticulocyte library identified a strong homology (over 80%) to the C-terminal CRD of the tandem-repeat-type galectin-9 (Gal-9C), and monitoring among mammalian genomes disclosed its status as being uniquely present in rats ^{[21][22][23][24]}. The exon profile assumed that the rGal-5 gene originated from a species-specific gene duplication event followed by partial deletion to maintain the first exon coding for 13 amino acids and then the three exons of Gal-9C ^{[12][24]} (**Figure 1**). Notably, duplications and copy number variability of the galectin genes between species are not uncommon among mammals ^[25], rGal-5 being a specially processed species-specific form.



Figure 1. (**A**) Gene structures for rGal-5 and -9. The size of the exons (boxes) is indicated, and introns are drawn as lines (not drawn to scale). The N- and C-terminal CRDs of rGal-9 are labelled and given in different grey levels. Homologous exons are indicated (double arrows). (**B**) Sequence alignment of rGal-5 with rat and human Gal-9. Strictly conserved residues (red) and similar residues (boxed red letters) between rat proteins are shown. The upper lane represents the secondary structure elements of rGal-5 (α represents α -helices, β represents β -sheets and TT represents β -turns).

In solution, the current status of analysis describes rGal-5 as a monomer with a weak haemagglutinin activity ^{[20][22]} ^[26]. Non-sialylated glycan termini are binding partners, especially when clustered, as is the case for Nacetyllactosamine (LacNAc) of the three complex-type N-glycans of the nonavalent pan-galectin-binding glycoprotein asialofetuin, and rGal-5 binding distinguishes late-stage apoptotic from secondary necrotic peripheral blood lymphocytes ^{[27][28][29][30]}. Selectivity in glycan binding is also implied in rGal-5's involvement in the sorting processes during reticulocyte membrane remodeling by exosomal release ^[31].

2. Glycan Array Data

rGal-5 is first tested to determine its binding profile to chip-presented substances, mostly glycans up to the molecular mass of bacterial polysaccharides. By using an array platform with 609 compounds, the spacered histoblood-group B (type 2) tetrasaccharide, LacNAc-based dimers and the xenoantigen with α 1,3-linked galactose added to a LacNAc core were found to be frontrunners in terms of signal intensity, together with several bacterial polysaccharides (**Figure 2**). rGal-5, in contrast to GRP, which has lost the ability to bind β -galactosides ^[19], thus presents a profile with typical selectivity among this class of glycans. To report the contact pattern between rGal-5 and the selected carbohydrate ligands, we then carried out systematic screening to find conditions for crystallization. In these experimental series, we used the full-length protein to obtain structural information on the N-terminal tail.



Figure 2. Top-12 glycans in the composition of the glycan array that exhibit binding with rGal-5.

3. Overall Crystallographic Structure of Full-Length rGal-5

Ligand-free full-length rGal-5 crystallizes in the monoclinic $P2_1$ space group and diffracts to a resolution of 1.7 Å. An estimation of the crystal solvent content suggested the presence of six galectin molecules in the asymmetric

unit (**Figure 3**A). The rGal-5–lactose complex crystals belong to space group $P22_12_1$, with only two molecules present in the asymmetric unit (**Figure 4**A), and diffract to a 1.9 Å resolution.



Figure 3. Structure of ligand-free rGal-5. (**A**) Ribbon diagram of the asymmetric unit of the crystals containing six molecules(A–F) of rGal-5 (helix in orange, β -strands in blue and the N-terminal extension in green). (**B**) Strands (labelled F0 to F5 on one side and S1 to S6 on the other) forming the characteristic β -sheets are labelled (helix in orange, β -strands in green and the N-terminal extension in magenta). An extra strand is found, named F0, placed immediately in front of a loop protruding from the CRD. (**C**) Intermolecular interactions stabilize the extended loop conformation. These interactions involve residues Gly52 (G52), Pro9 (P9), His142 (H142), Tyr10 (Y10), Glu103 (E103), Asn12 (N12), Gly52 (G52), Asn74 (N74). Symmetry-related molecules are shown in yellow.



Figure 4. Structure of the rGal-5–lactose complex. (**A**) Overall architecture of the asymmetric unit of the rGal-5–lactose complex, with two CRDs; in one of them, the N-terminal residues (in magenta) adopt an extended geometry interacting with the edge of the β-sandwich. Strands that form the characteristic β-sheets are labelled (S1 to S6 on one strand, F1 to F5 on the other), and lactose molecules represented in sticks showing the 1.9 Å resolution $2F_0$ - F_c electron density map (in blue) contoured at 1.0 σ. (**B**) Inter- and intra-molecular interactions that stabilize the extended conformation of the N-terminal residues. These interactions involve residues Ser2 (S2), Ser3 (S3), Ser39 (S39), Thr6 (T6) and Asp40 (D40). Symmetry-related molecules are represented in different colors. (**C**) Close-up view of the ligand-binding site of rGal-5 to show interactions between the protein and lactose. Key protein residues [His57 (H57), Asn59 (N59), Arg61 (R61), Asn70 (N70), Glu80 (E80) Arg82 (R82), Arg43 (R43), Glu64 (E64) and Trp77 (W77)] and lactose are represented in stick mode and water molecules as red spheres. (**D**) Superposition of the ligand-binding sites of rGal-5 (yellow) and the rGal-5–lactose complex (grey). Side-chain positions of residues at this site are not affected by ligand binding, indicating a preformed geometry. In the ligand-free structure, the position of the residues is kept by interactions with water or glycerol molecules. Water molecules from this last structure are shown in purple for clarity.

The overall fold in ligand-free (**Figure 3**B) and -loaded rGal-5 (**Figure 4**A) is composed of two antiparallel β -sheets (F1 to F5 and S1 to S6 strands) that form the characteristic β -sandwich structure. A short 3₁₀ helix is placed between strands F5 and S2. Beyond analyzing the architecture of the contact site for glycans (see below), these crystals offered the opportunity to examine whether the N-terminal extension presents well-ordered elements or high flexibility.

4. Structure of Ligand-Free rGal-5

In the ligand-free structure, six rGal-5 molecules are arranged in the asymmetric unit, as shown in **Figure 3**A. The core of the different protein units can readily be superimposed onto each other, as revealed by the low average root mean square deviation (RMSD) value among them of 0.26 Å for all C α atoms. Differences are attributed mainly to the N-terminus, and the six protein monomers can be divided into two groups (**Figure 3**A), based on the experimental electron density. In the first group (chains A–C), the 11 residues at the N-terminus are not visible in the electron density map. Their likely extended and flexible structure in solution can indeed be derived from our SAXS data: the ab initio model of rGal-5 calculated on this basis exhibits, expectably, a globular shape. Most interestingly, though, a cylindrical extension on its top was seen in the model. When placing the CRD within the spherical region, the extended N-terminal section matches the geometry of the cylindrical part of the SAXS model (see below).

When inspecting the second group (chains D–F), the electron density for this peptide stretch was clearly observed: the three amino acids from Ser2 to Ser5 form an extra β -strand, named F0, running in antiparallel direction to the C-terminal F1 strand. Residues Thr6 to Asn12 are in a loop, placed in parallel to the axis of the β -sandwich and protruding more than 10 Å from the S1 and F0 strands (**Figure 3**B).

The conformation within this loop is stabilized by interactions with symmetry-related molecules: hydrogen bonds between Pro9–His142, Tyr10–Glu103 and Asn12–Gly52 as well as a water bridge between Asn12 and Asn74 (**Figure 3**C).

5. Structure of Ligand-Loaded rGal-5

The two CRDs present in the asymmetric unit, which have bound lactose (Lac), exhibit very similar features to ligand-free rGal-5 (**Figure 4**A), with an RMSD value of only 0.3 Å for all C α atoms. One of the two monomers in the asymmetric unit exhibits strong electron density for the first 10 residues so that their structure could be modelled. Intriguingly, these residues run parallel to the edge of the β -sandwich (**Figure 4**A) instead of forming the F0 strand and the protuberant loop observed in the ligand-free state. Intramolecular (hydrogen bonds between Ser2 and Ser3 with Ser39) and intermolecular contacts with symmetry-related molecules (hydrogen bond between Thr6 and Asp40) stabilize this special spatial arrangement (**Figure 4**B).

The carbohydrate-binding site in the concave face of the β -sheet is constituted by β -strands S4 to S6. The amino acids of the signature sequence, i.e., His57, Asn59, Arg61, Asn70, Glu80 and Arg82, directly interact with lactose through hydrogen bonding interactions. Additionally, Arg43, Gln45 and Glu64 form water-mediated hydrogen bonds with the ligand. As commonly found in galectin–lactose complexes, the indole ring of Trp77 stacks to the β -face of the pyranose ring of galactose (**Figure 4**C). In the absence of lactose, these residues form contacts with water (or glycerol molecules under conditions used for crystallization) molecules. Only minor rearrangements are observed for residues Arg43 and Glu64, which interact through water molecules with lactose (**Figure 4**D). Moving beyond defining the contact pattern, the thermodynamics of the ligand binding was analyzed by ITC.

6. ITC Measurements

rGal-5 interact with Lac with a dissociation constant of $136 \pm 16 \mu$ M, which is lowered in the case of LacNAc to $30.5 \pm 1.9 \mu$ M and $5.5 \pm 0.6 \mu$ M for the blood-group B tetrasaccharide (**Table 1**). This stepwise affinity enhancement can be explained by the increased number of contacts that these ligands make with additional amino acids. In this case, we used its complex with an avian galectin cGRIFIN (see below) shown in **Figure 5** and the respective model building to obtain the relevant information for the new additional contacts, as described below, between the tetrasaccharide and rGal5.



Figure 5. (**A**) Close-up view of the carbohydrate-binding site (CBD) of cGRIFIN showing the interactions between the histo-blood-group B tetrasaccharide and the active site residues [Met32 (M32), Glu34 (E34), His48 (H48), Asn50 (N50), Arg52 (R52), Ser55 (S55), Asn61 (N61), Trp68 (W68), Glu71 (E71) and Val73 (V73)]. (**B**) Structural comparison between cGRIFIN bound to the blood-group B tetrasaccharide complex (carbons in white) with the rGal-5/lactose complex (lactose in green, carbons of the interacting residues in orange). While residues such as His57, Asn59, Arg61, Asn70, Glu80 and Arg82 occupy almost the same position than residues in the former structure, the presence of charged residues (Arg53, Glu64 and Arg82) (highlighted in semitransparent yellow color)

may lead to direct or water-mediated interactions with the ligand. (**C**) Superposition of the cGRIFIN/tetrasaccharide structure (grey; the histo-blood-group B tetrasaccharide in cyan) with the rGal-5–lactose complex (yellow; lactose in green) highlighting the differences in the active site residues between cGRIFIN and rGal-5 [Met32 (M32) to Arg43 (R43), Ser55 (S55) to Glu64 (E64), and Val73 (V73) to Arg82 (R82)]. (**D**) The rGal-5/histo-blood-group B tetrasaccharide modeled by superposition with the cGRIFIN/tetrasaccharide structure. The active site residues involved in bindig of the ligand are: Arg43 (R43), Gln45 (Q45), His57 (H57), Asn59 (N59), Arg61 (R61), Glu64 (E64), Asn70 (N70), Trp77 (W77), Glu80 (E80) and Arg82 (R82). Residues Arg43, Glu64 and Arg82 might explain the affinity of rGal-5 for the histo-blood-group B (type 2) tetrasaccharide.

Ligand	K _d (μΜ)	Stoichiometry	ΔG ⁰ _{obs} (kcal/mol)	ΔH ⁰ _{obs} (kcal/mol)	−T∆S ⁰ _{obs} (kcal/mol)
Lactose	121 ± 5	0.95 ± 0.05	-5.35	-4.99 ± 0.08	-0.36
	151 ± 5	0.99 ± 0.06	-5.22	-5.03 ± 0.41	-0.18
LacNAc	28.6 ± 2.0	0.92 ± 0.01	-6.1	-10.0 ± 0.2	3.87
	32.3 ± 7.1	0.94 ± 0.20	-6.0	-10.5 ± 2.6	4.43
Tetrasacc haride	6.1 ± 0.2	0.94 ± 0.01	-7.11	-5.60 ± 0.03	-1.51
	5.0 ± 0.2	0.98 ± 0.01	-7.11	-5.74 ± 0.03	-1.37

Table 1. ITC data for ligand binding to recombinant rGal-5 (at 25 °C).

7. Structure of Ligand-Loaded cGRIFIN

Our attempts to crystallize rGal-5 bound to the blood-group B tetrasaccharide were unsuccessful. Thus, we decided to test chicken GRIFIN (cGRIFIN) as a model for the binding of this compound. This very stable protein has been previously crystallized in several conditions ^[32]. We were able to obtain crystals of cGRIFIN in the presence of the blood-group B tetrasaccharide. These crystals diffracted up to a resolution of 1.14 Å. This high-resolution data allowed us to build the sugar structure in the electron density in both carbohydrate-binding sites of the dimer. A comparison of the lactose-bound (PDB 5NLE) and the tetrasaccharide-bound cGRIFIN structures shows the absence of any significant structural change between these two structures, the RMSD value being 0.382 Å for all Cα atoms. The GalB moiety fully superposes with the galactose moiety of lactose, forming H-bonds with His46, Asn48, Arg50, Asn59 and Glu69. On the other hand, the GlcNacB moiety is rotated in the tetrasaccharide compared to the glucose moiety of lactose. Despite this change in the conformation, the H-bond with Glu69 is

conserved. The acetamido group is exposed to the solvent as it is the FucA moiety. The GalA moiety establishes two additional H-bonds, one of them linking the 6'-hydroxyl group with the NE atom of Trp66. The second one extends the binding site beyond the S4 strand, linking the 2'-hydroxyl group with Glu32 (**Figure 5**A).

The superposition of the lactose-bound rGal-5 structure with the blood-group B tetrasaccharide-bound cGRIFIN gave an RMSD of 0.69 Å for all Cα atoms, showing the similarity of both complexes. This similarity allows us to analyze the interactions that could be established between this ligand and rGal-5 (**Figure 5**B). The GalB and GlcNacB moieties of the tetrasaccharide could stablish the same interactions as those observed for lactose, including the one with Arg82. The GalA moiety is properly placed to interact with the NE atom of Trp66 and with the side chain of Gln45, a residue from the S3 strand. In addition, Arg43 faces the FucA ring and could interact with this moiety, expanding the ligand-protein surface of contact (**Figure 5**C). This last residue belongs to the loop connecting the S3 and F2 strands, the region interacting with the N-terminal residues in the ligand bound rGal-5 structure.

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