Minireview

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I-type Lectins*

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Carbohydrate-binding proteins (lectins) are widespread among prokaryotes and eucaryotes. Among the latter, lectins mediate many specific biological functions including cell-cell interactions, protein trafficking, and primitive defense reactions (1–6). We describe here a newly recognized family of mammalian lectins belonging to the immunoglobulin superfamily (IgSF)[1] (7, 8). Relative emphasis is placed on a prototypic member, CD22. Previously known mammalian lectins can be classified into distinct families based on protein sequence homologies (1) (Table I). Recently, another family has emerged from independent investigations of the proteins CD22 and sialoadhesin (Sn) (see Table II). Unlike previously recognized animal lectins, these belong to the IgSF, and several have a characteristic V_1-$C2_n$ domain structure (Fig. 1) (9–16), suggesting the name "I-type" lectins. All are integral membrane proteins, preferentially expressed on the plasma membrane, and some (CD33, CD22, and MAG) have large cytosolic domains with multiple potential and established phosphorylation sites (both Ser/Thr and Tyr) (17–19). Here we focus primarily on the lectin properties of the extracellular domains.

CD22 Is a Sialic Acid-binding Lectin

CD22 is a cell surface phosphoglycoprotein detected on the majority of resting mature B cells. It appears to facilitate antigen-dependent B cell triggering by association with the B cell antigen receptor and with cytoplasmic tyrosine kinases (10, 17, 20–22). It can also induce intercellular adhesion, recognizing ligands on activated lymphocytes, monocytes, and endothelial cells (10, 12, 23–25). Sialic acids (Sias) are known to repel cell-cell interactions because of their negative charge (26), and sialidase treatments usually enhance such interactions. In contrast, treatment of target cells with sialidase abolished CD22-mediated adhesion, and *de novo* expression of a sialyltransferase induced binding (23). A positive role for Sias in CD22 recognition was confirmed by loss of binding upon treating target cells with mild sodium periodate, under conditions that selectively oxidize the C_7-C_9 exocyclic side chain of Sias (27–31). The predominant isoform of human CD22 has 7 extracellular domains, and isoforms lacking domains 3 and/or 4 have been reported (10, 12, 24). A soluble chimeric form containing the three amino-terminal domains fused to the hinge and two Fc domains of IgG (CD22Rg) was employed to study its interactions with lymphoid cells (23). From radiolabeled T and B cell lines, CD22Rg specifically precipitated several glycoproteins including CD45, the leukocyte-specific phosphotyrosine phosphatase (27, 28, 32). CD45 was also identified as a specific target for CD22 in cell adhesion assays (23, 27, 32). Blocking experiments with a panel of monoclonal antibodies mapped the binding region to the first two domains of CD22 (24, 33). In all of these studies, CD22 binding was Sia-dependent.

IgSF Members Homologous to CD22 Are Also Lectins

Sn was first identified on populations of bone marrow and tissue macrophages, mediating adhesion to various lymphohematopoietic cells (34–39) in a Sia-dependent manner. Elucidation of the primary sequence demonstrated it to be a member of the IgSF with 17 extracellular Ig-like domains (14). The first four NH_2-terminal domains showed considerable homology with CD22 (14) (Figs. 2 and 3), and soluble immunoglobulin fusion proteins containing these domains preserved the sialic acid-dependent binding (14, 40).

Some previously known proteins have considerable sequence homology to Sn and CD22 (Figs. 2 and 3). MAG is involved in the assembly of the myelin sheath and may control the growth properties of neurons (41). CD33 is a marker of early myeloid cells and some monocyte populations (9, 16, 42). Schwann cell myelin protein (SMP) is an avian protein with close homology to mammalian MAG (15). The function(s) of CD33 and SMP are currently unknown. Based on their close homology to CD22 and Sn, MAG (40), CD33 (43), and SMP[2] were studied for sialic acid-dependent recognition and found to share this property. As shown in Table II, these molecules vary widely in their number of Ig-like domains. However, in each case, the first two amino-terminal Ig-like domains (V- and C2-type, respectively) appear to be necessary and sufficient for sialic acid-dependent binding (40, 43). In CD33, the entire extracellular domain consists of just these two domains. Sequence comparisons of the corresponding regions of these proteins (Fig. 1) indicate several regions of close homology not universally found in IgSF members (7, 8). Notably, some of these residues are located in the predicted interstrand regions that form the antigen-binding site in classical immunoglobulins. In each case, the first V-type domain contains an unusual intradomain disulfide bond between the predicted *b* and *e* β-strands (rather than *b* and *f* β-strands classically found in immunoglobulins) (7, 8). Also, an interdomain disulfide bond is reported in MAG between unpaired cysteines in domains 1 and 2 (44), which are conserved in CD22, SMP, Sn, and CD33. This unpaired Cys residue is also found in some other IgSF adhesion proteins (ICAM-1, ICAM-2, ICAM-3, VCAM-1, and MAdCAM-1) as part of a C-X_{3-4}-C motif essential for integrin binding. However, by deletional mutagenesis experiments, this motif is not essential for CD22-sialic acid binding (33).

The Role of Sialic Acids in Recognition

Sias are a family of 9-carbon carboxylic acids usually found in the terminal position on vertebrate glycoconjugates (26, 45), attached by different α-ketosidic linkages from the 2-position to the underlying sugar chain (Fig. 3). CD22 interactions involve recognition of the structural motif Siaα2–6Galβ1–4GlcNAcβ1- (29, 30), known to occur in varying numbers on the *N*-linked oligosaccharides of some cell surface glycoproteins (45). The α2–6 linkage is an absolute requirement (Figs. 2 and 3), and other α2–6-linked Sia structures (including linkage to GalNAc and GlcNAc) may also be recognized with a lower affinity (46). In contrast, Sn binds to Siaα2–3-containing structures (Fig. 2) (37, 40). The binding specificity of CD33 appears to be similar to that of Sn (43), while MAG binding shows a somewhat more restricted range (see Fig. 2) (40). Another well known family of sialic acid-binding lectins (the selectins) recognizes a further variation on these terminal sequences (not shown in Fig. 2), involving fucosylation of Siaα2-(3)4Galβ1–4GlcNAcβ1- (5).

Each of the many types of sialic acid linkage is generated by one or more unique sialyltransferases, many of which have been characterized and/or cloned (45). With β-galactoside α-2,6-sialyltransferase (ST6N), which transfers terminal α2–6-linked Sia to Galβ1–4GlcNAcβ1- (45), tissue-specific promotors have been identified (47), and activation and/or cell cycle-dependent expression in lymphoid and endothelial cells have been demonstrated (48–51). Regulated expression of α2–6-specific and α2–3-specific sialyltransferases in other tissues and organs has also been shown (45, 52, 53). However, expression of a given sialyltransferase does not guarantee expression of its product, as they must compete with other enzymes for the same acceptors in the Golgi apparatus (Fig. 2).

The most common Sia is *N*-acetylneuraminic acid (see Fig. 3), believed to be the biosynthetic precursor for more than 25 others in the family (26). A common natural modification, the 9-*O*-acetylation of the polyhydroxy side chain, abrogates CD22 recognition

* This minireview will be reprinted in the 1995 Minireview Compendium, which will be available in December, 1995.

[1] The abbreviations used are: IgSF, immunoglobulin superfamily; Sia, sialic acid, type unspecified; CD, cluster of differentiation antigen; Sn, sialoadhesin; MAG, myelin-associated glycoprotein; SMP, Schwann cell myelin protein; CD22Rg, recombinant soluble CD22 with three amino-terminal domains fused to the hinge and two Fc domains of IgG; ST6N, β-galactoside α-2,6-sialyltransferase; NCAM, neural cell-adhesion molecule.

[2] M. Tropak and J. Roder, personal communication.

TABLE I
Animal lectins and families

Lectin groups	Number of members	Defining features in protein sequence	Calcium dependence	Carbohydrate recognition
"C-type"	>20	C-type lectin sequence motif	Yes (most)	Variable
"S-type" (galectins)	~8	S-type lectin sequence motif	No	β-Galactoside
"P-type" (M6PRs)	2	Unique repeating motif	Variable	Mannose-6-P
"I-type"	>5	Immunoglobulin-like domains	No	Sialic acids and other?
Pentraxins	>5	Multimeric binding motifs	Yes (most)	Variable
S4GGnM receptor	?1	Unknown	No	4-*O*-Sulfated GalNAc
Hyaluronan-binding proteins, *e.g.* CD44	>5	Sequence homology among some	No	Hyaluronan
Heparin-binding proteins	>20	Basic amino acid clusters (variable)	No	Heparin and heparan sulfate
Calnexin and calcireticulin	2	Sequence homology to each other	Yes	Glucosylated oligosaccharides
Ganglioside-binding proteins	Unknown	No sequence information known	No	Sialylated glycolipids
Sulfoglucuronosyl lipid-binding protein	Unknown	No sequence information known	Yes	Sulfoglucuronosyl glycolipids

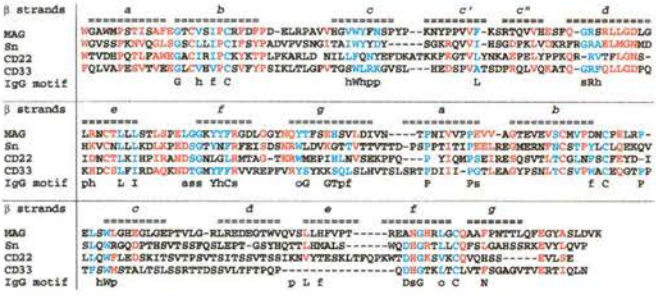

FIG. 1. **Sequence homologies among some I-type lectin.** Comparisons are made between the N-terminal two Ig-type domains (V and C2). All sequences are from the mouse. Predicted β strand assignments for each are indicated in the *top rows* by by *a, b, c, c'*, etc. Shared residues indicated in *blue* are homologous to previously established motifs of Ig V and C2 type domains (see *bottom rows*, where *a* is acidic, *f* is aliphatic, *h* is hydrophobic, *o* is aromatic, *p* is polar, and *s* is small (8)). Shared residues indicated in *red* appear to be common (identical or conserved) to these I-type lectins only.

(31). This fits with the earlier finding that chemical cleavage of this side chain abolishes binding (29, 30). Indeed, a major fraction of CD22 ligands on some murine lymphoid cells appears to be "masked" by 9-*O*-acetylation of the α2–6-linked sialic acids (31). Similar effects of 9-*O*-acetylation have been reported for Sn (54). Another common substitution of sialic acids is the conversion of the *N*-acetyl group at the 5-position to an *N*-glycolyl group. This modification has no major effect on recognition by human CD22 (31) but enhances binding by murine CD22 (54). The effects of the many other known natural modifications of sialic acids (26) remain unexplored.

Other IgSF Members That May Have Lectin-like Properties

The five I-type lectins described above share close homology as well as the ability to recognize sialic acid. Many classical immunoglobulins (antibodies) can of course recognize specific carbohydrate structures. However, the Ig superfamily itself is of ancient evolutionary origin, predating the establishment of the antibody response (7, 8, 55). Thus, lectin-like properties might be present in other IgSF members with more distant homologies. Indeed, the neural cell-adhesion molecule (NCAM) is reported to recognize high mannose oligosaccharides on other proteins, evidently via domain 4 (56, 57). This property is independent of its homotypic protein-based interactions. ICAM-1, another IgSF member with well known protein-based interactions, may also function as a receptor for the anionic oligosaccharide hyaluronan (58), as well as recognizing a heavily sialylated glycoprotein leukosialin (59). Indirect evidence suggests that the single anionic complex-type oligosaccharide present on P0 may be involved in modulating some of its binding functions (60–62). Furthermore NCAM and MAG interact with the anionic polysaccharide heparin (63). These findings suggest that carbohydrate recognition by IgSF members may be more widespread.

IgSF members are known to mediate homotypic or heterotypic binding via protein-protein interactions (7, 8). There is no reason why such roles would be completely supplanted in the I-type lectins by their carbohydrate recognition properties (NCAM and ICAM-1 may be examples). An interesting possibility is that the two types of recognition might even be related, *e.g.* the occupancy of the lectin sites on CD22 on activated B cells might unmask alternative cell-cell interactions mediated by this protein. In this regard, several internal C2-type domains of the Sia-binding I-type molecules share homology with the carcinoembryonic antigen-related family of IgSF proteins known to function as homotypic peptide binding partners (64).

Occupancy of the Lectin Site by Ligands in Cis

Activation of B cells increases expression of ST6N, the enzyme that generates α2–6-sialylated CD22 ligands (47, 53). Thus, recently activated B cells carry both CD22 and CD22 ligands (23, 47, 65), *e.g.* B cells in the mantle zone of secondary lymph node follicles (53, 65). Can CD22 can still mediate cell adhesion under such circumstances? Braesch-Andersen and Stamenkovic (66) first showed that when CD22 is transiently coexpressed with ST6N in COS cells, the lectin property is lost and can be restored by sialidase digestion. We confirmed and extended this observation both with Chinese hamster ovary cell lines stably expressing CD22 and/or ST6N (67) and with cultured B lymphoma cells co-expressing CD22 and its α2–6Sia ligands. Direct probing of the lectin function of CD22 on cell surfaces by ligand staining confirmed the loss of CD22 lectin function on the B lymphoma cells (67). Thus, the ST6N enzyme can regulate CD22-mediated adhesion either negatively (if expressed in cells with CD22) or positively (if expressed on potential target cells). Similar abrogation of lectin function *in cis* by endogenous ligands has been reported for CD33 and MAG (43) but not for sialoadhesin (37). With the latter, it is suggested that the length of the molecule allows its functional domains to protrude above the cellular glycocalyx containing the potential ligands (14, 40). Since the extracellular domains of CD33 and CD22 contain many *N*-linked oligosaccharides, they could potentially express their own ligands. Indeed, CD22Rg secreted from transfected cells co-expressing the ST6N sialyltransferase is functionally inactive until reactivated by sialidase digestion (66). It remains to be determined whether, in the native situation, an intermolecular inactivation is more important, involving recognition of other sialoglycoproteins. Regardless of the mechanism, the biological purpose of this "autoinactivation" of lectin function remains obscure. With NCAM, interactions of the fourth Ig-like domain with high mannose oligosaccharides on other cell surface molecules have been suggested to modulate the binding properties of other adhesion molecules such as L1 (57).

Further Studies of Carbohydrate Binding

Equilibrium dialysis studies with the soluble dimeric CD22Rg and the monomeric ligand α2–6 sialyllactose gave a stoichiometry of ~2:1, indicating that each native CD22 molecule has a single sialic acid-binding site (46) and predicting a single binding site for each of the other sialic acid-binding I-type lectins. The apparent affinity of the CD22-α2–6 sialyllactose interaction is ~30 μM.

The relatively weak affinity of the monovalent CD22 interaction indicates that, as with most lectins, functional avidity may be attained primarily by multivalent binding (3). Indeed, *N*-linked oligosaccharides with multiple α2–6-linked sialic acids interact better with CD22 in a column binding assay (30, 46). However, even though many cell surface and plasma glycoproteins carry such oligosaccharides, relatively few of these appear to be high affinity ligands (28, 29). Indeed, from among the large number of sialoglycoproteins in human plasma bearing α2–6-linked sialic acids, only two (IgM and haptoglobin) appear to bind with high affinity to bivalent recombinant CD22, and binding to IgM is diminished upon disruption of its pentameric structure (68). While the significance of these observations is uncertain, it shows that certain glycoproteins are able to create superior ligands for CD22 when properly sialylated. How does this high affinity recognition occur? Likely explanations are multivalency involving specific arrangements of α2–

TABLE II
Established and putative members of the I-type lectin family

Name	Tissue distribution	IgSF-type domains		Carbohydrate recognition properties	
		Types	Homology to CD22 in	Evidence for	Minimal carbohydrate structure(s) recognized
Established members					
CD22	B cells	$(V)_1$-$(C2)_{2-7}$		Binding	Siaα2–6Galβ1–4GlcNAc
Sialoadhesin	Macrophages in spleen, lymph nodes and bone marrow	$(V)_1$-$(C2)_{2-16}$	$(V)_1$-$(C2)_{2-3}$	Binding	Siaα2–3Galβ1–3(4)GlcNAc Siaα2–3Galβ1–3GalNAc
MAG	Peripheral nervous system	$(V)_1$-$(C2)_{2-5}$	$(V)_1$-$(C2)_{2-3}$	Binding	Siaα2–3Galβ1–3GalNAc
CD33	Myeloid cell lineage	$(V)_1$-$(C2)_2$	$(V)_1$-$(C2)_2$	Binding	Siaα2–3Galβ1–3(4)GlcNAc Siaα2–3Galβ1–3GalNAc
Possible members					
SCMP	Schwann cells	$(V)_1$-$(C2)_{2-5}$	$(V)_1$-$(C2)_{2-3}$	Binding	Sia linkage?
P0	Peripheral nervous system	$(V)_1$	Distant	Indirect	SO_3GlcUAβ1–3Galβ1-(HNK1 epitope)
NCAM	Peripheral and central nervous system	$(C2)_5$	$(C2)_{3-4}$	Indirect	High mannose oligosaccharide
ICAM-1	Blood cells, endothelium, etc.	$(C2)_5$	Distant	Indirect	Hyaluronan $(GlcNAc\beta1–3GlcUA\beta1–4)_n$ Leukosialin (sialylated mucin)

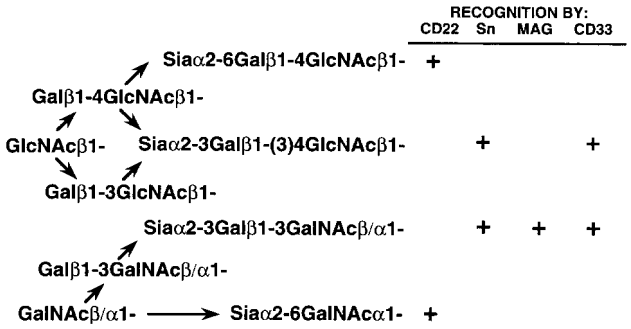

FIG. 2. **Biosynthetic pathways generating terminal sialylated oligosaccharides recognized by some I-type lectins.** GlcNAc or GalNAc residues of glycoproteins and/or glycolipids can be extended by several enzymes. Note that some theoretically possible structures, *e.g.* Sia2–6Galβ1–3GlcNAc, have not been reported in nature. The sialylated sequences shown are the minimal structural motifs necessary for binding. Natural high affinity ligands may be more complex.

6-linked sialic acids or additional protein-protein interactions. Given the plethora of ligands to which CD22 has been reported to bind, the latter appears less likely. The former is given considerable support by the finding that at least a portion of the CD22 on cell surfaces is presented in a multimeric form (46). These non-covalent homomultimers are found in non-lymphoid cells expressing transfected CD22, indicating that their formation does not require any other B cell-specific proteins (46).

Low Affinity Ligands and Soluble Inhibitors as Modulators of Biologically Relevant Recognition

Many cell surface proteins of CD22-positive B cells can bear α2–6-linked sialic acids, and some could potentially act as inhibitors or false ligands *in cis*. Likewise, CD33 is expressed on myeloid cells known to express α2–3-linked sialic acids (43). Furthermore, these lectins must function in a milieu of natural biological fluids (plasma, extracellular fluid, or lymph) that contain high concentrations of sialylated glycoproteins. Indeed, human plasma contains ~1 mM concentration of protein-bound α2–6-linked sialic acids (capable of strongly inhibiting CD22-based interactions) and ~0.5 mM concentration of α2–3-linked sialic acids (68). Interestingly, the major Sia-dependent plasma ligands for CD22 are haptoglobin (an acute phase reactant produced by the liver in inflammatory conditions) and IgM, the major downstream product of activation of CD22-positive B-lymphocytes (68). However, a large number of other plasma sialoglycoproteins can also interact with CD22 but with a lower affinity (30). Thus, although CD22 shows exquisite specificity in oligosaccharide recognition, it must function under markedly different conditions than other vertebrate lectins such as the asialoglycoprotein receptor (1), the mannose 6-phosphate receptors (2), and the hepatic receptor for sulfated oligosaccharide (6). In the latter cases, the cognate ligands are relatively rare structures that the receptors specifically recognize among a large excess of other non-competing glycoproteins. However, with CD22, CD33, and Sn (and possibly MAG), the primary oligosaccharide motif recognized is a common sequence found on the majority of glycoproteins encountered in the surrounding milieu. Nonetheless, the evolutionary conservation of the lectin properties indicates that they mediate specific biological functions (presumably mediated by high affinity ligands) despite this large excess of low affinity ligands. It is also notable that some large plasma sialoglycoproteins are present at much lower concentrations in extracellular fluid. Thus, functioning of these lectins might only be triggered when the level of soluble inhibitors falls below a threshold in certain privileged tissue compartments (68). Regardless of the precise significance of the low affinity inhibitors, *in vitro* assays done in sialoglycoprotein-poor fluids could show binding phenomena that do not necessarily predict biological relevance *in vivo*. The same caveat applies to the plethora of potential biological ligands for these lectins that can be detected *in vitro*. *In vivo* assays are required to determine which of these are biologically important.

Biological Roles and Evolutionary Considerations

The restricted expression of the I-type lectins (Table I) implies that they mediate specific biological functions. The selective occurrence of Sn at the contact sites between bone marrow macrophages and myeloid precursors (35) strongly suggests an adhesive role. This is supported by the selective interactions of Sn with cells of the myeloid lineage *in vitro* (39). However, the biological significance of these interactions remains obscure. The privileged location of MAG within the nervous system has suggested a specific role in axonal myelination. However, the results of homozygous MAG gene disruption in mice (69) indicate that MAG is not critical for myelin formation but is necessary for maintenance of the cytoplasmic collar and periaxonal space of myelinated fibers. Additionally, MAG has recently been shown to be a potent inhibitor of neurite outgrowth *in vitro* (41). CD22 is in a position to mediate interactions of B cells with T cells, other B cells, activated endothelial cells, or accessory cells (12, 24, 32). However, the *in vivo* occurrence and significance of such interactions have not been demonstrated. The same is true of CD33. CD22, MAG, and CD33 have cytosolic domains with potential phosphorylation sites that, at least in the case of CD22, are known to be utilized upon B cell activation (17). Thus, it is possible that the major role of these lectins is not in primary adhesive events but rather in secondary activation events caused by engaging either soluble ligands or cell surface ligands *in cis*.

Classical immunoglobulins can recognize oligosaccharides with a high degree of structural specificity. Indeed, many germline V regions appear to have native carbohydrate binding properties (55), suggesting the importance of carbohydrate recognition in the immune response (55). However, the IgSF is of more ancient evolutionary origin than the immunoglobulins of the vertebrate immune system (7, 8, 55). Thus, while I-type lectins may have evolved from carbohydrate-binding immunoglobulins, it is equally possible that they are products of a parallel evolutionary process, driven by the need to generate carbohydrate binding specificities in complex multicellular systems. If so, all I-type lectins might not be closely homologous to one another. Thus, the molecules closely related to CD22 (Sn, CD33, MAG, and SMP) may be only one subfamily of the larger group of I-type lectins. Indeed, the less clear-cut examples of potential I-type lectins presented in Table II (NCAM, P0, and ICAM-1) may give some hint to the true diversity of this family.

Future Directions

Investigators who have made the most contributions toward defining I-type lectins that recognize Sias (Sn, CD22, CD33, and MAG) have proposed that these should be collectively called the "sialoadhesins" (40,

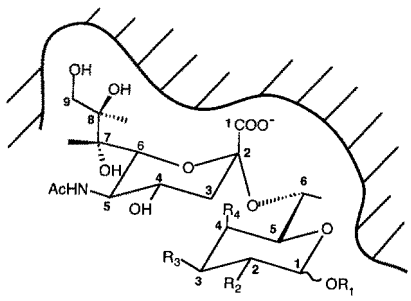

FIG. 3. **Proposed model of CD22-sialoside binding.** A disaccharide containing a 9-carbon sialic acid (*N*-acetylneuraminic acid) in α2–6 linkage to a Gal residue is presented interacting with the binding pocket of CD22 (based on the data in Ref. 46). In that study, R_1 could be GlcNAc, GalNAc, H, or a synthetic group. R_2, R_3, and R_4 could be substituted in various ways without substantially affecting binding.

43). While this is a very reasonable suggestion, each of these proteins has one name that is already well established in the literature, adhesive functions have not been conclusively shown for some, and at least some are thought to have other non-lectin-based functions as well. Furthermore, if more I-type lectins are discovered that do not recognize sialic acids, these could not be properly called sialoadhesins. Perhaps some more time should elapse before definitive nomenclature changes are adopted.

These recent advancements have established the principle that IgSF members other than immunoglobulins can specifically recognize and bind carbohydrates. It is reasonable to predict that there will be more members of this family, including some not closely homologous to those that bind Sias. Indeed, some as yet unidentified I-type lectins might be well known IgSF members whose carbohydrate binding properties have never been tested. It is important to know how the Sia-binding lectins mediate specific biological functions (presumably mediated by high affinity ligands) in the midst of a large excess of low affinity ligands. In this regard, it would be useful to know if the homomultimeric state discovered for CD22 is a feature of the other lectins. Specific focus upon the ligands with the highest apparent affinity (*e.g.* CD45 and IgM for CD22) also seems warranted. Ultimately, genetic manipulation of these lectins and of the glycosyltransferases that generate their ligands must be performed in transgenic animals.

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