

## STRUCTURAL SIMILARITY OF THE TERMINAL CARBOHYDRATE SEQUENCES OF GLYCOPROTEINS AND GLYCOLIPIDS

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### 1. Introduction

The carbohydrate chains of animal cell membranes are covalently linked to either protein or lipid. Both glycoproteins and glycolipids are asymmetrically oriented in cell membranes, with their saccharide chains projecting outwards from the membrane [1]. The carbohydrate chains of both classes of glycoconjugates have been suggested to be involved in many cell surface-associated phenomena, such as cell adhesion and recognition [2–4]. They have also been suggested to function as receptors for various biologically-active agents, such as hormones and toxins [5–7].

In spite of these similarities, glycoproteins and glycolipids have been generally considered two independent classes of glycoconjugates. They have been studied by different investigators, and consequently their structure, metabolism and function have generally been separately discussed. Due to recent advances in the analysis of complex carbohydrates, some structural similarities between glycoproteins and glycolipids have been discovered. In order to make the evaluation of these observations possible, it was found necessary to collect the scattered information concerning the structure of both classes of glycoconjugates. From the data presented a striking similarity between the glycoproteins and glycolipids becomes evident. The similarities occur in the terminal carbohydrate sequences of the molecules, whereas the portions near to protein or lipid carrier structure are different. The structural similarities may indicate that the terminal carbohydrate sequences are synthesized by common glycosyl transferases. It is furthermore possible that the structural similarities reflect similar functional properties.

### 2. Terminal sugar sequences of protein- and lipid-bound carbohydrates

The internal or 'core' portions of the carbohydrate chains of glycoproteins and glycolipids are different. Most glycolipids have as their carbohydrate core a lactose unit, which is linked to the lipid [8]. In the *N*-glycosidic type of glycoprotein saccharides a rather invariable core structure is also found, which consists of mannose and *N*-acetylglucosamine [9]. To this core structure are linked different carbohydrate chains, whereas these are directly linked to the peptide, without a distinct core portion, in the alkali-labile *O*-glycosidic type of heteroglycans [10]. Most of the structural variation in the carbohydrate chains of both glycoproteins and glycolipids is due to the structure of the nonreducing terminal sugar sequences. For the comparison of these structures, they have been collected in table 1. To facilitate the description of the structures, they are presented as derivatives of basic disaccharides. For brevity, the various types of sialic acids are not specified, although it should be realized that they may contribute significantly to the biological properties of the saccharide structures [11].

#### A. Structures related to galactosyl( $\beta$ 1–4)*N*-acetylglucosamine

Saccharide chains structurally related to Gal( $\beta$ 1–4)GlcNAc (structures 1–15) are commonly encountered in animal glycoproteins and glycolipids. The corresponding *N*-acetylglucosamine-terminated precursor structures also occur in glycoproteins [10] and glycolipids [59]. Most of the so-called acidic or complex *N*-glycosidic saccharides of glycoproteins [9,10] contain terminal sequences

Table 1  
Terminal sugar sequences of glycoproteins and glycolipids

Structure	References	
	Glycoproteins	Glycolipids
<b>A Sequences related to Gal(<math>\beta</math>1-4)GlcNAc</b>		
1	Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Sia $\alpha$ 2 3	[12,13] [14]
2	Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Sia $\alpha$ 2 6	[15,16] [17,18]
3	Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Fuc $\alpha$ 1 3	[12,19] [20]
4	Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Sia $\alpha$ 2 3 Fuc $\alpha$ 1 3	[21] [22]
5	Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Fuc $\alpha$ 1 2	[23] [24]
6	Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Fuc $\alpha$ 1 2 Fuc $\alpha$ 1 3	[21,25] [26,27]
7	Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Fuc $\alpha$ 1 2	[28] [29]
8 <sup>a</sup>	GalNAc( $\alpha$ 1-3)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Fuc $\alpha$ 1 2	[12,25] [30,31]
9 <sup>a</sup>	Gal( $\alpha$ 1-3)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-2	[12,25] [27,32]
10	Gal( $\alpha$ 1-3)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-3	[33]
11	Gal( $\alpha$ 1-4)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-3	[34] [35]
12	Gal( $\beta$ 1-3)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-Sia $\alpha$ 2 3	[36] [37]
13	Gal( $\beta$ 1-3)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-3	[38]
14	GlcNAc( $\alpha$ 1-4)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-3	[39]
15	GlcNAc( $\beta$ 1-4)Gal( $\beta$ 1-4)GlcNAc( $\beta$ 1-3	[40]
<b>B Sequences related to Gal(<math>\beta</math>1-3)GlcNAc</b>		
16	Gal( $\beta$ 1-3)GlcNAc( $\beta$ 1-Fuc $\alpha$ 1 4	[12,21] [41]
17	Gal( $\beta$ 1-3)GlcNAc( $\beta$ 1-Fuc $\alpha$ 1 2	[21] [29,42]

Table 1 (continued)  
Terminal sugar sequences of glycoproteins and glycolipids

Structure	References	
	Glycoproteins	Glycolipids
18	Gal(β1-3)GlcNAc(β1- Fucα1 2 Fucα1 4	[12,25]
19	Gal(β1-3)GlcNAc(β1- Fucα1 2	[12,25] [29]
20	GalNAc(α1-3)Gal(β1-3)GlcNAc(β1- Fucα1 2	[12,25] [31]
21	Gal(α1-3)Gal(β1-3)GlcNAc(β1- 2	[12,25] [43]
<u>C Sequences related to Gal(β1-3)GalNAc</u>		
22 <sup>b</sup>	Gal(β1-3)GalNAc- Siaα2 3	[44,45] [46]
23 <sup>b</sup>	Gal(β1-3)GalNAc- Fucα1 2	[44,47] [48]
24 <sup>b</sup>	Gal(β1-3)GalNAc- Fucα1 2	[49,50] [20,51]
25 <sup>b</sup>	GalNAc(α1-3)Gal(β1-3)GalNAc- Fucα1 2	[49]
26	Gal(α1-3)Gal(β1-3)GalNAc- Siaα2 3	[52]
27	GalNAc(β1-4)Gal(β1-3)GalNAc-	[53]
<u>D. Globoside-like structures</u>		
28 <sup>c</sup>	GalNAc(β1-3)Gal(α1- 29 GalNAc(α1-3)GalNAc(β1-3)Gal(α1-	[54] [55] [33]
<u>E. Oligosialosyl sequences</u>		
30	Sia(α2-8)Sia(α2-	[56] [48,57]
31	Sia(α2-8)Sia(α2-8)Sia(α2-	[57,58]

<sup>a</sup> Similar structures with an additional Fuc(α1-3)-substitution on the GlcNAc residue occur both in glycoproteins and in glycolipids

<sup>b</sup> Similar structures with an additional Sia(α2-6)-substitution on the GalNAc residue also exist in glycoproteins

<sup>c</sup> Occurrence in glycoproteins suggested on the basis of immunological data

of this series (structures 1–3). Only in the case of certain immunoglobulins have the peripheral chains been suggested to contain a different structure, namely Gal( $\beta$ 1–6)GlcNAc [60]. Both in glycoproteins and in glycolipids the sialosylated forms predominate. Although fucose and sialic acid residues can be alternative substituents, which compete for a common acceptor structure [61], it has recently been shown that these sugars may occur simultaneously in the same terminal sequence (structure 5) in both glycoproteins and glycolipids.

The blood group H active derivative (structure 6) and the A and B active derivatives (structures 8 and 9) have been characterized from glycolipids of erythrocyte membrane and gastrointestinal mucosa, and from the alkali-labile *O*-glycosidic glycans of the ovarian blood group substances. It has recently been shown that these blood group antigens also exist in alkali-stable carbohydrate chains of erythrocyte glycoproteins (see section 3). The P<sub>1</sub> blood group activity has recently been ascribed to the structure 11 [62].

#### B. Structures related to galactosyl( $\beta$ 1–3)*N*-acetylglucosamine

Blood group A, B and H active sequences (structures 20, 21 and 18) are also found as derivatives of Gal( $\beta$ 1–3)GlcNAc. These structures are present in glycolipids and in the *O*-glycosidic carbohydrate units of glycoproteins. Although Gal( $\beta$ 1–3)GlcNAc has been observed in a partial acid hydrolysate of *N*-glycosidic carbohydrate units of brain glycoproteins [24], it is not known, whether it may generally occur as a terminal sequence in this type of glycoprotein saccharides. In addition to the ABH active structures, Gal( $\beta$ 1–3)GlcNAc gives rise to the carbohydrate determinants of Le<sup>a</sup> and Le<sup>b</sup> antigens (structures 17 and 19). These cannot be formed from Gal( $\beta$ 1–4)GlcNAc (section 2A). The possible occurrence of sialic acid containing structures related to Gal( $\beta$ 1–3)GlcNAc has not been confirmed for either glycoproteins or glycolipids.

#### C. Structures related to galactosyl( $\beta$ 1–3)*N*-acetylgalactosamine

The glycolipids containing the sequence Gal( $\beta$ 1–3)-GalNAc and the *N*-acetylgalactosamine-terminated precursor structure [63] occur almost exclusively

as gangliosides, i.e. the lactosylceramide core of these glycolipids is sialosylated. This type of gangliosides are especially abundant in the brain, but they also occur in extraneural tissues [20,64]. The majority of the alkali-labile *O*-glycosidically-linked glycolipids the sialosylated form (structure 23) derivatives of Gal( $\beta$ 1–3)GalNAc [65]. As in the glycolipids the sialosylated form (structure 23) commonly occurs, and the basic disaccharide can also give rise to blood group H, A and B active sequences (structures 24, 25 and 26).

The similarity of the glycoprotein and glycolipid saccharides is also expressed by the finding of glycoproteins reacting with anti-ganglioside GM<sub>1</sub> and GM<sub>2</sub> antibodies [54]. It is further known that the glycoproteins carrying the Gal( $\beta$ 1–3)GalNAc sequence and similar glycolipids can function as T (Thomsen-Friedenreich) antigens [66].

Although the sugar sequences described are similar in glycoproteins and glycolipids, the galactosaminidic linkage is different, being  $\alpha$ -glycosidic in glycoproteins [67] and  $\beta$ -glycosidic in glycolipids [45]. Also, these glycoprotein carbohydrates are directly linked to the protein and not to a core saccharide. These differences could cause the fact that the glycoprotein structures 22–25 are also found as sialosylated at the C-6 of the *N*-acetylgalactosamine residue. As a further difference compared to the glycolipids, an isomer of the basic disaccharide, Gal( $\alpha$ 1–3)GalNAc, has only been found in glycoproteins [68].

#### D. Globoside-like structures

Globoside, a major glycolipid of human erythrocytes and kidney (structure 28) has recently been identified as the P antigen [62]. An isomer of globoside (cytolipin R) has been found from a sarcoma of the rat [69]. The Forssman antigen (structure 29) is a derivative of globoside. These structures have not been found as sialosyl derivatives.

The globoside-like structures have not been chemically characterized from glycoproteins. However, glycoproteins reacting with anti-globoside antibody were recently found in human erythrocyte membrane [54], and Forssman activity could also be present in glycoproteins [8]. It is therefore possible that these carbohydrate sequences also occur in glycoproteins.

### E. *Oligosialosyl sequences*

Sialic acid residues occur at a terminal position in the carbohydrate chains of glycoconjugates (see sections 2A–2C). In addition, they may be joined together to form the disialosyl (structure 30) and trisialosyl (structure 31) sequences. These structures were previously considered typical of glycolipids, and they were mainly found in the brain gangliosides (section 2C). Recently it was, however, shown that the sialosyl–sialosyl sequences also occur in glycoproteins [56], especially in the membrane glycoproteins of brain [70]. The sialosyl–sialosyl sequences mainly occur in the *N*-glycosidic chains which have peripheral chains related to Gal( $\beta$ 1–4)GlcNAc (section 2A), but they are also found in the *O*-glycosidic chains (section 2C). Very recently, the sialosyl–sialosyl sequence was also shown to occur as linked to the terminal Gal( $\beta$ 1–4)-GlcNAc unit of a glycolipid [57].

Glycolipids containing the sialosyl–sialosyl sequence have been implicated as cell-surface receptors for some biologically-active substances, like protein hormones and serotonin [5,6]. The finding of similar sequences in glycoproteins demonstrates that structural requirements for this type of sugar-containing membrane receptors could also exist in glycoproteins.

### 3. Poly(glycosyl)chains

The occurrence of a new type of heteroglycans containing saccharide chains of 20–60 sugar residues was recently demonstrated for glycolipids [71,72] and glycoproteins [73] of human erythrocyte membrane. This type of chains account for a major fraction of the carbohydrates of glycolipids [74] and glycoproteins [75–77] of the erythrocyte membrane.

The structural features of the protein- and lipid-bound forms of these glycans are very similar. They are composed of highly branched chains containing the repeating unit [...–3)Gal( $\beta$ 1–4)GlcNAc( $\beta$ 1–...)]. In glycolipids the carbohydrate is joined to the ceramide via a lactose unit [71,72]. The glycopeptides from the erythrocyte membrane do not contain glucose, but they contain mannose, and have an alkali-stable linkage to asparagine [73,76]. The core region of the protein-bound poly(glycosyl)chains thus resembles that of the known *N*-glycosidic type of

carbohydrate units [9], and it is possible that the only difference from the lipid-bound poly(glycosyl)-chains is found in the core structure. The peripheral sequences are structurally related to Gal( $\beta$ 1–4)GlcNAc (section 2A), and they are composed of ABH blood group determinants, their precursors and related sialic acid-containing sequences [76].

The structural features of the poly(glycosyl)chains are in many respects similar to those described for keratan sulphate, the main difference being the presence of sulphate in the latter. Thus, it might be better to classify keratan sulphate as a sulphated carbohydrate unit of glycoproteins rather than an 'unusual' type of glycosaminoglycan [78].

### 4. Other structures

In spite of the similarities discussed above, many differences also exist between glycoproteins and glycolipids. A major group of glycoprotein saccharides are the neutral or mannose-rich *N*-glycosidic glycans. They have been characterized from soluble [79,80] and membrane-bound [81,82] glycoproteins of several sources. Similar mannose-rich chains have not been described in animal glycosphingolipids. However, mannose and *N*-acetylglucosamine-containing saccharides are found as linked to polyisoprenoid lipids, and they function as carbohydrate donors in the biosynthesis of glycoproteins [83,84]. Another major class of protein-bound carbohydrates that does not have its counterpart among glycolipids is glycogen [85].

With the exceptions of the mannose-rich chains and glycogen, most protein- and lipid-bound saccharides that occur only in glycoproteins or glycolipids are of comparatively small size. Carbohydrate chains that have been found only in glycoproteins include the Glc( $\alpha$ 1–2)Gal- and Gal-units of collagen [86] and the *S*-glycosidically-linked Glc–Glc–Glc- and Gal–Gal-units of erythrocyte membrane and urinary glycopeptides [87]. Glucosyl- and galactosylceramide occur in several tissues and give rise to galactose, sialic acid and sulphate-containing glycolipids [8] with up to four sugar units, which are not comparable to protein-bound carbohydrates. In addition, galactose and glucose are components of animal glyceroglycolipids [88].

## 5. Implications for metabolism and function

It is unlikely that the occurrence of many similar sugar sequences in glycoproteins and glycolipids would be only incidental. Instead, the possibility that these saccharides may be synthesized by the same glycosyl transferases should be considered.

Studies on the acceptor specificity of glycosyl transferases have shown that in many cases these enzymes recognize a short terminal sequence of only few sugar units on the acceptor molecule [89–91]. It is therefore possible that glycoproteins and glycolipids which contain a similar carbohydrate sequence, separated from the protein or lipid carrier by a sugar chain of a few monosaccharides, could serve as acceptors for the same glycosyl transferases. The differences in the internal portions of the molecule would be beyond the binding site of these enzymes. Such a situation is suggested to exist for the ABH blood group antigen determinants, the protein- and lipid-bound forms of which are thought to be synthesized by the same enzymes. On the other hand, with carbohydrate units of smaller size, the influence of the protein or lipid portion may be essential, and protein- and lipid-bound carbohydrates would not serve as acceptors for the same glycosyl transferases. This is supported by the finding that the structures of the short saccharide units of glycoproteins and glycolipids are mostly different, whereas with increasing chain length the resemblance between glycoproteins and glycolipids increases.

The possibility that some protein- and lipid-bound heteroglycans may also be degraded by the same glycosidases is indicated by the accumulation of both glycolipids and glycoprotein-derived oligosaccharides or glycopeptides in certain glycosidase deficiencies, such as GM<sub>1</sub> and GM<sub>2</sub> gangliosidosis and fucosidosis [92,93].

The biological role of the protein- and lipid-bound carbohydrates of cell membranes is still for the most part unknown. Some physico-chemical functions, such as stabilization and protection of the cell membranes as well as binding of inorganic ions [94] have been suggested. It is apparent that the carbohydrates of both glycoproteins and glycolipids may be involved in such functions. More specific functions suggested for glycoproteins and glycolipids include roles in cell-to-cell recognition [2–4] and as receptors of many

biologically-active agents, such as protein hormones, antibodies, lectins and toxins [5–7]. In such functions the terminal carbohydrate sequences of glycoproteins or glycolipids are thought to have an essential role. Although glycoproteins and glycolipids represent different molecular species, their similar carbohydrate terminals could have similar functions. The terminal sugar sequences, being responsible for most of the structural variation found in cell surface saccharides, could serve as 'affinity ligands' enabling the recognition of the target cells by biologically-active agents.

## 6. Conclusions

It has become evident that many similarities exist between the structure of the carbohydrate chains of glycoproteins and glycolipids. The degree of the similarity is a function of the chain length. Three classes of saccharide chains can be discerned:

1. Short saccharides of only few sugar units, which are usually different in glycoproteins and glycolipids, and which also occur as protein- or lipid-linked cores of more extended carbohydrate chains;
2. Oligosaccharide units of intermediate size, which have many common terminal sugar sequences;
3. Large poly(glycosyl) units, the structure of which is very similar in glycoproteins and glycolipids.

The structural similarity may indicate that our view of glycoproteins and glycolipids as two independent classes of glycoconjugates has to be modified. It is possible that the peripheral sugar sequences of many glycoproteins and glycolipids, especially of those which have extended carbohydrate units, are synthesized by common glycosyl transferases and also degraded by common glycosidases. The structural similarity of the terminal sugar sequences of glycoproteins and glycolipids might also mean that some biological functions, such as cell surface-associated functions involving interactions of proteins with membrane saccharides, are shared by protein- and lipid-linked carbohydrates.

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