Minireview

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 264, No. 30, Issue of October 25, pp. 17615-17618, 1989

Glycosyltransferases

STRUCTURE, LOCALIZATION, AND CONTROL OF CELL TYPE-SPECIFIC GLYCOSYLATION

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Glycosyltransferases involved in the biosynthesis of glycoprotein and glycolipid sugar chains are resident membrane proteins of the endoplasmic reticulum and the Golgi apparatus. Although the glycosylation pathways in which they participate have been extensively studied and reviewed (1–3), major questions remain concerning the molecular basis for the subcellular organization of the glycosylation machinery and how cells are able to regulate the expression of specific carbohydrate sequences. This latter subject is of current interest in view of increasing evidence that cell surface carbohydrate groups mediate a variety of cellular interactions during development, differentiation, and oncogenic transformation (4–8). This review examines insights into these areas afforded by recent successes in the cloning and expression of several glycosyltransferases involved in the synthesis of terminal sequences of glycoproteins and glycolipids.

Terminal Glycosyltransferases in the Synthesis of Glycoproteins and Glycolipids

Glycosyltransferases transfer sugar residues from an activated donor substrate, usually a nucleotide sugar, to a growing carbohydrate group. The specificity of the enzymes for their donor and acceptor substrates constitutes the primary basis for determining the structures of the sugar chains produced by a cell. It is estimated that 100 or more glycosyltransferases are required for the synthesis of known carbohydrate structures on glycoproteins and glycolipids, and most of these are involved in elaborating the highly diverse terminal sequences (2, 9). These enzymes are typically grouped into families based on the type of sugar they transfer (galactosyltransferases, sialyltransferases, etc.).

Listed in Table I are six glycosyltransferases for which cDNAs have been obtained (10–18).[1,2] Each enzyme elaborates common terminal glycosylation sequences which have been reported to occur on *N*- and *O*-linked sugar chains of glycoproteins and on sugar chains of glycolipids (2, 4–8, 20). It is likely that common terminal sequences of glycoprotein and glycolipid sugar chains are synthesized by the same glycosyltransferases. Indeed, each of the cloned glycosyltransferases represented in Table I has been purified to homogeneity from one or more mammalian sources (2, 9, 21–24), and several have been shown to utilize both glycolipids and glycoproteins as acceptor substrates *in vitro*.

‡ Supported by United States Public Health Service Grant GM-11557.

[1] J. Lowe, L. Ernst, J. Kukowska-Lattallo, and R. Larson, personal communication.

[2] F. Yamamoto, J. Marken, T. Tsuji, T. White, H. Clausen, and S. Hakomori, *J. Biol. Chem.*, submitted for publication.

Domain Structure of Glycosyltransferases

Glycosyltransferases Share a Common Domain Structure—Comparison of the deduced amino acid sequences of the cDNA clones encoding the glycosyltransferases listed in Table I (10–18)[1,2] reveals that these enzymes have virtually no sequence homology. However, as depicted in Fig. 1, they all have a short NH_2-terminal cytoplasmic tail, a 16–20-amino acid signal-anchor domain, and an extended stem region which is followed by the large COOH-terminal catalytic domain (26). Signal-anchor domains (25) act as both uncleavable signal peptides and as membrane-spanning regions and orient the catalytic domains of these glycosyltransferases within the lumen of the Golgi apparatus, as illustrated in Fig. 2.

Relationship between the Stem Region and Occurrence of Soluble Glycosyltransferases—The stem region depicted in Fig. 2 should serve as a flexible tether, allowing the catalytic domain to glycosylate carbohydrate groups of membrane-bound and soluble proteins of the secretory pathway enroute through the Golgi apparatus. Direct evidence for a "stem" or spacer region has been obtained for the Gal α2,6-ST and the GlcNAc β1,4-GT[3] (13, 18). Results from NH_2-terminal sequence analysis of soluble forms of these enzymes suggest a luminal stem region of at least 35 and 62 residues for the two enzymes, respectively, which separates the catalytic domain from the transmembrane domain and is exposed to proteases.

Soluble forms of glycosyltransferases have been demonstrated and purified from milk, serum, and other body fluids (2, 9), and increased serum levels have been noted in disease states (28) and inflammation (29). The origin of these enzymes has long been thought to result from proteolytic release from the membrane-bound forms of the enzymes (reviewed in Refs. 2, 9, 26, 27). Recently results of Jamieson and colleagues suggest that the Gal α2,6-ST is released from rat liver Golgi membranes in response to induced inflammation as a result of cleavage by a cathepsin D-like protease within the acidic *trans* Golgi compartment (29). These observations suggest that soluble glycosyltransferases could result from the release of membrane-bound enzymes by endogenous proteases, presumably by cleavage between the catalytic domain and the transmembrane domain (26, 29).

Lack of Sequence Homology within Glycosyltransferase Families—Common amino acid sequences would be expected within families of glycosyltransferases which share similar acceptor or donor substrates; however, surprisingly few regions of homology have been found within the catalytic domains of glycosyltransferases, and no significant sequence homology is found with any other protein in GenBank (10–18).[1,2] This is especially surprising for the Gal α1,3-GT and GlcNAc β1,4-GT, two galactosyltransferases. However, while these galactosyltransferases exhibit no overall homology, Jo-

[3] The abbreviations used are: GlcNAc β1,4-GT, β-*N*-acetylglucosaminide β1,4-galactosyltransferase; GlcNAc α1,3/4-FT, *N*-acetylglucosaminide α1,3/4-fucosyltransferase; Gal α1,3-GT, β-galactoside α1,3-galactosyltransferase; Gal α2,6-ST, Galβ1,4GlcNAc α2,6-sialyltransferase; Gal α1,2-FT, β-galactoside α1,2-fucosyltransferase; Gal α1,3-GalNAcT,β-(Fucα1,2)Gal α1,3-*N*-acetylgalactosaminyltransferase; SSEA, stage-specific embryonic antigen; ER, endoplasmic reticulum; TPA, tetradecanoylphorbol acetate; G_{D3}, NeuAcα2,8NeuAcα-2,3Galβ1,4Glc-ceramide; sialoparagloboside, NeuAcα2,3Galβ1,4-GlcNAcβ1,3Galβ1,4Glc-ceramide; G_{M3}, NeuAcα2,3Galβ1,4Glc-ceramide.

TABLE I

Cloned glycosyltransferases involved in the synthesis of terminal sequences in sugar chains of glycoproteins and glycolipids

Abbreviated names combine the acceptor sugar, the linkage formed, and the glycosyltransferase family (GT, galactosyltransferase; ST, sialyltransferase; FT, fucosyltransferase; GalNAcT, *N*-acetylgalactosaminyltransferase). For the *sequence formed*, the sugar transferred is highlighted in boldface, and the acceptor sequence is shown in lightface. R represents the remainder of the glycoprotein or glycolipid sugar chain.

GLYCOSYLTRANSFERASE	DONOR SUBSTRATE	SEQUENCE FORMED
Galactosyltransferases		
GlcNAc β1,4-GT (10-15) (E.C. 2.4.1.38)	UDP-Gal	**Galβ1,4**GlcNAc-R
Gal α1,3-GT (16,17) (E.C. 2.4.1.151)	UDP-Gal	**Galα1,3Galβ1,4**GlcNAc-R
Sialyltransferase		
Gal α2,6-ST (18) (E.C. 2.4.99.1)	CMP-NeuAc	**NeuAcα2,6Galβ1,4**GlcNAc-R
Fucosyltransferases		
GlcNAc α1,3-FT [1] (E.C. 2.4.1.65)	GDP-Fuc	**Fucα1,3** (Galβ1,4) GlcNAc-R
		Fucα1,4 (Galβ1,3) GlcNAc-R
Gal α1,2-FT [1] (E.C. 2.4.1.69)	GDP-Fuc	**Fucα1,2Galβ1,4**GlcNAc-R
		Fucα1,2Galβ1,3 GalNAc-R
N-Acetylgalactosaminyltransferase		
Gal α1,3-GalNAcT [2] (Blood group A transferase)	UDP-GalNAc	**GalNAcα1,3** (Fucα1,2) Gal-R

ziasse *et al.* (16) have pointed out a common hexapeptide KDKKND for the Gal α1,3-GT (bovine, 304–309 (16); and RDKKNE for the GlcNAc β1,4-GT (bovine, human, murine amino acids 346–351 (10–15)). Although the significance of this homology is unknown, a possible role in UDP-Gal binding has been suggested (16).

More extensive amino acid sequence homologies may be found for some enzymes that are yet to be cloned. For example, both blood group A Gal α1,3-GalNAc transferase and blood group B Gal α1,3-GT share the same acceptor substrate, Fuc α1,2-Gal-R, and have been shown to have similar amino acid compositions, cross-react with one another's antibodies, and share the same genetic locus (reviewed in Refs. 2 and 24), suggesting that they have similar nucleotide and amino acid sequences with subtle alterations to accommodate their different donor substrates.[2]

Species Variations in Glycosyltransferase Sequence—The overall amino acid sequence homology for a glycosyltransferase cloned from different species is quite high (80% or greater), with the least homology found in the stem regions (10–18).[2] The bovine (16) and murine (17) Gal α1,3-GTs differ in the predicted lengths of their cytoplasmic tails with the murine enzyme containing an extra 35 amino acids at the NH_2 terminus. However, inspection of the sequence surrounding the ATG start site of the murine Gal α1,3-GT suggests a weak translation start site (TTCATGA (30)), allowing the possibility that the internal ATG may be used, resulting in the same length NH_2-terminal cytoplasmic tails for both species. Two mRNAs that differ in length by 200 base pairs at the 5′ end have also been reported for the murine GlcNAc β1,4-GT which code for enzymes that differ only by 13 amino acids at the NH_2 terminus (10).

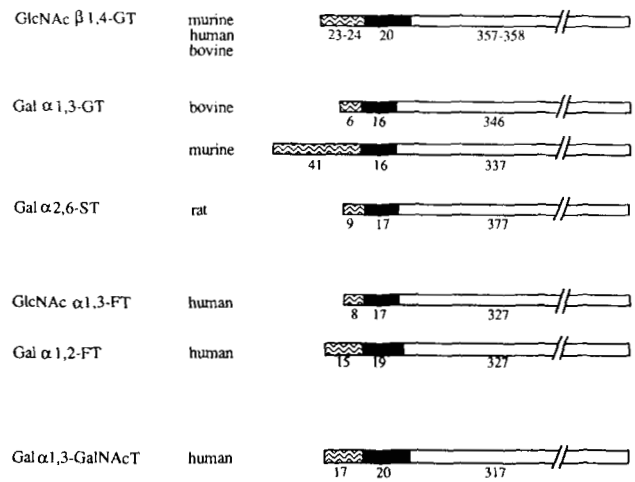

FIG. 1. **Amino acid sequences of cloned terminal glycosyltransferases predict NH_2-terminal signal-anchor domains.** Compared are the predicted domain structures of six glycosyltransferases listed in Table I. The number of amino acids in each domain is listed beneath it. ▨, cytoplasmic domain; ■, signal-anchor domain; □, luminal domain.

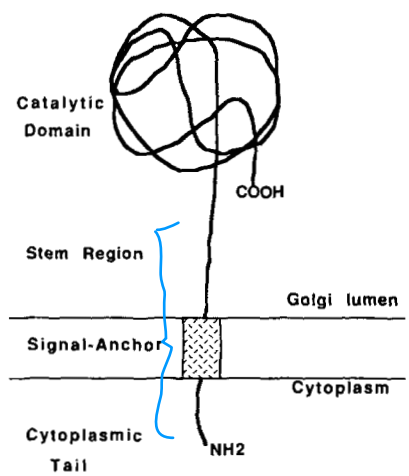

FIG. 2. **Common topology of cloned terminal glycosyltransferases.** Deduced amino acid sequences of the terminal glycosyltransferases cloned to date predict that these enzymes have a characteristic topology in the Golgi apparatus consisting of a short NH_2-terminal cytoplasmic tail, a signal-anchor domain which spans the membrane, an extended stem region, and a large COOH-terminal catalytic domain oriented within the lumen of the Golgi cisternae.

Subcellular Localization of Glycosyltransferases

The subcellular localization of the enzymes involved in *N*- and *O*-linked glycosylation has been extensively studied, with terminal glycosyltransferases being found in the Golgi apparatus (1, 31–33). Subcompartmentation within the Golgi apparatus is also well documented, with *N*-acetylglucosaminyltransferase I localized to the *medial* cisternae and the GlcNAc β1,4-GT, Gal α2, 6-ST, and the Gal α1,3-GalNAcT localized to the *trans* cisternae and *trans* Golgi network (33–36). However, recent studies of the localization of Gal α2,6-ST and the Gal α1,3-GalNAcT and the localization of various sialylglycoproteins have suggested that terminal glycosyltransferases may have diffuse distributions throughout the Golgi stack in some cells (33, 37–39).

Although the basis for the localization of glycosyltransferases in the Golgi apparatus has not been elucidated, it is widely believed that membrane proteins of the Golgi apparatus possess specific retention signals that are absent in plasma membrane proteins and proteins that are secreted from the cell (reviewed in Ref. 40). The demonstration of a KDEL sequence that mediates the retention and return of soluble ER proteins provides ample precedence for this concept (41). Evidence cited above for secretion of soluble glycosyltransferases following proteolytic release from the NH_2-terminal signal-anchor implies that the retention signal is not associated with the catalytic domain. Colley *et al.* (42) have tested this hypothesis by replacing the first 57 amino acids of the Gal α2,6-ST, including the cytoplasmic tail, signal-anchor, and stem regions, with the cleavable signal peptide of γ-interferon. This fusion protein when expressed in Chinese hamster ovary cells results in the secretion of a catalytically active, soluble enzyme. A similar result was obtained by Larsen *et al.* (17) when they expressed in Cos-1 cells a fusion protein containing a secretable form of protein A fused to the putative stem and catalytic domains of the Gal α1,3-GT (amino acids 63–394) and found galactosyltransferase activity secreted into the cell media. These data demonstrate that the Golgi apparatus retention signal of these glycosyltransferases must reside in the NH_2-terminal portion of the enzymes, which includes the cytoplasmic tail, signal-anchor, and stem regions.

Regulation of Terminal Glycosylation

Differential Expression of Glycosyltransferases—There is abundant evidence that terminal glycosylation sequences are differentially expressed in cells and are subject to change during development, differentiation, and oncogenic transformation (reviewed in Refs. 4, 5, and 7). The concept that the cellular glycosylation machinery largely determines the structures of glycoprotein sugar chains stems from observed differences in the carbohydrate structures elaborated on viral glycoproteins and recombinant glycoproteins produced in various cultured cell lines (43, 44) and from the sugar structures of glycoproteins naturally expressed in different tissues (reviewed in Ref. 5). Although protein structure places secondary constraints of accessibility on the glycosylation machinery (1) and in the extreme provides recognition determinants for glycosyltransferases that act on sugar chains of one protein or class of proteins (1, 45–47), the terminal glycosylation sequences produced by a cell are presumed to reflect the expression of the corresponding glycosyltransferases which synthesize them.

Strong support for this idea comes from recent examples of altering the cellular glycosylation machinery by transfection of cells with DNA fragments or expression vectors containing cDNAs coding for glycosyltransferases which synthesize terminal glycosylation sequences (17, 37, 48–50). For example, although wild type Chinese hamster ovary cells produce *N*-linked carbohydrate groups with the NeuAcα2,3Gal linkage, Lee *et al.* (37) demonstrated that stably transfected Chinese hamster ovary cells expressing the Gal α2,6-ST (Table I) produce both the NeuAcα2,6Gal and NeuAcα2,3Gal linkages. Similarly, Larsen *et al.* (17) showed that Cos-1 cells transfected with the cDNA for the Gal α1,3-GT (Table I) produce the Galα1,3Gal-R sequence on cell surface carbohydrate groups, a structure not expressed on wild type cells. Lowe and co-workers (17, 49, 50)[1] have exploited such observations in developing strategies for the functional cloning of glycosyltransferases, successfully cloning three of the six glycosyltransferases listed in Table I.

Glycosyltransferase expression is most likely regulated at the level of transcription. In support of this suggestion, the level of Gal α2,6-ST mRNA varies 50–100-fold in various rat tissues, correlating with the activity of the enzyme (51). The level of the Gal α2,6-ST has also been demonstrated to increase 4–5-fold in the liver after induction of inflammation, presumably to provide for the increased production of liver glycoproteins such as α_1 acid glycoprotein and α_1 antitrypsin during the acute phase response (28, 29). Wang *et al.* (53) have recently demonstrated an equivalent induction of sialyltransferase and sialyltransferase mRNA in primary hepatocyte cultures treated with dexamethasone, suggesting that the increased expression following inflammation is controlled by plasma levels of glucocorticoids (53, 54). In contrast to the sialyltransferase, the ubiquitous GlcNAc β1,4-GT is expressed rather uniformly in most murine tissues. However, during spermatogenesis, novel mRNA species are produced which exhibit developmental regulation (52).

Several reports have demonstrated that the changes in glycolipid or glycoprotein glycosylation in transformed cells correspond to quantitative or qualitative changes in the expression of the relevant glycosyltransferases (55–58). The *de novo* expression of a terminal glycosylation sequence is especially interesting with respect to the regulation of glycosylation, because it implies the expression of a glycosyltransferase not expressed in the normal tissue.

Exposure of cells to differentiation agents such as butyrate (19), phorbol esters (59), or retinoic acid (60–62) has also been reported to produce qualitative changes in levels of cell surface terminal glycosylation sequences as well as the specific glycosyltransferases that produce them. Such results are particularly intriguing in view of evidence that terminal glycosylation sequences may play an important role in differentiation pathways, as will be discussed further below.

Biological Implications of Regulated Expression of Terminal Glycosylation Sequences—All the observations cited above suggest that cell type-specific glycosylation sequences can result from regulated expression of glycosyltransferase genes. While not all glycoprotein or glycolipid carbohydrate structures produced by a cell have functional significance (6), it is increasingly apparent that specific sequences in the proper context play important roles in biological recognition.

Developmentally regulated expression of specific glycosylation sequences has been implicated in a variety of cell-cell interactions. Polysialic acid addition onto the neural cell adhesion molecule occurs only in early development and is thought to regulate the adhesive properties of the homotypic neural cell adhesion molecule interactions (47). The embryonic antigen SSEA-1, the product of the GlcNAc α1,3/4-FT (Table I), is expressed at the 16 cell stage of mouse embryo, coincident with the process of compaction (4). Because analogs of the SSEA-1 structure can inhibit compaction, its expression has been suggested to mediate the compaction process (63, 64) and to occur directly through a carbohydrate-carbohydrate interaction rather than a carbohydrate-protein interaction (65). Developmentally regulated glycosylation events have also been implicated in the induction of ureter bud growth into the undifferentiated mesenchyme of the embryonic kidney (66) and in the maturation of thymocytes (67).

Specific gangliosides (sialic acid-containing glycosphingolipids) have been implicated in cell differentiation and cell cycle control (59, 68–73). Retinoic acid-induced differentiation of the hematopoetic precursor cell line HL-60 to granulocytes and TPA-induced differentiation of the same cells to monocytes have been associated with qualitative changes in the expression of sialic acid-containing glycolipids (59, 69,

70). Indeed, TPA-induced monocyte differentiation increased synthesis of ganglioside G_{M3} and the sialyltransferase, G_{M3} synthetase (59). A direct role of ganglioside G_{M3} is suggested by the fact that differentiation to monocytes can be induced without TPA by adding exogenous G_{M3} to the culture media (69). Although the mechanism by which gangliosides might participate in differentiation pathways is not clear at present, specific gangliosides have been implicated in the modulation of growth factor receptor protein kinase activities (72, 73) and in the control of the cell cycle (71).

Glycoprotein and glycolipid sugar chains have been implicated in many other examples of protein targeting and cell-cell interactions too numerous to mention here (4–6, 8, 45, 46, 74, 75). Such observations mark the elucidation of the biological roles of glycoprotein and glycolipid sugar chains as an emerging fronteir. In the future, understanding the regulation of the cellular glycosylation machinery, which produces the specific sugar sequences required for recognition events, will take on increasing importance.

Summary and Future Prospects

It is striking that the glycosyltransferases cloned to date have similar domain structure but little sequence homology. As additional glycosyltransferase cDNAs are cloned and sequenced, it will be of interest to establish the degree to which this diverse group of enzymes might have evolved from common ancestral genes. The availability of a variety of glycosyltransferase cDNAs should allow production of these enzymes through standard expression technology, allowing their use as enzymatic reagents in glycoconjugate research and in the large scale synthesis of oligosaccharides (76). Through gene transfer technologies, glycosyltransferase cDNAs can also be expected to be used in various strategies to explore the biological roles of glycoprotein and glycolipid sugar chains (17, 37).

Acknowledgments—We are grateful to the many investigators who generously shared ideas, unpublished results, and manuscripts prior to publication: Dr. Giacomo D'Agostaro, Dr. Brad Bediak, Dr. Senitiroh Hakomori, Dr. James Jamieson, Dr. David Joziasse, Dr. John Lowe, Drs. Nancy and Joel Shaper, and Dr. Fumi-ichiro Yamamoto.

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