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Review

The galactosyltransferase family

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Abstract. Galactose is transferred via several linkages to acceptor structures by galactosyltransferase enzymes. In prokaryotes, galactose is mainly found on lipopolysaccharides and capsular polysaccharides. In eukaryotes, galactosyltransferases, which are localized in the Golgi apparatus, are involved in the formation of several classes of glycoconjugates and in lactose biosynthesis. Although they sometimes catalyze identical reactions, prokaryotic and eukaryotic galactosyltransferases share only little structural similarities. In mammals, 19 distinct galactosyltransferase enzymes have been characterized to date. These enzymes catalyze the transfer of galactose via β1-4, β1-3, α1-3 and α1-4 linkages. The present review focuses on the description of these mammalian galactosyltransferases.

Key words. Glycosylation; galactose; enzyme; Golgi; cell biology; gene family.

Introduction

Galactose is commonly found in several classes of glycoconjugates in both prokaryotes and eukaryotes. Various galactosyltransferase (GalT) enzymes catalyze the addition of galactose (Gal) in two anomeric configurations through α1-2, α1-3, α1-4, α1-6 or β1-3, β1-4 linkages following the standard reaction:

$$\text{UDP-Gal} + \text{acceptor} \rightarrow \text{Gal-acceptor} + \text{UDP}$$

The variety of galactosylation reactions significantly contributes to the tremendous diversity of oligosaccharide structures expressed by living organisms. In prokaryotes, GalTs are involved in the biosynthesis of the lipopolysaccharide O-antigen [1], capsular polysaccharides [2] and pilin glycans [3]. In the yeast *Schizosaccharomyces pombe*, a GalT participates in the formation of cell wall galactomannan [4], and in plants several GalTs synthesize plastid galactolipids [5, 6], galactosylated flavonols [7], galactomannan [8] as well as complex asparagine-linked glycans [9]. In keeping with the overall complexity of higher eukaryotes, the vast diversity of galactosylated structures is paralleled by several GalT gene duplication events that give rise to several groups of enzymes with different acceptor specificities and distinct patterns of tissue expression.

Although GalT activity is widespread among living organisms, prokaryotic and eukaryotic GalT enzymes share little structural homology. Even between bacterial GalTs, it is difficult to recognize conserved domains that may be related to the enzymatic activity, thereby rendering the formal identification of GalT dependent on functional assays. In addition, the bacterial enzymes do not share a unique topology: some GalTs are membrane bound, like RfpB, whereas others function as soluble enzymes, as for example RfbF. In consequence, relatively few bacterial GalTs have been characterized to date (table 1). The sequencing of additional bacterial genomes will eventually contribute to the identification of novel glycosyltransferase genes encoding, among others, GalT enzymes. The bacterial GalTs described so far catalyze a wide range of structures by transferring Gal to various acceptor substrates through α1-3, α1-4, α1-6, β1-3 and β1-4 linkages.

Table 1. Bacterial galactosyltransferases.

Enzyme	Gene	Organism	Product	References
α1-3 GalT	*RfpB*	*Shigella dysenteriae*	LPS	116
α1-3 GalT	*RfbF*	*Klebsiella pneumoniae, Campylobacter coli, Serratia marcescens*	LPS	117, 118
α1-3 GalT	*RfaI*	*Salmonella typhimurium*	LPS	119
α1-4 GalT	*LgtC*	*Neisseria gonorrhoeae, Neisseria meningitidis*	LOS	120
α1-6 GalT	*AmsD*	*Erwinia amylovora*	exopolysaccharide	121
α1-6 GalT	*RfaB*	*Escherichia coli, Salmonella typhimurium*	LPS	122, 123
α1-6 GalT	*LpcA*	*Rhizobium leguminosarum*	LPS	124
β1-3 GalT	*CgtB*	*Campylobacter jejuni*	LOS	125
β1-3 GalT	*WlaN*	*Campylobacter jejuni*	LOS (GM1 analog)	126
β1-4 GalT	*LgtB*	*Neisseria gonorrhoeae, Neisseria meningitidis*	LOS	49
β1-4 GalT	*LgtE*	*Neisseria gonorrhoeae, Neisseria meningitidis*	LOS	49
β1-4 GalT	*Cps14G, Cps14J*	*Streptococcus pneumoniae*	capsular polysaccharides	2
β1-4 GalT	*WaaX*	*Escherichia coli*	LPS	127
β1-4 GalT	*HpgalT*	*Helicobacter pylori*	LPS	128
β1-4/α1-3 GalT	*PglA*	*Neisseria meningitidis*	Pilin-linked glycan	3

In contrast to bacterial glycosyltransferases, nearly all eukaryotic GalTs are type II transmembrane proteins featuring a short cytosolic segment, a single transmembrane domain of about 20 amino acids and a large luminal catalytic domain. GalTs are anchored in the Golgi apparatus. This topology and localization are common for GalT proteins from yeast, such as the Gma12 GalT from *Schizosaccharomyces cerevisiae* [4] up to the mammalian enzymes. As with every rule, the exception is represented by the ceramide:UDP-Gal GalT (CGT) enzyme that catalyzes the formation of galactocerebroside [10]. This protein has in fact a type I topology and is localized to the endoplasmic reticulum [11]. CGT constitutes a structurally distant member of the GalT family, as it is more related to glucuronyltransferases active in the hepatic detoxification of xenobiotics than to classical enzymes involved in glycoconjugate synthesis. For a more detailed discussion on the structural relations between prokaryotic and eukaryotic galactosyltransferases, see [12].

The activity and biological functions of galactosyltransferases have been most thoroughly characterized in mammals. In this class, Gal occurs β1-4, β1-3, α1-3 and α1-4 linked to accepting templates in various types of glycoconjugates (fig. 1). An early concept was that each glycosidic linkage is catalyzed by a specific enzyme [13]. However, with the discovery of multiple isozymes for several glycosyltransferase activities, this ‘one linkage, one enzyme’ rule has rapidly become ‘one linkage, many enzymes’. Along this line, several enzymes have been characterized for each kind of GalT activity. Because of the availability of genome databases and convenient homology search algorithms [14], several novel GalT genes have been described in the last years. The next sections will outline the specificity of the enzymes and discuss their relevance in biological systems.

β1-4 Gal-Ts

Seven β1-4 GalT enzymes have been described to date. These proteins share an extensive homology, which was in fact applied as a tool to clone the genes encoding six members of this family. Recent searches of mammalian genome databases using known β1-4 GalT sequences as queries has failed to reveal additional related genes. However, these searches do not exclude the existence of other β1-4 GalT genes that may present little structural similarity to the known enzymes. In most cases, the identity of β1-4 GalT proteins has been confirmed by heterologous expression of recombinant proteins. Whereas this approach clearly establishes the enzymatic activity, a comparison of the β1-4 GalT isozymes is difficult to address because the expression systems as well as the type of recombinant β1-4 GalT proteins often differ in the first reports. For example, the acceptor substrate specificity attributed to single β1-4 GalTs may have to be revised or extended to the light of new experiments. Along this line, a recent study investigating the specificity of six β1-4 GalTs expressed under identical conditions showed that all these enzymes, including β4GalT6 previously described as a lactosylceramide synthase, can transfer Gal to N-glycan acceptors (product B of N-glycan on fig. 1) [15]. This apparent redundancy renders even more difficult the determination of the biological relevance of the single β1-4 GalT proteins. Knockout mouse models and the clinical evaluation of human cases of β1-4 GalT deficiency will contribute delineating the biological specificity of the isozymes.

β4GalT1

The first mammalian GalT characterized biochemically, β4GalT1, was also the first one to be cloned [16, 17]. Using a classical approach, the β4GalT1 protein has been

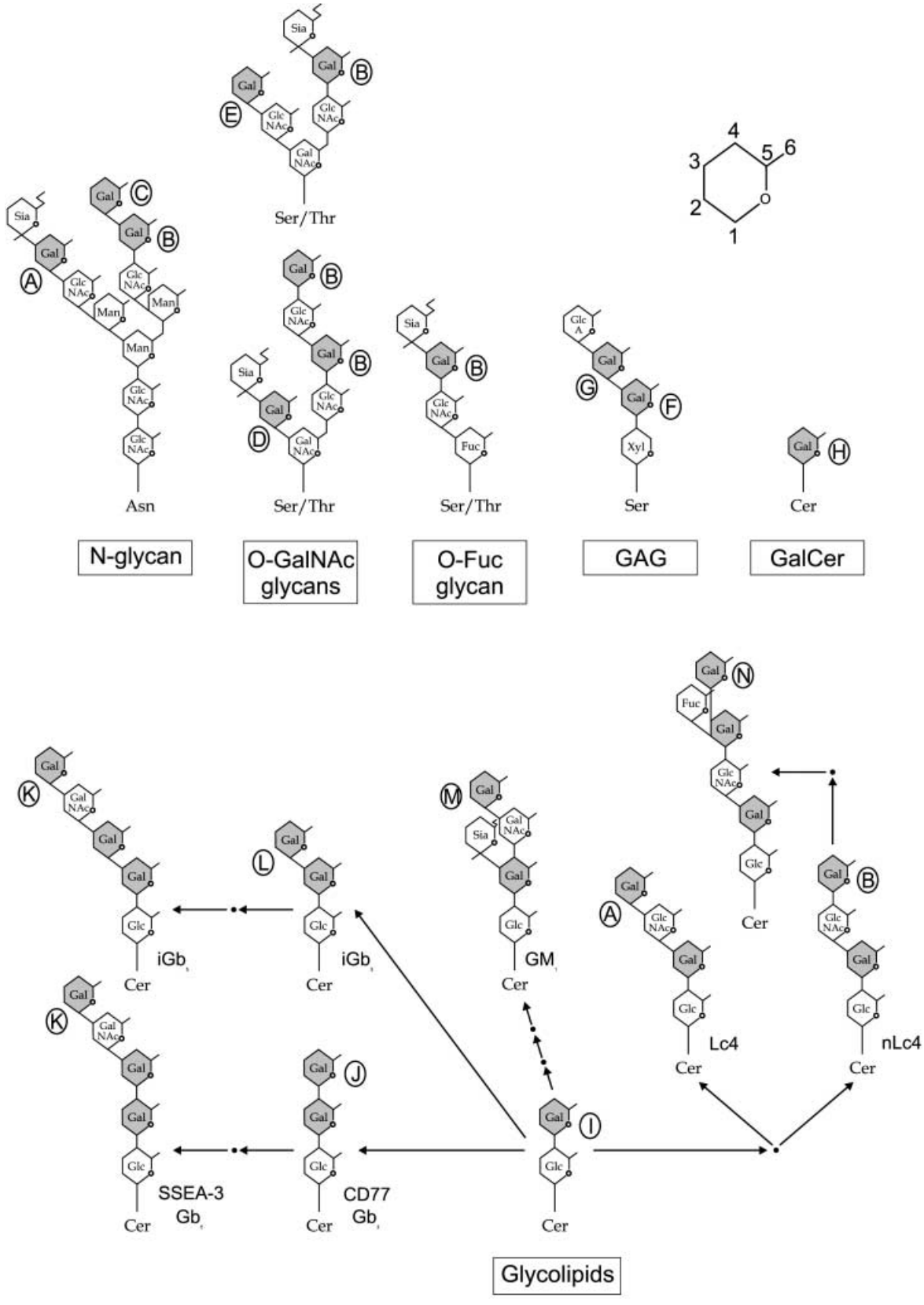

Figure 1. Glycoconjugate structures including galactose. The carbon atoms of hexoses are numbered from 1 to 6 as exemplified by the hexagon at the top right corner. The anomerization of the sugar units is not visualized. The structures shown belong to several glycoconjugate classes, namely N-glycans, O-linked GalNAc glycans, O-linked fucose glycans, glycosaminoglycans (GAG), galactosylceramide (GalCer) and glycolipids. The encircled letters refer to the galactosyltransferase enzymes listed on table 2.

purified and either partially sequenced [17] or applied as antigen to generate anti-β4GalT1 polyclonal antibodies, which were subsequently used in expression gt11 λ-phage library screenings [16]. β4GalT1 has two enzymatic activities: as a monomer it transfers Gal to GlcNAc-based acceptors (fig. 1, products B) and when associated to α-lactalbumin, β4GalT1 catalyzes the transfer of Gal to Glc, yielding lactose [18]. Logically, the lactose synthase activity is important in mammary glands, a tissue in which the β4GalT1 gene expression is induced during lactation [19]. In other tissues, the β4GalT1 gene appears to be constitutively expressed. The β4GalT1 protein is localized in the Golgi apparatus [20, 21], and the suggestion that the enzyme may be at the cell surface in some cases [22] needs to be confirmed by ruling out carbohydrate specificities in the antibodies used as histochemical reagents [23]. The β4GalT1 gene is split in six exons spanning about 50,000 bp of genomic DNA [24]. The human β4GalT1 gene maps to chromosome 9 band p13 (table 2).

The β4GalT1 enzyme is also the first mammalian glycosyltransferase whose three-dimensional structure has been elucidated [25]. This study showed that the β4GalT1 enzyme can be schematically represented as a cone with a large open pocket. Two disulfide bridges stabilize the β4GalT1 protein. The analysis of the crystal structure also confirmed the importance of GalT-conserved amino acid residues, such as the DxD motif, in the binding of the UDP-Gal substrate. A second study reported the crystal structure of β4GalT1 complexed to α-lactalbumin [26],

Table 2. Mammalian GalTs.

Enzyme	Gene	Human chromosome	Expression (UniGene)	Products (see fig. 1)	GenBank accession #*	References
β1-4 GalT	B4GALT1	9p13	ubiquitous	B, I	NM_001497	16
β1-4 GalT	B4GALT2	1p34-p33	ubiquitous	B	NM_030587	32
β1-4 GalT	B4GALT3	1q21-q23	ubiquitous	B	NM_003779	32
β1-4 GalT	B4GALT4	3q13	ubiquitous	B	NM_003778	34
β1-4 GalT	B4GALT5	20q13	ubiquitous	B, I	NM_004776	36
β1-4 GalT	B4GALT6	18q11	bone marrow, brain, breast, lung, pancreas, skin, whole embryo	B, I	NM_004775	40
β1-4 GalT	B4GALT7	5q35	ubiquitous	F	NM_007255	43, 45
β1-3 GalT	B3GALT1	2p14	germ cells, brain	A	NM_020981	55
β1-3 GalT	B3GALT2	1q31	blood, bone, brain, colon, heart, pancreas, skin, whole embryo, lung, nervous system, prostate	A	NM_003783	55, 57, 58
β1-3 GalT	B3GALT3	3q25	bladder, bone, brain, breast, colon, foreskin, germ cell, heart, kidney, lung, ovary, prostate, testis, uterus, whole embryo	A	NM_003781	55, 58, 59
β1-3 GalT	B3GALT4	6p21	brain, colon, lung, ovary, pancreas, lung, testis, kidney, stomach, prostate	M	NM_003782	63
β1-3 GalT	B3GALT5	21q22	breast, colon, pancreas, testis, nervous system	A, E, K	NM_006057	66–68
β1-3 GalT	B3GALT6	1	ubiquitous	G	AY050570	71
β1-3 GalT	B3GALT7, C1GALT1	7	bone marrow, brain, colon, germ cell, kidney, pancreas, placenta, small intestine, stomach, uterus	D	NM_020156	72
α1-3 GalT	ABO	9q34	colon, blood	N	NM_020469	84
α1-3 GalT	Ggta1	–	embryo, heart, lung, mammary gland, pancreas, salivary gland, skin, spleen, uterus	C	NM_010283	87
α1-3 GalT	(iGb3s)	–	lung, uterus, pituitary, thymus, skeletal muscle, brain, spleen, kidney	L	AF248543	96
α1-4 GalT	A4GALT1	22q13	ubiquitous	J	NM_017436	102,104
Cer GalT	CGT	4q26	brain, kidney	H	NM_003360	10

* The accession numbers refer to the human genes, except for the two α1-3 GalT Ggta1 and iGb3 synthase, where the numbers point to the mouse and rat cDNA, respectively.

showing that the binding to α-lactalbumin conditions conformational changes in the β4GalT1 structure. These changes modify the catalytic pocket of the enzyme, enabling the transfer of Gal to the Glc acceptor.

The β4GalT1 enzyme is active toward GlcNAc in a broad range of glycoconjugates (fig. 1, product B). β4GalT1 also elongates *O*-fucose glycans found on several epidermal growth factor (EGF)-like protein domains [27]. It is noteworthy that the action of β4GalT1 is required to achieve the Fringe-mediated modulation of Notch signaling [28]. Although several β4GalTs share similar enzymatic properties suggesting functional redundancy, the integrity of the β4GalT1 protein is important in mammalian development and physiology. Mice bearing an inactivated β4GalT1 gene show retarded growth with increased lethality. The β4GalT1 knockout mice also presented skin lesions, endocrine insufficiency, decreased fertility and absence of lactose in milk [29–31]. The critical involvement of β4GalT1 in physiological pathways is also supported by the recent description of a human patient with a complete deficiency of β4GalT1 [C. Körner, personal communication[1]]. This patient showed severe psychomotor retardation and muscle weakness.

β4GalT2

With the emergence of genome databases, novel cDNAs structurally related to β4GalT1 have been identified. The cloning and expression of these complementary DNAs (cDNAs) confirmed their identities as additional members of the β4GalT family. β4GalT2 is structurally and functionally the closest to β4GalT1 [32]. Both proteins share 52% sequence identity, and both genes contain six exons. The human β4GalT2 gene is localized on chromosome 1 at position p33. Like β4GalT1, the β4GalT2 enzyme has a lactose synthase activity in the presence of α-lactalbumin. However, this lactose synthase activity is probably physiologically irrelevant since the lack of lactose in β4GalT1-null mice is not compensated by the action of β4GalT2. The β4GalT2 gene is widely expressed in human tissues, where highest messenger RNA (mRNA) levels are detected in fetal brain and in adult muscle [33]. The β4GalT2 enzyme works in vitro on GlcNAc [32] as well as on glycoprotein acceptors [34]. The relevance of β4GalT2 in animal development and physiology is so far unknown; no mutant organism and no disease related to this gene have been described yet.

β4GalT3

The human β4GalT3 gene was described together with β4GalT2 [32]. The overall identity to the β4GalT1 protein reaches 44%, and several domains show a strict conservation with the other β4GalT proteins. The β4GalT3 gene is like β4GalT1 and β4GalT2 split in six exons, and maps to human chromosome 1 band q21-23. When expressed as a recombinant soluble protein, β4GalT3 utilizes GlcNAcβ- [32] and asialo-agalacto-glycoproteins as acceptors [34]. In addition, β4GalT3 shows significant GalT activity toward the neutral glycolipid acceptor Lc3 [GlcNAc(β1-3)Gal(β1-4)Glc(β1-)ceramide] [32]. The β4GalT3 gene is ubiquitously expressed in human tissues. The biological relevance of β4GalT3 is presently unknown.

β4GalT4

The human β4GalT4 gene was cloned through similarity searching of expressed sequence tag (EST) databases [34]. At the protein level, β4GalT4 shares about 40% identity with the other members of the β4GalT family. The human β4GalT4 gene is on chromosome 3 at position q13 and, like β4GalT1-3, contains six exons. This similar genomic organization and the extensive conservation of the protein-coding sequence suggest that β4GalT1-4 genes have evolved by gene duplication. The β4GalT4 transcript is detected in all human tissues, though the levels of expression vary considerably. Highest mRNA levels are detected in placenta and pancreas. The β4GalT enzyme is specific toward GlcNAcβ-based acceptors. It showed activity with glycoprotein acceptors as well as with the glycolipid acceptors Lc3 and Lc5 [GlcNAc(β1-3)Gal(β1-4)GlcNAc(β1-3)Gal(β1-4)Glc(β1-)ceramide] [34]. β4GalT4 has no lactose synthase activity. In a comparative study, β4GalT4 was the most efficient β4GalT enzyme in catalyzing the extension of poly-*N*-aceyllactosamine chains on GlcNAc(β1-6) branched O-glycans [35]. The biological significance of the β4GalT4 enzyme in vivo remains to be established.

β4GalT5

The molecular cloning of the β4GalT5 cDNA [36] relied on polymerase chain reaction (PCR) amplification using degenerate primers designed after regions conserved between β4GalT1 and a structurally related β1-4 GlcNAc-transferase from the snail *Lymnaea stagnalis* [37]. The β4GalT5 gene maps to chromosome 20q13. Unlike β4GalT1 to 4, the β4GalT5 gene contains 9 exons, suggesting a more distant evolutionary relationship to the previous members of the β4GalT gene family. Also, the β4GalT5 protein shows only about 35% identity to β4GalT1 to 4. The human β4GalT5 cDNA was expressed as a soluble protein A-fusion construct [36]. The activity toward GlcNAc was quite low. The apparent K_m for the GlcNAc acceptor was 33 mM compared with a K_m of 0.6 mM for β4GalT1 [38]. The addition of α-lactalbumin had no inhibitory effect on the *N*-acetyllactosamine syn-

[1] This study has now been published, see Hansske et al. (2002) J. Clin. Invest. 109: 725–733.

thase activity of β4GalT5. Further characterizations have shown that β4GalT5 participates in the biosynthesis of N-glycans [15], whereas a preference toward O-linked acceptors has been noted by others [39]. The biological relevance of β4GalT5 is currently unknown.

β4GalT6

The synthesis of the glycolipid lactosylceramide requires the action of a β4GalT activity. Recombinant β4GalT1 can transfer Gal to Glc-ceramide (fig. 1, product I), though to low efficiency compared with its activity toward GlcNAc acceptors. To identify a better catalyst for the lactosylceramide synthase reaction, Nomura et al. [40] have purified the activity from rat brain, which led to the cloning of a novel cDNA called β4GalT6. The corresponding gene is localized on chromosome 18 at position q11. Its genomic organization, including 9 exons, is similar to that of β4GalT5. The identity at the amino acid level was also highest with β4GalT5, reaching 68%. A comparison of the lactosylceramide synthase activity between the known β4GalT enzymes was not included in the primary description of β4GalT6 [40], but the subsequent description of the Pro$^-$5Lec20 Chinese hamster ovary (CHO) cell deficient for β4GalT6 showed that the loss of this enzyme has no effect on glycolipid profiles, thus indicating that other β4GalTs can also function as lactosylceramide synthase in cells [41]. The characterization of N-glycans in Pro$^-$5Lec20 CHO cells demonstrated that β4GalT6 also accounts for N-glycan biosynthesis, a finding that has been confirmed by the recent characterization of recombinant β4GalT6 activity [15]. No data exist about the roles of β4GalT6 in animal development and physiology.

β4GalT7

The last member of the β4GalT gene family, β4GalT7, was identified by similarity searches of EST databases [42, 43]. At the amino acid level, it is also the farthest member of the family. For example, four cysteines conserved among the other β4GalT are absent in β4GalT7. Also, the sequences of the β4GalT-conserved motifs show significant variations in β4GalT7. The β4GalT7 gene is found on chromosome 5q35 and is split in six exons. The β4GalT7 enzyme specifically recognizes Xyl as acceptor, suggesting that this enzyme represents the XGalTI that catalyzes the first addition of Gal onto the glycosaminoglycan core of proteoglycans (fig. 1, product F). This view was confirmed by finding mutations in the β4GalT7 gene of human patients with decreased XGalTI activity [44]. These patients presented a disease of connective tissues characterized as a progeroid form of the Ehlers-Danlos syndrome [45]. The importance of β4GalT7 in animal development is further supported by the identification of the *sqv*-3 mutant *Caenorhabditis elegans* strain, in which the orthologous β4GalT7 is mutated. The *sqv-3* worms show perturbed epithelium invagination that result in morphological alterations of the vulva [46].

β1-3 Gal-Ts

Back in the early eighties, Sheares and Carlson [47, 48] identified a β3GalT activity derived from pig trachea. They found that this β3GalT activity was directed toward GlcNAc-based acceptors and was not inhibited by α-lactalbumin or by elevated GlcNAc concentrations. It took another 10 years until the first β3GalT genes were cloned and characterized as recombinant proteins. Seven β3GalT genes have been described to date. There is no significant homology between β3GalT and β4GalT proteins, suggesting a separate evolutionary lineage. In fact, β3GalT share some similarities with bacterial galactosyltransferases such as *LgtB* and *LgtE* [49]. β3GalT proteins are structurally related to β1-3 GlcNAc-transferases [50–53], indicating that the maintenance of a β1-3 linkage, rather than of the donor substrate, has dictated the conservation of domains within these proteins (fig. 2).

β3GalT1

The first β3GalT gene was cloned from the human WM266-4 melanoma cell line by expression cloning method [54]. Although the cloning procedure remained unpublished, it appears that the cDNA isolated mediated the expression of the Lewis a antigen when expressed in WM266-4 cells. The mouse orthologous gene was cloned together with two additional β3GalT genes using an EST database screening approach [55]. The entire protein-coding region of the β3GalT1 gene is included in a single exon. In the human genome, the β3GalT1 gene maps to chromosome 2p14. This gene is mainly expressed in brain tissue. Low mRNA levels were also detected in all mouse tissues analyzed [55]. By contrast, the UniGene database only reports expression of β3GalT1 in human brain and germ cells (table 2). The investigation of human and mouse recombinant β3GalT1 proteins confirmed their activity toward GlcNAcβ-linked and glycoprotein acceptors (fig. 1, products A). β3GalT1 can also transfer Gal to both branches of a biantennary asialo-agalacto-N-linked glycan [D. Zhou and F. Altmann, personal communication]. Elevated occurrence of β1-3 galactosylated N-glycans have been reported in rat brain [56], suggesting a relation between this type of galactosylation and the extensive sialylation of brain N-glycans. However, further work will be required to establish the relevance of β3GalT1 in biological processes.

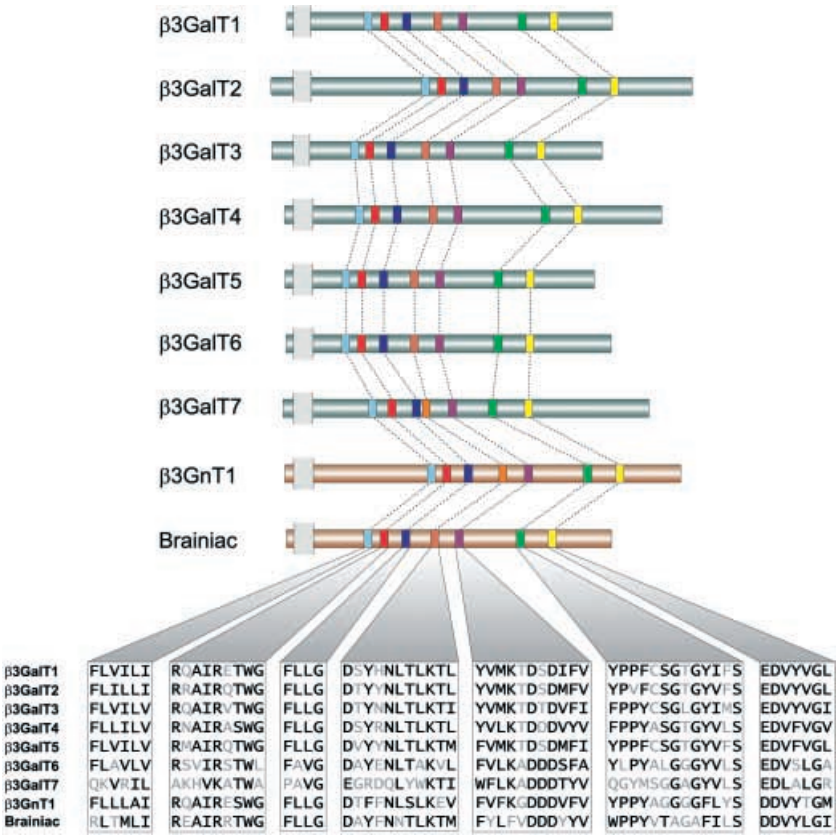

Figure 2. Schematic alignment of β3GalT and β1-3 GlcNAcT (b3GnT) enzymes. Proteins are schematically represented by horizontal bars. Human β3GalT1 to 7 proteins are shown at the top followed by the human β3GnT1 enzyme and the *Drosophila* Brainiac β1-3 GlcNAcT protein. The positions of the conserved domains are indicated as colored rectangles. The bottom panel shows the amino acid sequences of the respective proteins in single-letter code, whereas conserved residues appear in black and nonconserved residues in gray.

β3GalT2

The β3GalT2 gene was also cloned by sequence similarity searches of EST databases, [55, 57, 58]. The β3GalT2 protein includes all β1-3-specific motifs (fig. 2) and shares 51% identity with β3GalT1. A single exon contains the entire protein-coding sequence. The highest β3GalT2 mRNA levels are detected in heart and brain tissues, whereas the gene is also expressed at lower levels in additional tissues. The β3GalT2 enzyme was active toward GlcNAcβ, egg ovalbumin and the Lc3 glycolipid (fig. 1, products A). The specificity of β3GalT2 toward more physiological acceptors as well as the biological functions of the enzyme has not been elucidated yet.

β3GalT3

The β3GalT3 gene was identified together with β3GalT1 and β3GalT2 [55, 58]. The β3GalT3 gene is localized on human chromosome 3 band q25, and like most β3GalT genes, the protein-coding region is included in a single exon. The β3GalT3 protein has about 35% identity to β3GalT1 and β3GalT2. β3GalT3 mRNA is found in several tissues. Highest levels are detected in brain, whereas lower levels are detected in several tissues. When expressed as a full-length recombinant protein, β3GalT3 showed a low GalT activity to GlcNAcβ acceptors compared with the β3GalT enzymes discussed above. Recently, β3GalT3 was also reported to catalyze the transfer of GalNAc onto the terminal Gal unit of the Gb3 glycolipid [59], thereby representing a Gb4 synthase activity. The mouse β3GalT3 gene, which had incorrectly been identified as a mammalian homolog to the *Drosophila melanogaster* Brainiac gene [60, 61], has been inactivated in the mouse germline [62]. The β3GalT3-null embryos die around implantation day E4, indicating that β3GalT3 activity is essential during development. However, the phenotype reported by Vollrath et al. [62] relied on the analysis of mice derived from a single embryonic stem cell clone, which does not exclude the eventuality of a serendipitous unrelated recombination event as the cause of this dramatic phenotype.

β3GalT4

Using an expression cloning strategy aimed at the isolation of cDNAs involved in the biosynthesis of the GD_{1b} ganglioside, Miyazaki et al. [63] identified the rat β3GalT4 gene. Whereas some stretches of the β3GalT4 do not align with the other β3GalTs, all β1-3 motifs domains are conserved (fig. 2). The human β3GalT4 gene is localized on chromosome 6 band p21. The entire protein-coding sequence is included in a single exon. β3GalT4 mRNA is found in several tissues, though at varying levels. The recombinant β3GalT4 enzyme was hardly active on GalNAc alone but worked efficiently on the ganglioside acceptors GM_2, GD_2 and asialo GM_2 (fig. 1, product M) [63]. A β3GalT4 mutant model has not been described yet. However, mice lacking the β1-4 GalNAc-transferase synthesizing GM2, GD2, i. e. the substrates of β3GalT4, have been previously described [64, 65]. These mice present myelination defects and male sterility, thus supporting the importance of complex gangliosides in mammalian physiology.

β3GalT5

An additional β3GalT gene has been isolated by sequence homology search strategy [66, 67]. This gene was named β3GalT5 and was shown to encode a protein that includes all β1-3 sequence motifs (fig. 2). The β3GalT5 gene was split in four exons, whereas the open reading frame was completely found in exon 4. The β3GalT5 gene is mainly expressed in colon, stomach, pancreas and testis. When tested on monosaccharide acceptors, the recombinant β3GalT5 enzyme is only active on GlcNAcβ. Unique among β3GalT enzymes, β3GalT5 shows a marked preference for the O-linked *core3* GlcNAcβ1-3GalNAc structure (fig. 1, product E), suggesting that β3GalT5 probably represents the mucin-specific β3GalT activity characterized by Sheares and Carlson in 1983 [47, 48]. The β3GalT5 enzyme is also unique among glycosyltansferases, as it expresses a second acceptor substrate specificity. Whereas β3GalT5 cannot utilize GalNAc as monomeric acceptor, it does transfer Gal efficiently to the terminal GalNAc unit of the Gb4 glycolipid [68], thereby catalyzing the formation of Gb5 (fig. 1, products K), also known as stage-specific embryonic antigen-3 (SSEA-3) [69]. Moreover, β3GalT5 induction in gastrointestinal and pancreatic tumors mediates the expression of Lewis A and sialyl-Lewis A antigens [66], which is often seen as a negative prognostic for metastatic behaviour. However, the exact role of β3GalT5 in these processes as well as in mammalian development remains to be established. On the other hand, a specific phenotype has been described in a mutant *C. elegans* strain. Mutations in the *bre-5* gene, probably the worm ortholog to β3GalT5, did not cause any developmental abnormality but conferred a resistance to Bt toxin [70].

β3GalT6

The β3GalT6 was identified from genome databases as an open reading frame (ORF) containing the β1-3-specific sequence motifs [71]. This gene mapping to chromosome 1 includes a single exon; β3GalT6 transcripts are detected in all tissues investigated. The β3GalT6 enzyme catalyzes the transfer of Gal to the Gal(α1-4)Xyl acceptor, thus completing the formation of the glycosaminoglycan (GAG) core of proteoglycans (fig. 1, product G). None of the other β3GalT enzymes showed any significant activity toward Gal(α1-4)Xyl, suggesting that β3GalT6 is the only enzyme acting on the GAG core. This hypothesis was confirmed by small interfering RNA (siRNA)-mediated silencing of the β3GalT6 gene in HeLa cells. The addition of siRNA indeed caused a decrease of glycosaminoglycan biosynthesis in the cells. The loss of β3GalT6 activity has not been reported in an animal model yet. However, it is predicted that such a defect would be incompatible with life.

β3GalT7

In contrast to most β3GalT, the gene encoding the β3GalT7 enzyme, which is also called *core1* galactosyltransferase (C1GALT), has been cloned [72] after purification of the protein by affinity chromatography and peptide sequencing [73]. β3GalT7 is structurally the most distant member of the β3GalT protein family. The sequence motifs conserved among β1-3 glycosyltransferases are hardly recognizable in the β3GalT7 protein sequence (fig. 2). The genomic organization of β3GalT7 also differs from the other β3GalTs, as the protein-coding sequence of β3GalT7 is included in three exons. The human β3GalT7 gene is found on chromosome 7; it is widely expressed, although not ubiquitously according to Northern blot data and the UniGene database, raising the possibility that additional proteins with *core1* synthase activity may exist. In fact, at least two homologous genes have been identified in the *Drosophila* genome [72]. The β3GalT7 enzyme catalyzes the formation of the O-linked *core1* glycan, Gal(β1-3)GalNAc-O (fig. 1, product D), which is widespread on mucin glycoproteins. β3GalT7 efficiently utilized GalNAc(α1-)phenyl as acceptor, whereas a glycopeptide acceptor derived from the N-terminal sequence of the human P-selectin glycoprotein ligand-1 was an even better substrate [73]. To date, one disease has been related to defective β3GalT7 activity. The Tn syndrome is a rare acquired mild hemolytic anemia caused by the presence of bare GalNAc O-linked glycans (Tn antigen) on blood cells [74]. The molecular basis of this disease is still unclear, but it leads to an absence of β3GalT7 activity restricted to blood cells [75, 76]. Furthermore, the abnormal O-linked galactosylation of serum IgA_1 has been postulated to account for the mesangial deposition of this class of antibody in IgA nephropa-

thy [77, 78]. The availability of the β3GalT7 gene sequence will now allow determining whether alterations of this gene are indeed causally related to the disease.

α1-3 Gal-Ts

Three structurally related α3GalT genes have been cloned to date. The α3GalT family has the particularity that the majority of the human population does not express any α3GalT activity. Despite the apparent lack of known function, α3GalT have been among the first glycosyltransferase genes to be cloned.

α3GalT (ABO)

The structural nature of the ABO blood group system has been established by the work of Morgan [79], Kabat [80] and their colleagues [81], which opened the way to the biochemical characterization of the glycosyltransferase enzymes involved in this biosynthetic pathway. The A enzyme activity, i.e. α1-3 GalNAc-transferase, was the first to be purified to homogeneity [82, 83]. Partial peptide sequences enabled the isolation of a cDNA encoding a predicted polypeptide of 41 kDa [84]. The gene coding for the B enzyme with the α3GalT activity was isolated by homology screening with the A enzyme cDNA [84]. This seminal work defined the genetic basis of the ABO blood group system, showing that only four nucleotide changes differentiate the A from the B enzyme and that only two amino acid substitutions define the change of donor substrate specificity. In O persons, the ABO gene includes nucleotide deletions and point mutations that inactivate the enzymatic activity. The ABO gene is split in seven exons [85] that are localized on chromosome 9 band q34. The gene is differentially expressed in human tissues; high mRNA levels are found in epithelial cells, low levels in liver, kidney, spleen and blood cells. The ABO gene is not expressed in brain tissue. The B enzyme transfers Gal in a α1-3 linkage to Galβ acceptors found on glycolipids (fig. 1, product N) and glycoproteins. The deficiency of both A and B enzymes does not apprear to be detrimental to individuals of blood group O. The biological functions of the ABO blood group system remain unknown.

α3GalT (Ggta1)

As much as 1% of circulating antibodies in humans recognize a disaccharide antigen, the Gal(α1-3)Gal epitope. The Gal(α1-3)Gal structure (fig. 1, product C), which differs from the fucosylated blood group B antigen (fig. 1, product N), does not occur in humans. By contrast, a α3GalT activity catalyzing the formation of Gal(α1-3)Gal is found in nearly all mammalian species. The bovine α3GalT enzyme Ggta1 was purified from calf thymus [86] and applied as antigen to generate anti-α3GalT antibodies. This antiserum was used to isolate bovine cDNA from by immunoscreening from a gt11 λ-phage cDNA library [87]. Bovine Ggta1 cDNA encodes a protein of 368 amino acids, which shows about 45% identity to the B enzyme α3GalT. The genomic organization of the murine Ggta1 gene has been determined, showing the presence of nine exons [88]. The catalytic domain of the bovine Ggta1 has been crystallized, and its structure was determined at 2.3 Å [89] and at 1.53 Å [90]. The Ggta1 protein shows a globular shape, with a UDP binding domain similar to those visualized in β4GalT1 [25] and in the rabbit *N*-acetylglucosaminyltransferase GnT1 [91]. Humans, apes and Old-World monkeys do not express the α3GalT Ggta1 activity but carry two Ggta1 pseudogenes in their genomes [92]. This deficiency resulted from an inactivation of the α3GalT gene in a common ancestral genome between 22 and 32 million years ago [93]. The loss of the Ggta1 gene does not appear to be detrimental for the species concerned, and the biological significance of the presence or absence of the α3GalT Ggta1 activity is still unclear. The Ggta1 gene has been disrupted in mice. Ggta1-null animals develop normally. They are fertile and have a normal life expectancy [94]. The only abnormality detected was the development of cortical cataracts [95].

α3GalT (iGb3s)

The isoglobo-series glycolipid pathway is enabled by the expression of a α3GalT active on the lactosylceramide acceptor giving rise to the iGb3 glycolipid (fig. 1, product L). The rat gene encoding the iGb3 synthase enzyme has been isolated by expression cloning strategy [96]. The rat iGb3 synthase protein shares about 39% identity with the other α3GalTs and with the Forssman α1-3 GalNAc-transferase [97]. A human iGb3 synthase gene has not been described yet, and it would probably not encode a functional enzyme. In fact, both the human homologs to the α3GalT Ggta1 gene [92] and to the α1-3 GalNAc-transferase Forssman synthase [98] do not yield active proteins, supporting the idea of a selection pressure exerted against the expression of Gal(α1-3)Gal and GalNAc(α1-3)Gal antigens in humans. (Iso)globo-series glycolipids often function as receptors for pathogens like bacteria, viruses and toxins [99]. It is possible that the suppression of Gal(α1-3)Gal-related epitopes may confer an advantage for the respective hosts toward various microbes and toxins.

α1-4 Gal-T

In mammals, the occurrence of α1-4-linked Gal is restricted to glycolipids. α1-4 GalT activities have been re-

lated to the formation of Gb3 [Gal(α1-4)Gal(β1-4)Glc(β1-)ceramide] (fig. 1, product J), also known as the B cell differentiation marker CD77 [100], and to the formation of the P_1 glycolipid [Gal(α1-4)Gal(β1-4)GlcNAc(β1-3)Gal(β1-4)Glc(β1-)ceramide]. Differential presentation of the glycolipids P [GalNAc(β1-3)Gal(α1-4)Gal(β1-4)Glc(β1-)ceramide] and P_1 constitutes the basis of the P histo-blood group system [101].

α4GalT1

The rat [102] and the human [103] genes encoding the Gb3 synthase enzyme have been isolated by expression cloning approaches and by EST screening for similarity to a known α1-4 glycosyltransferase [104]. The human gene includes a single exon that maps to chromosome 22 at position q13. The human α4GalT1 gene is highly expressed in kidney and to lower levels in all tissues investigated. The α4GalT1 protein is about 40% identical to a α1-4 GlcNAc-transferase enzyme, which is involved in the formation of the GlcNAc(α1-4)Gal(β1-4) glycan in class III mucin proteins [105]. The recombinant α4GalT1 enzyme efficiently transferred Gal to lactosylceramide, thus yielding the Gb3 glycolipid (fig 1, product J). By contrast, α4GalT1 could not catalyze the formation of the P_1 glycolipid from the paragloboside [Gal(β1-4)GlcNAc(β1-3)Gal(β1-4)Glc(β1-)ceramide] acceptor. A missense mutation in the α4GalT1 gene has been described in bearers of the rare p blood group [104]. These individuals show elevated lactosylceramide levels on erythrocyte membranes and absence of P^K and P_1 structures. Work from several groups has shown that women of p phenotype are at risk for early abortion because of circulating anti-PP_1P^k antibodies reacting with fetus structures [106, 107]. Individuals expressing the P_1 structure are more susceptible to urinary tract infections by pyelonephritogenic *Escherichia coli*, whose p-fimbriae preferentially bind the P_1 glycolipid [108]. Since α4GalT1 cannot synthesize the P_1 glycolipid in vitro [104], it is possible that a second α4GalT enzyme exists with a specificity toward paragloboside.

Ceramide Gal-T

Myelin is mainly composed of lipids, and galactosylceramide (GalCer), also known as galactocerebroside, represents by far the most abundant glycolipid among them. The formation of GalCer (fig. 1, product H) is catalyzed by CGT, an activity found in the myelinating brain [109]. The gene encoding the CGT enzyme was first cloned from rat brain tissue [10]. The characterization of the protein encoded by the CGT gene revealed some surprising features. First, the CGT protein is localized in the endoplasmic reticulum and has a type I topology unlike the Golgi glycosyltransferases. Second, CGT shares significant homology with the family of hepatic UDP-glucuronyltransferase enzymes, which are involved in the detoxification of xenobiotics. By contrast, CGT shows no structural similarity to any other mammalian GalTs. The human CGT gene maps to chromosome 4, band q26. CGT transcripts are principally found in myelinating oligodendrocytes in the central nervous system and in Schwann cells in the peripheral nervous system. Very low mRNA levels are also detected in kidney, colon, pancreas, lung and testis. Mice lacking CGT activity have been engineered by targeted gene disruption [110, 111]. These animals develop normally, showing a normal brain structure, ultrastructurally normal myelin sheets and normal oligodendrocyte count. The loss of GalCer was compensated by a novel species, GlcCer, which is normally not found in myelin. However, GlcCer does not functionally replace GalCer, and the CGT-null mice progressively develop severe paralysis due to impaired nerve conduction. This knockout mouse model clearly illustrates the importance and specificity of carbohydrates in biological processes; even a slight change in the sugar moiety of a given molecule can have dramatic consequences for an organism.

Conclusions

With the availability of the complete human genome sequence, it is likely that nearly all human GalT genes have been identified. So what can we learn from the study of the GalT family in its present form?

We have seen that several GalT enzymes generate a variety of galactosylated structures in almost all glycoconjugate classes. Through the catalysis of four different linkage types, GalT enzymes contribute a great deal to the number of possible combinations in binding carbohydrate units to each other, thereby contributing to the diversity of the glycoconjugate repertoire. In addition, terminal Gal functions as ligand for endogenous lectins, such as the family of galectins that bind β-Gal [112]. The regulated expression of multiple GalT enzymes allows tight control of the presentation of the ligand Gal in a variable structural and temporal context.

The identification of several structurally related GalT genes implies a selection pressure favouring gene duplication events and enabling the evolution of GalT enzymes with specific properties. Similar expansion in the number of related genes also occurs in other glycosyltransferase families, which suggests a general pressure aimed at increasing the structural diversity of glycoconjugates in mammals. The phenotypes observed in mice bearing inactivated glycosyltransferase genes supports the high degree of cell specificity for the functions associated to terminal glycan structures [113].

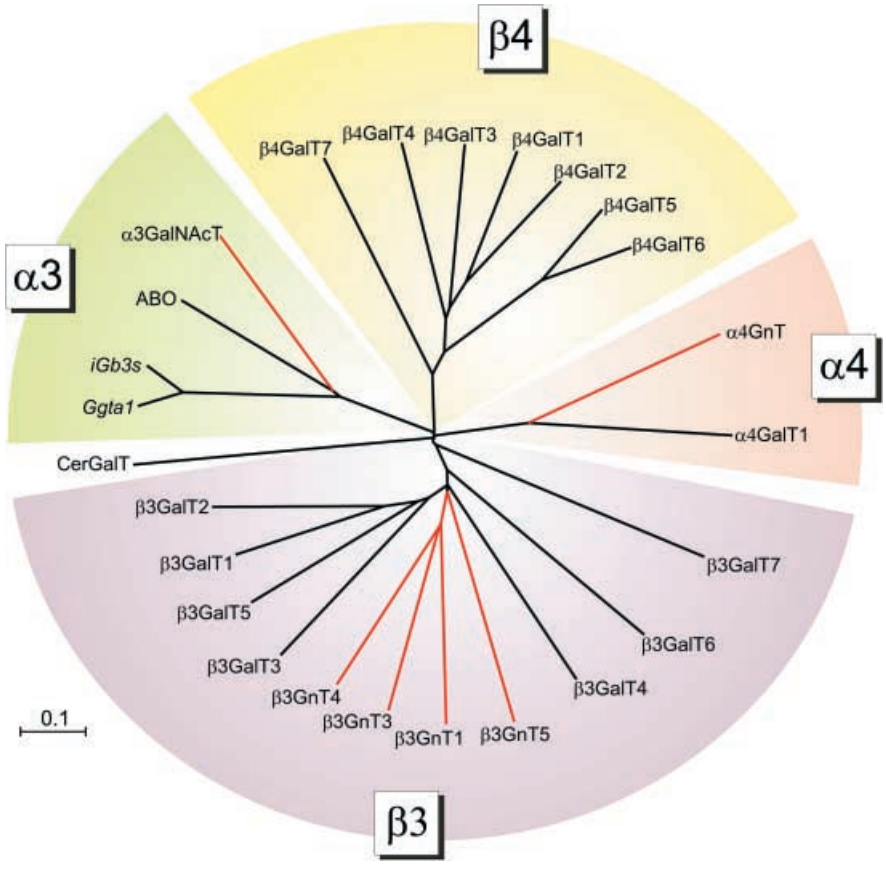

Figure 3. Phylogenetic analysis of human GalTs and related proteins. ClustalW alignment was performed on the full-length protein sequences of the human proteins, except for the α3GalT Ggta1 and iGb3s where mouse sequences have been used. The α3GalNAcT represents the inactive human Forssman synthase protein [98]. The α4GnT represents the human class-III mucin-specific α4GlcNAcT [105]. The β3GnT1, 3, 4, 5 represent β3GlcNAcT enzymes [50–53]. The relationship between the protein sequences is represented as an unrooted cladogram. The branches connecting non-GalT enzymes are shown in red. The scale bar indicates the number of substitutions per site.

There appear to have been evolutionary pressures toward the development of multiple GalT genes. Opposite pressures are also apparent as observed by the inactivation of α1-3 GalT and α1-3 GalNAcT genes in humans. The absence of Gal[NAc](α1-3)Gal epitopes allows an efficient immune response against pathogens that express this disaccharide. Along this line, serum anti-α1-3 Gal antibodies have been shown to protect human cells from infection with mammalian C-type retroviruses [114]. On the other hand, glycans are also used by infectious bacteria as protection from complement, serum and polymorphonuclear cell-mediated cytotoxicity. The presence of galactosylated glycans on bacteria also allows mimicking of surface structures of host organisms and thus evasion of immune surveillance. As discussed by Gagneux and Varki [115], the gains and losses of glycosyltransferase genes can be considered in an evolutionary perspective where hosts and pathogens try to maintain optimal chances of survival.

Finally, looking at the phylogenetic tree of human GalT proteins (fig. 3), one might claim that there is no such thing as a GalT family. In fact, β1-3 GalTs share more structural similarity to β1-3 GlcNAcT enzymes than to β1-4 GalTs, and the same observation applies to the other types of GalT proteins. The comparison of the GalT protein sequences shows that changes of donor substrate specificity seem to be more easily convened than conversions to another type of linkage. In view of these structural considerations, the grouping of enzymes as either β1-4, β1-3, α1-3 or α1-4 UDP-glycosyltransferases would appear more appropriate.

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1 Preston A., Mandrell R. E., Gibson B. W. and Apicella M. A. (1996) The lipooligosaccharides of pathogenic gram-negative bacteria. Crit Rev. Microbiol. **22:** 139–180
2 Kolkman M. A., van der Zeijst B. A. and Nuijten P. J. (1997) Functional analysis of glycosyltransferases encoded by the capsular polysaccharide biosynthesis locus of *Streptococcus pneumoniae* serotype 14. J. Biol. Chem. **272:** 19502–19508

3 Jennings M. P., Virji M., Evans D., Foster V., Srikhanta Y. N., Steeghs L. et al. (1998) Identification of a novel gene involved in pilin glycosylation in *Neisseria meningitidis*. Mol. Microbiol. **29:** 975–984

4 Chappell T. G., Hajibagheri M. A., Ayscough K., Pierce M. and Warren G. (1994) Localization of an α1,2 galactosyltransferase activity to the Golgi apparatus of *Schizosaccharomyces pombe*. Mol. Biol. Cell **5:** 519–528

5 Miege C., Marechal E., Shimojima M., Awai K., Block M. A., Ohta H. et al. (1999) Biochemical and topological properties of type A MGDG synthase, a spinach chloroplast envelope enzyme catalyzing the synthesis of both prokaryotic and eukaryotic MGDG. Eur. J. Biochem. **265:** 990–1001

6 Awai K., Marechal E., Block M. A., Brun D., Masuda T., Shimada H. et al. (2001) Two types of MGDG synthase genes, found widely in both 16:3 and 18:3 plants, differentially mediate galactolipid syntheses in photosynthetic and nonphotosynthetic tissues in *Arabidopsis thaliana*. Proc. Natl. Acad. Sci. USA **98:** 10960–10965

7 Miller K. D., Guyon V., Evans J. N., Shuttleworth W. A. and Taylor L. P. (1999) Purification, cloning and heterologous expression of a catalytically efficient flavonol 3-O-galactosyltransferase expressed in the male gametophyte of *Petunia hybrida*. J. Biol. Chem. **274:** 34011–34019

8 Edwards M. E., Dickson C. A., Chengappa S., Sidebottom C., Gidley M. J. and Reid J. S. (1999) Molecular characterisation of a membrane-bound galactosyltransferase of plant cell wall matrix polysaccharide biosynthesis. Plant J. **19:** 691–697

9 Fitchette A. C., Cabanes-Macheteau M., Marvin L., Martin B., Satiat-Jeunemaitre B., Gomord V. et al. (1999) Biosynthesis and immunolocalization of Lewis a-containing N-glycans in the plant cell. Plant Physiol. **121:** 333–344

10 Schulte S. and Stoffel W. (1993) Ceramide UDPgalactosyltransferase from myelinating rat brain: purification, cloning and expression. Proc. Natl. Acad. Sci. USA **90:** 10265–10269

11 Sprong H., Kruithof B., Leijendekker R., Slot J. W., van Meer G. and van der S. P. (1998) UDP-galactose:ceramide galactosyltransferase is a class I integral membrane protein of the endoplasmic reticulum. J. Biol. Chem. **273:** 25880–25888

12 Breton C., Bettler E., Joziasse D. H., Geremia R. A. and Imberty A. (1998) Sequence-function relationships of prokaryotic and eukaryotic galactosyltransferases. J. Biochem. (Tokyo) **123:** 1000–1009

13 Hagopian A. and Eylar E. H. (1968) Glycoprotein biosynthesis: studies on the receptor specificity of the polypeptidyl: *N*-acetylgalactosaminyltransferase from bovine submaxillary glands. Arch. Biochem. Biophys. **128:** 422–433

14 Altschul S. F., Boguski M. S., Gish W. and Wootton J. C. (1994) Issues in searching molecular sequence databases. Nat. Genet. **6:** 119–129

15 Guo S., Sato T., Shirane K. and Furukawa K. (2001) Galactosylation of N-linked oligosaccharides by human β-1,4- galactosyltransferases I, II, III, IV, V and VI expressed in Sf-9 cells. Glycobiology **11:** 813–820

16 Shaper N. L., Shaper J. H., Meuth J. L., Fox J. L., Chang H., Kirsch I. R. et al. (1986) Bovine galactosyltransferase: identification of a clone by direct immunological screening of a cDNA expression library. Proc. Natl. Acad. Sci. USA **83:** 1573–1577

17 Narimatsu H., Sinha S., Brew K., Okayama H. and Qasba P. K. (1986) Cloning and sequencing of cDNA of bovine N-acetylglucosamine (β1-4)galactosyltransferase. Proc. Natl. Acad. Sci. USA **83:** 4720–4724

18 Brodbeck U., Denton W. L., Tanahashi N. and Ebner K. E. (1967) The isolation and identification of the B protein of lactose synthetase as α-lactalbumin. J. Biol. Chem. **242:** 1391–1397

19 Rajput B., Shaper N. L. and Shaper J. H. (1996) Transcriptional regulation of murine β1,4-galactosyltransferase in somatic cells. Analysis of a gene that serves both a housekeeping and a mammary gland-specific function. J. Biol. Chem. **271:** 5131–5142

20 Berger E. G., Mandel T. and Schilt U. (1981) Immunohistochemical localization of galactosyltransferase in human fibroblasts and HeLa cells. J. Histochem. Cytochem. **29:** 364–370

21 Roth J. and Berger E. G. (1982) Immunocytochemical localization of galactosyltransferase in HeLa cells: codistribution with thiamine pyrophosphatase in trans-Golgi cisternae. J. Cell Biol. **93:** 223–229

22 Shur B. D., Evans S. and Lu Q. (1998) Cell surface galactosyltransferase: current issues. Glycoconj. J. **15:** 537–548

23 Childs R. A., Berger E. G., Thorpe S. J., Aegerter E. and Feizi T. (1986) Blood-group-related carbohydrate antigens are expressed on human milk galactosyltransferase and are immunogenic in rabbits. Biochem. J. **238:** 605–611

24 Hollis G. F., Douglas J. G., Shaper N. L., Shaper J. H., Stafford-Hollis J. M., Evans R. J. et al. (1989) Genomic structure of murine β-1,4-galactosyltransferase. Biochem. Biophys. Res. Commun. **162:** 1069–1075

25 Gastinel L. N., Cambillau C. and Bourne Y. (1999) Crystal structures of the bovine β4galactosyltransferase catalytic domain and its complex with uridine diphosphogalactose. EMBO J. **18:** 3546–3557

26 Ramakrishnan B. and Qasba P. K. (2001) Crystal structure of lactose synthase reveals a large conformational change in its catalytic component, the β1,4-galactosyltransferase-I. J. Mol. Biol. **310:** 205–218

27 Moloney D. J. and Haltiwanger R. S. (1999) The *O*-linked fucose glycosylation pathway: identification and characterization of a uridine diphosphoglucose: fucose-β1,3-glucosyltransferase activity from Chinese hamster ovary cells. Glycobiology **7:** 679–687

28 Chen J., Moloney D. J. and Stanley P. (2001) Fringe modulation of Jagged1-induced Notch signaling requires the action of β4galactosyltransferase-1. Proc. Natl. Acad. Sci. USA **98:** 13716–13721

29 Asano M., Furukawa K., Kido M., Matsumoto S., Umesaki Y., Kochibe N. et al. (1997) Growth retardation and early death of β-1,4-galactosyltransferase knockout mice with augmented proliferation and abnormal differentiation of epithelial cells. EMBO J. **16:** 1850–1857

30 Lu Q. and Shur B. D. (1997) Sperm from β1,4-galactosyltransferase-null mice are refractory to ZP3-induced acrosome reactions and penetrate the zona pellucida poorly. Development **124:** 4121–4131

31 Lu Q., Hasty P. and Shur B. D. (1997) Targeted mutation in β1,4-galactosyltransferase leads to pituitary insufficiency and neonatal lethality. Dev. Biol. **181:** 257–267

32 Almeida R., Amado M., David L., Levery S. B., Holmes E. H., Merkx G. et al. (1997) A family of human β-4-galactosyltransferases; cloning and expression of two novel UDP-galactose: β-*N*-acetylglucosamine β1,4-galactosyltransferases, β4Gal-T2 and β4Gal-T3. J. Biol. Chem. **272:** 31979–31991

33 Lo N. W., Shaper J. H., Pevsner J. and Shaper N. L. (1998) The expanding β4-galactosyltransferase gene family: messages from the databanks. Glycobiology **8:** 517–526

34 Schwientek T., Almeida R., Levery S. B., Holmes E. H., Bennett E. and Clausen H. (1998) Cloning of a novel member of the UDP-galactose-β-*N*-acetylglucosamine β-1,4-galactosyltransferase family, β-4Gal-T4, involved in glycosphingolipid biosynthesis. J. Biol. Chem. **273:** 29331–29340

35 Ujita M., McAuliffe J., Schwientek T., Almeida R., Hindsgaul O., Clausen H. et al. (1998) Synthesis of poly-*N*-acetyllactosamine in core 2 branched O-glycans. The requirement of novel β-1,4-galtactosyltransferase IV and β-1,3-N-acetylglucosaminyltransferase. J. Biol. Chem. **273:** 34843–34849

36 Sato T., Furukawa K., Bakker H., van den Eijnden D. H. and Van Die I. (1998) Molecular cloning of a human cDNA encoding β-1,4-galactosyltransferase with 37% identity to mammalian UDP-Gal:GlcNAc β-1,4-galactosyltransferase. Proc. Natl. Acad. Sci. USA **95:** 472–477

37 Bakker H., Agterberg M., Van Tetering A., Koeleman C. A., van den Eijnden D. H. and Van Die I. (1994) A *Lymnaea stagnalis* gene, with sequence similarity to that of mammalian β1,4-galactosyltransferases, encodes a novel UDP-GlcNAc:GlcNAc β-r β1-4-*N*-acetylglucosaminyltransferase. J. Biol. Chem. **269:** 30326–30333

38 Furukawa K. and Sato T. (1999) β-1,4-galactosylation of N-glycans is a complex process. Biochim. Biophys. Acta **1473:** 54–66

39 Van Die I., Van Tetering A., Schiphorst W. E., Sato T., Furukawa K. and van den Eijnden D. H. (1999) The acceptor substrate specificity of human β4-galactosyltransferase V indicates its potential function in O-glycosylation. FEBS Lett. **450:** 52–56

40 Nomura T., Takizawa M., Aoki J., Arai H., Inoue K., Wakisaka E. et al. (1998) Purification, cDNA cloning and expression of UDP-Gal: glucosylceramide β-1,4-galactosyltransferase from rat brain. J. Biol. Chem. **273:** 13570–13577

41 Lee J., Sundaram S., Shaper N. L., Raju T. S. and Stanley P. (2001) Chinese hamster ovary (CHO) cells may express six β4- galactosyltransferases (β4GalTs). Consequences of the loss of functional β4GalT-1, β4GalT-6, or both in CHO glycosylation mutants. J. Biol. Chem. **276:** 13924–13934

42 Okajima T., Yoshida K., Kondo T. and Furukawa K. (1999) Human homolog of *Caenorhabditis elegans* sqv-3 gene is galactosyltransferase I involved in the biosynthesis of the glycosaminoglycan-protein linkage region of proteoglycans. J. Biol. Chem. **274:** 22915–22918

43 Almeida R., Levery S. B., Mandel U., Kresse H., Schwientek T., Bennett E. P. et al. (1999) Cloning and expression of a proteoglycan UDP-galactose:β-xylose β1,4-galactosyltransferase I. A seventh member of the human β4- galactosyltransferase gene family. J. Biol. Chem. **274:** 26165–26171

44 Quentin E., Gladen A., Roden L. and Kresse H. (1990) A genetic defect in the biosynthesis of dermatan sulfate proteoglycan: Galactosyltransferase I deficiency in fibroblasts from a patient with a progeroid syndrome. Proc. Natl. Acad. Sci. USA **87:** 1342–1346

45 Okajima T., Fukumoto S., Furukawa K. and Urano T. (1999) Molecular basis for the progeroid variant of Ehlers-Danlos syndrome. Identification and characterization of two mutations in galactosyltransferase I gene. J. Biol. Chem. **274:** 28841–28844

46 Herman T. and Horvitz H. R. (1999) Three proteins involved in *Caerohhabditis elegans* vulval invagination are similar to components of a glycosylation pathway. Proc. Natl. Acad. Sci. USA **96:** 974–979

47 Sheares B. T., Lau J. T. and Carlson D. M. (1982) Biosynthesis of galactosyl-β1,3-N-acetylglucosamine. J. Biol. Chem. **257:** 599–602

48 Sheares B. T. and Carlson D. M. (1983) Characterization of UDP-galactose:2-acetamido-2-deoxy-D-glucose 3β-galactosyltransferase from pig trachea. J. Biol. Chem. **258:** 9893–9898

49 Gotschlich E. C. (1994) Genetic locus for the biosynthesis of the variable portion of *Neisseria gonorrhoeae* lipooligosaccharide. J. Exp. Med. **180:** 2181–2190

50 Zhou D., Dinter A., Gutierrez Gallego R., Kamerling J. P., Vliegenthart J. F. G., Berger E. G. et al. (1999) A β-1,3-*N*-acetylglucosaminyltransferase with poly-*N*-acetyllactosamine synthase activity is structurally related to β-1,3-galactosyltransferases. Proc. Natl. Acad. Sci. USA **96:** 406–411, correction in Proc. Natl. Acad. Sci. USA **97:** 11673–11675

51 Shiraishi N., Natsume A., Togayachi A., Endo T., Akashima T., Yamada Y. et al. (2000) Identification and characterization of three novel β1,3-*N*-acetylglucosaminyltransferases structurally related to the β1,3-galactosyltransferase family. J. Biol. Chem. **276:** 3498–3507

52 Togayachi A., Akashima T., Ookubo R., Kudo T., Nishihara S., Iwasaki H. et al. (2001) Molecular cloning and characterization of UDP-GlcNAc:lactosylceramide β1,3-N-acetylglucosaminlytransferase (β3Gn-T5), an essential enzyme for the expression of the HNK-1 and Lewis X epitopes on glycolipids. J. Biol. Chem. **276:** 22032–22040

53 Henion T. R., Zhou D., Wolfer D. P., Jungalwala F. B. and Hennet T. (2001) Cloning of a mouse β1,3 N-acetylglucosaminyltransferase GlcNAc(β1,3)Gal(β1,4)Glc-ceramide synthase gene encoding the key regulator of lacto-series glycolipid biosynthesis. J. Biol. Chem. **276:** 30261–30269

54 Sasaki K., Sasaki E., Kawashima K., Hanai N., Nishi T. and Hasegawa M. (1994) β-galactosyl-transferase DNA and protein: useful for production of saccharide chains, Japanese patent 6181759

55 Hennet T., Dinter A., Kuhnert P., Mattu T. S., Rudd P. M. and Berger E. G. (1998) Genomic cloning and expression of three murine UDP-galactose:β-*N*-acetylglucosamine β1,3-galactosyltransferase genes. J. Biol. Chem. **273:** 58–65

56 Zamze S., Harvey D. J., Chen Y. J., Guile G. R., Dwek R. A. and Wing D. R. (1998) Sialylated N-glycans in adult rat brain tissue – a widespread distribution of disialylated antennae in complex and hybrid structures. Eur. J. Biochem. **258:** 243–270

57 Kolbinger F., Streiff M. B. and Katopodis A. G. (1998) Cloning of a human UDP-galactose:2-acetamido-2-deoxy-D-glucose 3β-galactosyltransferse catalyzing the formation of type 1 chains. J. Biol. Chem. **273:** 433–440

58 Amado M., Almeida R., Carneiro F., Levery S. B., Holmes E. H., Nomoto M. et al. (1998) A family of human β-3-galactosyltransferases: characterization of four members of a UDP-galactose-*N*-acetylglucosamine/β-*N*-acetylgalactosamine β-1,3-galactosyltransferase family. J. Biol. Chem. **273:** 12770–12778

59 Okajima T., Nakamura Y., Uchikawa M., Haslam D. B., Numata S. I., Furukawa K. et al. (2000) Expression cloning of human globoside synthase cDNAs. Identification of β3Gal-T3 as UDP-*N*-acetylgalactosamine:globotriaosylceramide β1,3-*N*-acetylgalactosaminyltransferase. J. Biol. Chem. **275:** 40498–40503

60 Goode S., Melnick M., Chou T. B. and Perrimon N. (1996) The neurogenic genes *egghead* and *brainiac* define a novel signaling pathway essential for epithelial morphogenesis during *Drosophila* oogenesis. Development **122:** 3863–3879

61 Yuan Y. P., Schultz J., Mlodzik M. and Bork P. (1997) Secreted Fringe-like signaling molecules may be glycosyltransferases. Cell **88:** 9–11

62 Vollrath B., Fitzgerald K. J. and Leder P. (2001) A murine homologue of the *Drosophila brainiac* gene shows homology to glycosyltransferases and is required for preimplantation development of the mouse. Mol. Cell Biol. **21:** 5688–5697

63 Miyazaki H., Fukumoto S., Okada M., Hasegawa T. and Furukawa K. (1997) Expression cloning of rat cDNA encoding UDP-galactose:G_{D2} β1, 3-galactosyltransferase that determines the expression of $G_{D1b}/G_{M1}/G_{A1}$. J. Biol. Chem. **272:** 24794–24799

64 Sheikh K. A., Sun J., Liu Y., Kawai H., Crawford T. O., Proia R. L., Griffin J. W. et al. (1999) Mice lacking complex gangliosides develop Wallerian degeneration and myelination defects. Proc. Natl. Acad. Sci. USA **96:** 7532–7537

65 Takamiya K., Yamamoto A., Furukawa K., Zhao J., Fukumoto S., Yamashiro S. et al. (1998) Complex gangliosides are essential in spermatogenesis of mice: possible roles in the transport of testosterone. Proc. Natl. Acad. Sci. USA **95:** 12147–12152

66 Isshiki S., Togayachi A., Kudo T., Nishihara S., Watanabe M., Kubota T. et al. (1999) Cloning, expression and character-

ization of a novel UDP-galactose: β-*N*-acetylglucosamine β1,3-galactosyltransferase (β3Gal-T5) responsible for synthesis of type 1 chain in colorectal and pancreatic epithelia and tumor cells derived therefrom. J. Biol. Chem. **274:** 12499–12507

67 Zhou D., Berger E. G. and Hennet T. (1999) Molecular cloning of a human UDP-galactose: GlcNAcβ1,3GalNAc β1,3 galactosyltransferase gene encoding an O-linked *core3*-elongation enzyme. Eur. J. Biochem. **263:** 571–576

68 Zhou D., Henion T., Jungalwala F. B., Berger E. G. and Hennet T. (2000) The β1,3-galactosyltransferase β3GalT-V is a stage-specific embryonic antigen-3 (SSEA-3) synthase. J. Biol. Chem. **275** 22631–22634

69 Shevinsky L. H., Knowles B. B., Damjanov I. and Solter D. (1982) Monoclonal antibody to murine embryos defines a stage-specific embryonic antigen expressed on mouse embryos and human teratocarcinoma cells. Cell **30:** 697–705

70 Griffitts J. S., Whitacre J. L., Stevens D. E. and Aroian R. V. (2001) Bt toxin resistance from loss of a putative carbohydrate-modifying enzyme. Science **293:** 860–864

71 Bai X., Zhou D., Brown J.R., Crawford B., Hennet T., and Esko J.D. (2001) Biosynthesis of the linkage region of glycosaminoglycans: cloning and activity of galactosyltransferase II, the sixth member of the β1,3galactosyltransferase family (β3GalT6). J. Biol. Chem. **276:** 48189–48195

72 Ju T., Brewer K., D'Souza A., Cummings R. D. and Canfield W. M. (2002) Cloning and expression of human core 1 β1,3 galactosyltransferase. J. Biol. Chem. **277:** 178–186

73 Ju T., Cummings R. D. and Canfield W. M. (2001) Purification, characterization and subunit structure of rat core 1 β1,3 galactosyltransferase. J. Biol. Chem. **277:** 169–177

74 Berger E. G. (1999) Tn-syndrome. Biochim. Biophys. Acta **1455:** 255–268

75 Berger E. G. and Kozdrowski I. (1978) Permanent mixed-field polyagglutinable erythrocytes lack galactosyltransferase activity. FEBS Lett. **93:** 105–108

76 Cartron J. P. and Nurden A. T. (1979) Galactosyltransferase and membrane glycoprotein abnormality in human platelets from Tn-syndrome donors. Nature **282:** 621–623

77 Tomana M., Julian B. A., Waldo F. B., Kulhavy R. and Mestecky J. (1995) IgA nephropathy. A disease of incomplete IgA_1 glycosylation? Adv. Exp. Med. Biol. **376:** 221

78 Allen A. C., Bailey E. M., Barratt J., Buck K. S. and Feehally J. (1999) Analysis of IgA_1 O-glycans in IgA nephropathy by fluorophore-assisted carbohydrate electrophoresis. J. Am. Soc. Nephrol. **10:** 1763–1771

79 Painter T. J., Watkins W. M. and Morgan W. T. (1965) Serologically active fucose-containing oligosaccharides isolated from human blood-group A and B substances. Nature **206:** 594–597

80 Kabat E. A. (1982) Contributions of quantitative immunochemistry to knowledge of blood group A, B, H, Le, I and i antigens. Am. J. Clin. Pathol. **78:** 281–292

81 Morgan W. T. and Watkins W. M. (1969) Genetic and biochemical aspects of human blood-group A-, B-, H-, Le-a- and Le-b-specificity. Br. Med. Bull. **25:** 30–34

82 Nagai M., Dave V., Kaplan B. E. and Yoshida A. (1978) Human blood group glycosyltransferases. I. Purification of N-acetylgalactosaminyltransferase. J. Biol. Chem. **253:** 377–379

83 Nagai M., Dave V., Muensch H. and Yoshida A. (1978) Human blood group glycosyltransferase. II. Purification of galactosyltransferase. J. Biol. Chem. **253:** 380–381

84 Yamamoto F., Clausen H., White T., Marken J. and Hakomori S. (1990) Molecular genetic basis of the histo-blood group ABO system. Nature **345:** 229–233

85 Yamamoto F., McNeill P. D. and Hakomori S. (1995) Genomic organization of human histo-blood group ABO genes. Glycobiology **5:** 51–58

86 Blanken W. M. and van den Eijnden D. H. (1985) Biosynthesis of terminal Gal α1-3Gal β1-4GlcNAc-R oligosaccharide sequences on glycoconjugates. Purification and acceptor specificity of a UDP-Gal:N-acetyllactosaminide α1-3-galactosyltransferase from calf thymus. J. Biol. Chem. **260:** 12927–12934

87 Joziasse D. H., Shaper J. H., van den Eijnden D. H., Van Tunen A. J. and Shaper N. L. (1989) Bovine α1-3-galactosyltransferase: isolation and characterization of a cDNA clone. identification of homologous sequences in human genomic DNA. J. Biol. Chem. **264:** 14290–14297

88 Joziasse D. H., Shaper N. L., Kim D., van den Eijnden D. H. and Shaper J.H. (1992) Murine α1,3-galactosyltransferase. A single gene locus specifies four isoforms of the enzyme by alternative splicing. J. Biol. Chem. **267:** 5534–5541

89 Gastinel L. N., Bignon C., Misra A. K., Hindsgaul O., Shaper J. H. and Joziasse D. H. (2001) Bovine α1,3-galactosyltransferase catalytic domain structure and its relationship with ABO histo-blood group and glycosphingolipid glycosyltransferases. EMBO J. **20:** 638–649

90 Boix E., Swaminathan G. J., Zhang Y., Natesh R., Brew K. and Acharya K. R. (2001) Structure of UDP complex of UDP-galactose:β-galactoside-α-1,3-galactosyltransferase at 1.53-Å resolution reveals a conformational change in the catalytically important C terminus. J. Biol. Chem. **276:** 48608–48614

91 Unligil U. M., Zhou S., Yuwaraj S., Sarkar M., Schachter H. and Rini J. M. (2000) X-ray crystal structure of rabbit *N*-acetylglucosaminyltransferase I: catalytic mechanism and a new protein superfamily. EMBO J. **19:** 5269–5280

92 Joziasse D. H., Shaper J. H., Jabs E. W. and Shaper N. L. (1991) Characterization of an α1-3-galactosyltransferase homologue on human chromosome 12 that is organized as a processed pseudogene. J. Biol. Chem. **266:** 6991–6998

93 Galili U. and Swanson K. (1991) Gene sequences suggest inactivation of α-1,3-galactosyltransferase in catarrhines after the divergence of apes from monkeys. Proc. Natl. Acad. Sci. USA **88:** 7401–7404

94 Thall A. D., Maly P. and Lowe J. B. (1995) Oocyte Gal α1,3Gal epitopes implicated in sperm adhesion to the zona pellucida glycoprotein ZP3 are not required for fertilization in the mouse. J. Biol. Chem. **270:** 21437–21440

95 Tearle R. G., Tange M. J., Zannettino Z. L., Katerelos M., Shinkel T. A., Van Denderen B. J. et al. (1996) The α-1,3-galactosyltransferase knockout mouse. Implications for xenotransplantation. Transplantation **61:** 13–19

96 Keusch J. J., Manzella S. M., Nyame K. A., Cummings R. D. and Baenziger J. U. (2000) Expression cloning of a new member of the ABO blood group glycosyltransferases, iGb3 synthase, that directs the synthesis of isoglobo-glycosphingolipids. J. Biol. Chem. **275:** 25308–25314

97 Haslam D. B. and Baenziger J. U. (1996) Expression cloning of Forssman glycolipid synthetase: a novel member of the histo-blood group ABO gene family. Proc. Natl. Acad. Sci. USA **93:** 10697–10702

98 Xu H., Storch T., Yu M., Elliott S. P. and Haslam D. B. (1999) Characterization of the human Forssman synthetase gene. An evolving association between glycolipid synthesis and host-microbial interactions. J. Biol. Chem. **274:** 29390–29398

99 Karlsson K. A. (1995) Microbial recognition of target-cell glycoconjugates. Curr. Opinion Struc. Biol. **5:** 622–635

100 Mangeney M., Richard Y., Coulaud D., Tursz T. and Wiels J. (1991) CD77: an antigen of germinal center B cells entering apoptosis. Eur. J. Immunol. **21:** 1131–1140

101 Cartron J. P. (1996) A molecular approach to the structure, polymorphism and function of blood groups. Transfus. Clin. Biol. **3:** 181–210

102 Keusch J. J., Manzella S. M., Nyame K. A., Cummings R. D. and Baenziger J. U. (2000) Cloning of Gb3 Synthase, the key enzyme in globo-series glycosphingolipid synthesis, predicts

a family of α1,4-glycosyltransferases conserved in plants, insects, and mammals. J. Biol. Chem. **275:** 25315–25321
103 Kojima Y., Fukumoto S., Furukawa K., Okajima T., Wiels J., Yokoyama K. et al. (2000) Molecular cloning of globotriaosylceramide/CD77 synthase, a glycosyltransferase that initiates the synthesis of globo series glycosphingolipids. J. Biol. Chem. **275:** 15152–15156
104 Steffensen R., Carlier K., Wiels J., Levery S. B., Stroud M., Cedergren B. et al. (2000) Cloning and expression of the histo-blood group Pk UDP-galactose: Ga1β-4G1cβ1-cer α1,4-galactosyltransferase. Molecular genetic basis of the p phenotype. J. Biol. Chem. **275:** 16723–16729
105 Nakayama J., Yeh J. C., Misra A. K., Ito S., Katsuyama T. and Fukuda M. (1999) Expression cloning of a human α1,4-N-acetylglucosaminyltransferase that forms GlcNAcα1$\rightarrow$4Gal-$\beta\rightarrow$R, a glycan specifically expressed in the gastric gland mucous cell-type mucin. Proc. Natl. Acad. Sci. USA **96:** 8991–8996
106 Lopez M., Cartron J., Cartron J. P., Mariotti M., Bony V., Salmon C. et al. (1983) Cytotoxicity of anti-PP_1Pk antibodies and possible relationship with early abortions of p mothers. Clin. Immunol. Immunopathol. **28:** 296–303
107 Hansson G. C., Wazniowska K., Rock J. A., Ness P. M., Kickler T. S., Shirey R. S. et al. (1988) The glycosphingolipid composition of the placenta of a blood group P fetus delivered by a blood group Pk1 woman and analysis of the anti-globoside antibodies found in maternal serum. Arch. Biochem. Biophys. **260:** 168–176
108 Svanborg Eden C., Hagberg L., Hanson L. A., Hull S., Hull R., Jodal U. et al. (1983) Bacterial adherence: a pathogenetic mechanism in urinary tract infections caused by *Escherichia coli*. Prog. Allergy **33:** 175–188
109 Brenkert A. and Radin N. S. (1972) Synthesis of galactosyl ceramide and glucosyl ceramide by rat brain: assay procedures and changes with age. Brain Res. **36:** 183–193
110 Bosio A., Binczek E. and Stoffel W. (1996) Functional breakdown of the lipid bilayer of the myelin membrane in central and peripheral nervous system by disrupted galactocerebroside synthesis. Proc. Natl. Acad. Sci. USA **93:** 13280–13285
111 Koike C., Katayama A., Kadomatsu K., Hiraiwa N., Hayashi S., Kobayashi T. et al. (1997) Reduction of α-Gal epitopes in transgenic pig by introduction of human α1-2 fucosyltransferase. Transpl. Proc. **29:** 894
112 Cooper D. N. and Barondes S. H. (1999) God must love galectins; he made so many of them. Glycobiology **9:** 979–984
113 Hennet T. and Ellies L. G. (1999) The remodeling of glycoconjugates in mice. Biochim. Biophys. Acta **1473:** 123–136
114 Takeuchi Y., Porter C. D., Strahan K. M., Preece A. F., Gustafsson K., Cosset F. L. et al. (1996) Sensitization of cells and retroviruses to human serum by (α1-3) galactosyltransferase. Nature **379:** 85–88
115 Gagneux P. and Varki A. (1999) Evolutionary considerations in relating oligosaccharide diversity to biological function. Glycobiology **9:** 747–755
116 Gohmann S., Manning P. A., Alpert C. A., Walker M. J. and Timmis K. N. (1994) Lipopolysaccharide O-antigen biosynthesis in *Shigella dysenteriae* serotype 1: analysis of the plasmid-carried rfp determinant. Microb. Pathog. **16:** 53–64
117 Korolik V., Fry B. N., Alderton M. R., van der Zeijst B. A. and Coloe P. J. (1997) Expression of *Campylobacter hyoilei* lipo-oligosaccharide (LOS) antigens in *Escherichia coli*. Microbiology **143:** 3481–3489
118 Clarke B. R., Bronner D., Keenleyside W. J., Severn W. B., Richards J. C. and Whitfield C. (1995) Role of Rfe and RfbF in the initiation of biosynthesis of D-galactan I, the lipopolysaccharide O antigen from *Klebsiella pneumoniae* serotype O1. J. Bacteriol. **177:** 5411–5418
119 Kadam S. K., Rehemtulla A. and Sanderson K. E. (1985) Cloning of rfaG, B, I and J genes for glycosyltransferase enzymes for synthesis of the lipopolysaccharide core of *Salmonella typhimurium*. J. Bacteriol. **161:** 277–284
120 Persson K., Ly H. D., Dieckelmann M., Wakarchuk W. W., Withers S. G. and Strynadka N. C. (2001) Crystal structure of the retaining galactosyltransferase LgtC from *Neisseria meningitidis* in complex with donor and acceptor sugar analogs. Nat. Struct. Biol. **8:** 166–175
121 Bugert P. and Geider K. (1995) Molecular analysis of the ams operon required for exopolysaccharide synthesis of *Erwinia amylovora*. Mol. Microbiol. **15:** 917–933
122 Traurig M. and Misra R. (1999) Identification of bacteriophage K20 binding regions of OmpF and lipopolysaccharide in *Escherichia coli* K-12. FEMS Microbiol. Lett. **181:** 101–108
123 Wollin R., Creeger E. S., Rothfield L. I., Stocker B. A. and Lindberg A. A. (1983) *Salmonella typhimurium* mutants defective in UDP-D- galactose:lipopolysaccharide alpha 1,6-D-galactosyltransferase. Structural, immunochemical, and enzymologic studies of rfaB mutants. J. Biol. Chem. **258:** 3769–3774
124 Kadrmas J. L., Allaway D., Studholme R. E., Sullivan J. T., Ronson C. W., Poole P. S. et al. (1998) Cloning and overexpression of glycosyltransferases that generate the lipopolysaccharide core of *Rhizobium leguminosarum*. J. Biol. Chem. **273:** 26432–26440
125 Gilbert M., Brisson J. R., Karwaski M. F., Michniewicz J., Cunningham A. M., Wu Y. et al. (2000) Biosynthesis of ganglioside mimics in *Campylobacter jejuni* OH4384. Identification of the glycosyltransferase genes, enzymatic synthesis of model compounds, and characterization of nanomole amounts by 600-Mhz (1)h and (13)C NMR analysis. J. Biol. Chem. **275:** 3896–3906
126 Linton D., Gilbert M., Hitchen P. G., Dell A., Morris H. R., Wakarchuk W. W. et al. (2000) Phase variation of a β-1,3 galactosyltransferase involved in generation of the ganglioside GM1-like lipo-oligosaccharide of *Campylobacter jejuni*. Mol. Microbiol. **37:** 501–514
127 Heinrichs D. E., Yethon J. A., Amor P. A. and Whitfield C. (1998) The assembly system for the outer core portion of R1- and R4-type lipopolysaccharides of *Escherichia coli*. The R1 core-specific β-glucosyltransferase provides a novel attachment site for O-polysaccharides. J. Biol. Chem. **273:** 29497–29505
128 Endo T., Koizumi S., Tabata K. and Ozaki A. (2000) Cloning and expression of β1,4-galactosyltransferase gene from *Helicobacter pylori*. Glycobiology **10:** 809–813