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Introduction**BBA - Molecular Basis of Disease****Title: "Glycosylation diseases: quo vadis?"****Authors: Harry Schachter and Hudson Freeze**

Abstract

About 250 to 500 glycogenes (genes that are directly involved in glycan metabolism) are in the human genome representing about 1-2% of the total genome. Over 40 human congenital diseases associated with glycogene mutations have been described to date. It is almost certain that the causative glycogene mutations for many more congenital diseases remain to be discovered. Some glycogenes are involved in the synthesis of only a specific protein and/or a specific class of glycan whereas others play a role in the biosynthesis of more than one glycan class. Mutations in the latter type of glycogene result in complex clinical phenotypes that present difficult diagnostic problems to the clinician. In order to understand in biochemical terms the clinical signs and symptoms of a patient with a glycogene mutation, one must understand how the glycogene works. That requires, first of all, determination of the target protein or proteins of the glycogene followed by an understanding of the role, if any, of the glycogene-dependent glycan in the functions of the protein. Many glycogenes act on thousands of glycoproteins. There are unfortunately no general methods to identify all the potentially large number of glycogene target proteins and which of these proteins are responsible for the mutant phenotypes. Whereas biochemical methods have been highly successful in the discovery of glycogenes responsible for many congenital diseases, it has more recently been necessary to use other methods such as homozygosity mapping. Accurate diagnosis of many recently discovered diseases has become difficult and new diagnostic procedures must be developed. Last but not least is the lack of effective treatment for most of these children and of animal models that can be used to test new therapies.

Introduction

Glycans are significantly more complex than nucleic acids and proteins, the other two major information-bearing biological macromolecules. Nucleic acids and proteins are linear molecules in which the individual subunits (nucleotides and amino acids respectively) are linked respectively by identical phospho-diester and peptide bonds. In contrast, linkages between the individual carbohydrate subunits of glycans are not all the same and the glycan polymers are commonly branched rather than linear. The apparatus required for glycan assembly is unique. Whereas the biosynthesis of nucleic acids and proteins is carried out by relatively simple template mechanisms, glycans require a complex non-template assembly line along which many different enzymes and other proteins work together to make the final glycan product. The spectrum of all glycan structures - the glycome - is immense; in humans, the number of glycan structures is orders of magnitude greater than the number of proteins that are encoded by the genome [1]. Francis Crick's original Central Dogma ignored post-translational modifications (such as protein glycosylation). It is now widely recognized that post-translational modifications can greatly magnify the functions of a single gene [2,3]. This review discusses the nature of glycozymes involved in glycan metabolism, the extremely complex multi-systemic phenotypes that result from congenital defects in glycozymes, the discovery of new glycozymes, and the diagnosis and treatment of glycozyme diseases.

Glycozymes

At least half of all the proteins in the human genome are probably *N*-glycosylated [4]. The number of genes directly involved in glycan metabolism (glycozymes [5,6]) in the human genome is large (~ 250 to 500 genes representing ~ 1-2% of the total number of human genes) and encode many different types of protein: glycosyltransferases, sulfotransferases that act on glycans, oligosaccharyltransferases, nucleotide-sugar transporters and synthases, glycosidases, lectins, genes required for the synthesis or utilization of dolichol-phosphate-mannose and dolichol-phosphate-glucose, glycan flippases, Conserved Oligomeric Golgi (COG) complex proteins required for normal traffic in the Golgi apparatus, various kinases, mutases, isomerases and other enzymes that act on carbohydrates, chaperones and other proteins that ensure proper folding of glycozyme-encoded proteins, and probably many others. Although patients with congenital abnormalities in glycan metabolism (glycan biosynthesis, catabolism or binding) are relatively rare, well over 40 human congenital diseases associated with glycozyme mutations have been described to date: 16 Type I Congenital Disorders of Glycosylation (CDG-Ia to CDG-Ip) [7-14], 8 Type II CDGs (CDG-IIa to CDG-IIh) [7,15-19], 6 Congenital Muscular Dystrophies (CMDs) [20], 2 involving GalNAc α 1-*O*-Ser/Thr glycans [21-24], 2 involving Fuc α 1-*O*-Ser/Thr glycans [25-28], 5 glycosaminoglycan-related diseases [29-36], diseases involving defective glycosphingolipid [37,38] and glycosylphosphatidylinositol [39] synthesis, galactosemia [40-42], I-cell disease and pseudo-Hurler polydystrophy (lysosomal storage diseases) caused by mutations in the gene encoding UDP-*N*-acetylglucosamine:glycoprotein *N*-acetylglucosaminylphosphotransferase [43,44], and hereditary inclusion body myopathy caused by mutations in the UDP-*N*-acetylglucosamine 2-epimerase/*N*-

acetylmannosamine kinase (GNE) gene [45]. It is almost certain that the causative glycogene mutations for many more congenital diseases remain to be discovered.

Some glycogenes are involved in the synthesis of only a specific protein and/or a specific class of glycan, e.g., the six genes involved in the CMDs appear to act primarily on α -dystroglycan, and three of these genes act only on $\text{Man}\alpha 1\text{-O-Ser/Thr}$ -protein, i.e., the genes encoding protein *O*-mannosyltransferases 1 and 2 (*POMT1*, *POMT2*) and protein *O*-mannosyl $\beta 1,2\text{-N-acetylglucosaminyltransferase I}$ (*POMGNT1*). Unlike the CDGs, these *O*-linked disorders possess distinctive muscle, eye, and brain phenotypes [46,47]. Peters-plus syndrome is a rare autosomal recessive disorder involving defects in multiple organ systems. The syndrome is a newly-discovered CDG due to mutations in the $\beta 1,3\text{-glucosyltransferase}$ that adds glucose to $\text{Fuc}\alpha 1\text{-O-Ser/Thr}$ to form a disaccharide specific to thrombospondin type 1 repeats (TSRs). This disaccharide is only found on thrombospondin 1 and a few other other TSR-containing proteins [25].

On the other hand, many glycogenes are involved in the biosynthesis of more than one glycan class because the biosynthetic pathways for glycosphingolipids and for protein-bound $\text{GlcNAc}\beta 1\text{-N-Asn}$, $\text{GalNAc}\alpha 1\text{-O-Ser/Thr}$, $\text{Man}\alpha 1\text{-O-Ser/Thr}$, $\text{Fuc}\alpha 1\text{-O-Ser/Thr}$ and $\text{Xyl}\beta 1\text{-O-Ser}$ (proteoglycans) glycans share glycogenes. For example, several sialyl- [48,49], galactosyl- [50-52] and fucosyltransferases [53-56] are common to two or more of the above pathways, as are various nucleotide-sugar transporters and synthases, members of the COG complex, and others.

Although the clinical presentations of "congenital glycosylation diseases" (this term is used in a very general way in this chapter to include CDGs, CMDs and other glycogene-deficient congenital diseases) may be quite distinct, clinical overlaps occur when mutations occur in glycogenes common to more than one biosynthetic pathway. The following CDGs clearly have the potential to involve both *N*-glycans and other glycan types.

- (i) Defective availability of dolichol-phospho-mannose (Dol-P-Man): CDG-Ia (phosphomannomutase), -Ib (phosphomannose isomerase), -Ie (Dol-P-Man synthase), -If (Dol-P-Man utilization), -Im (dolichol kinase). However, since complete absence of the Type I CDG pathway is lethal, these diseases are all due to "leaky" (hypomorphic) mutations; therefore clinical symptoms of diseases other than those of Type I CDG (e.g., CMD) are unlikely to be visible.
- (ii) Nucleotide-sugar transporter defects: CDG-IIc (GDP-Fuc transporter), -IId (UDP-Gal transporter), -IIIf (CMP-sialic acid transporter).
- (iii) Conserved Oligomeric Golgi (COG) complex proteins: CDG-IIe (COG7), -IIg (COG1), -IIh (COG8). Defects in other COG subunits are also likely to be found. The COG complex consists of 8 Golgi-associated cytoplasmic proteins required for maintaining the structure and function of the Golgi apparatus and for the efficient trafficking of proteins within the Golgi and export out of the Golgi [8,15-19,57]. Mutations in COG proteins therefore alter the activities of glycosyltransferases, glycosidases, nucleotide-sugar transporters and other Golgi-localized proteins with resultant defects in the biosynthesis of $\text{GlcNAc}\beta 1\text{-N-Asn}$, $\text{GalNAc}\alpha 1\text{-O-Ser/Thr}$, $\text{Man}\alpha 1\text{-O-Ser/Thr}$ (defective in the CMDs) and other glycan types [58,59].

(iv) A group of mentally retarded dysmorphic patients with cutis laxa (a condition characterized by sagging skin) probably represents a novel CDG type with defects in either *N*-glycan or both *N*- and *O*-glycan synthesis and an unusual cobblestone-like cortical malformation over the frontal and parietal regions similar to the lesions found in muscle-eye-brain type CMD [60,61]. Loss-of-function mutations in the gene encoding a subunit of the V-type H⁺ ATPase in several of these patients result in abnormal glycosylation of serum proteins and cause an impairment of Golgi trafficking in fibroblasts from affected individuals [62].

Proteins like the COG complex subunits and ATPases are not "glycogenes" in the strict sense since they may be involved in pathways other than glycosylation. Therefore the clinical presentations of such patients may contain elements that are not glycosylation-dependent.

How do glycogenes work?

In order to understand in biochemical terms the clinical signs and symptoms of a patient with a glycogene mutation, one must understand how the glycogene works. That requires, first of all, determination of the target protein or proteins of the glycogene followed by an understanding of the role, if any, of the glycogene-dependent glycan in the functions of the protein. In the case of the CMDs (often called α -dystroglycanopathies [63]), the target protein is known but the role of the Man α 1-*O*-Ser/Thr glycan in α -dystroglycan function is not clear. The target protein problem becomes much more difficult in the CDGs because thousands of glycoproteins share the same glycan structures and a mutation in a particular glycogene affects the glycosylation of many proteins in most, if not all, cells in the body.

A classic approach to determination of gene target proteins and functions is the creation of animals with null mutations in the gene under study. Glycan function has been studied in many mutant organisms: yeast [7,64], mice [3,65,66], flies [67-69], worms [70-72], zebrafish [73,74] and, of course, human "congenital glycosylation diseases". The identities of some of the target proteins of a mutant gene can be determined using mass spectrometry to compare glycopeptides isolated from wild type and mutant organisms [75]. However, only a relatively small number of glycogene target proteins can be identified by current methods.

Taniguchi *et al* [76] have reviewed their approach to the identification of target proteins of three glycosyltransferases involved in *N*-glycan synthesis: β 1,6-*N*-acetylglucosaminyltransferase V (GlcNAcTV; adds a branch to the *N*-glycan core), β 1,4-*N*-acetylglucosaminyltransferase III (GlcNAcTIII; adds the bisecting GlcNAc to the *N*-glycan core), and α 1,6-fucosyltransferase VIII (FucTVIII; adds a fucose residue to the *N*-glycan core).

(i) GlcNAcTV has been shown to stimulate tumor metastasis in mice [77]. Mammary tumor growth and metastases induced by the polyomavirus middle T oncogene were considerably less in GlcNAcTV-null mice than in transgenic littermates expressing GlcNAcTV [77]. Matriptase (a metal-dependent serine protease) was identified as a

GlcNAcTV target protein that enhances cancer invasion and metastasis if a specific Asn residue undergoes GlcNAcTV-dependent glycosylation [76].

(ii) E-cadherin, a homophilic adhesion molecule, has been identified as a GlcNAcTIII target protein [76,78]. The addition of a bisecting GlcNAc by GlcNAcTIII inhibits the action of GlcNAcTV on the same *N*-glycan [79,80]. GlcNAcTIII overexpression has an anti-metastatic effect that may be due, at least in part, to altered *N*-glycan structures on E-cadherin [76,78].

(iii) The transforming growth factor- β (TGF- β) receptors are targets for FucTVIII [76]. FucTVIII down-regulation inhibits TGF- β signaling resulting in increased production of several metalloproteinases (MMPs). The increased levels of MMPs in FucTVIII-null mice causes emphysema-like degeneration of lung tissues [81].

While these results are of great interest, it is important to note that all three of the above enzymes also have many other target proteins that may also play a role in the respective phenotypes. There is unfortunately no general solution to identification of all the potentially large number of glycoenzyme target proteins nor for the identification of which protein(s) are responsible for the mutant phenotypes. There is a very strong possibility that in many "congenital glycosylation diseases", it will not be possible to explain the phenotype on the basis of one or a small number of abnormally glycosylated proteins.

Another aspect of the problem is a possibly deleterious role of hypomorphic alleles and heterozygous mutations in the etiology of disease. Sub-optimal glycosylation may have its impact in a larger context and only under stressed conditions. Work with model organisms is usually carried out with null mutants; perhaps we also need to study the effects of hypomorphic and heterozygous mutations in animal models.

Some pathology in glycosylation disorders is seen only when environmental insult(s) collide with the genetic insufficiency [82]. For instance, protein-losing enteropathy (PLE, loss of plasma proteins through the intestine) occurred in a CDG-Ic patient only during periods of intestinal rotavirus infections [83]. CDG-Ib patients also develop PLE in inflammatory settings [84]. The effects of proinflammatory cytokines and portal hypertension caused by their abnormal liver architecture synergize with loss of heparan sulfate from the intestinal epithelial cells and cascade into a PLE avalanche [82,85,86]. Even small decreases in glycosylation can be deleterious. Mice with 50% normal phosphomannose isomerase have no obvious phenotype, but they show a significant increase in enteric protein loss, which is reversed by adding mannose to their drinking water. Increased pressure and exposure to proinflammatory cytokines further exacerbates protein leakage in these phosphomannose isomerase heterozygotes; mannose reverses the glycosylation-related contribution [82].

Gene discovery and diagnosis

Discovery of glycoenzymes for novel "congenital glycosylation diseases" and diagnosis of known diseases, especially of the Type I and some Type II Congenital Disorders of Glycosylation, have been carried out for many years by various well-established biochemical methods: (i) determination of protein-bound glycan structures, e.g., the

GlcNAc β 1-*N*-Asn *N*-glycans present on serum transferrin and other proteins by isoelectric focusing and mass spectrometry [87], (ii) analysis of biochemical pathways in radio-labeled patient fibroblasts [88-91], and (iii) functional assays (if available) of the enzymes and other proteins known to be involved in glycan synthesis [8].

More recently, a candidate gene approach in combination with homozygosity mapping has been used to discover new disease-causing glycogenes when consanguineous families are available. An excellent example has been the discovery of some of the genes involved in the heterogeneous Walker-Warburg Syndrome (WWS), an autosomal recessive developmental disorder characterized by CMD and complex brain and eye abnormalities. A genomewide linkage analysis in 10 consanguineous families with WWS was reported in 2002 and indicated the existence of at least three WWS loci [92]. A candidate-gene approach in combination with homozygosity mapping was subsequently carried out in 15 consanguineous families with WWS [92]. On the basis of previous work on another CMD, the gene encoding protein O-mannosyl transferase 1 (*POMT1*) was chosen as a candidate gene. Analysis of the locus for *POMT1* revealed homozygosity in 5 of 15 families. Sequencing of the *POMT1* gene revealed mutations in 6 of the 30 unrelated patients with WWS. A similar homozygosity mapping approach reported in 2005 [93] identified WWS patients with mutations in the gene encoding *POMT2*. Homozygosity was found for the *POMT2* locus at 14q24.3 in 4 of 11 consanguineous WWS families; homozygous *POMT2* mutations were present in two of these families as well as in one patient from another cohort of six WWS families. Mutations in four glycogenes are currently known to cause WWS, i.e., the genes encoding *POMT1*, *POMT2*, fukutin and fukutin related protein (FKRP) [94]. These four genes account for approximately one third of the WWS cases indicating that other WWS genes remain to be discovered [93].

Homozygosity mapping methods were also used in the discovery of the defective β 1,3-glycosyl transferase glycogene in Peters'-plus syndrome (see above) [25], of the V-type H⁺ ATPase-dependent CDG (see above) [60,62], and of the role of a mutant oligosaccharyltransferase subunit in autosomal-recessive nonsyndromic mental retardation [10,11]. Homozygosity mapping is a powerful method of gene discovery if consanguineous families are available. The biochemical methods that served so well in the early days of CDG discovery are often not successful in the more complex "congenital glycosylation diseases" but will remain an important part of the tool box to understand the mechanisms of action and biology of the glycogenes being discovered by other methods.

Many patients with "congenital glycosylation diseases" have been reported in which the function of the mutant gene is not known or in which no gene locus has as yet been identified [7,8,95-97]. For example, three CMD genes have no known function: fukutin [98], fukutin-related protein (FKRP) [99] and LARGE [100]. A long-standing puzzle is hereditary erythroblastic multinuclearity with a positive acidified-serum lysis test (HEMPAS; congenital dyserythropoietic anemia type II). HEMPAS presents as a relatively mild genetic dyserythropoietic anemia caused by an unknown glycosylation defect [101-103]. Erythrocyte membrane glycoproteins, such as band 3 and band 4.5, which are normally glycosylated with polylactosamines lack these carbohydrates in

HEMPAS. Polylactosamines accumulate as glycolipids in HEMPAS erythrocytes. Analysis of *N*-glycans from HEMPAS erythrocyte membranes revealed a series of incompletely processed *N*-glycan structures. Linkage analysis of HEMPAS cases from southern Italy have excluded two long-suspected candidate genes (encoding α -mannosidase II and GlcNAc-transferase II) as the causative gene, but identified a gene on chromosome 20q11 [104-106].

The problem of accurate diagnosis of "congenital glycosylation diseases" has become more difficult due to the rapid rate of discovery of new glycogenes that do not fit neatly into the pattern of genes involved primarily in *N*-glycan biosynthesis. Some patients do not show an abnormal serum transferrin, the classic screening test for CDGs, e.g., autosomal-recessive nonsyndromic mental retardation associated with a mutant oligosaccharyltransferase, defects in the GDP-fucose and CMP-Sia transporters and in glucosidase I, and in some cases of phosphomannomutase deficiency (CDG-Ia).

The diversity of proteins that can be affected by a glycogene mutation results in defective development of multiple organ systems (brain, gastrointestinal tract, liver, vision, and the endocrine and immune systems). The biochemically and clinically heterogeneous pictures of these patients indicate the importance of normal glycosylation in these organs and present difficult diagnostic problems to the clinician. It is clear that the current diagnostic approaches have to be expanded and that some of these methods may have to target only one or a few glycogenes.

There are many surprises waiting for us and we should consider a "congenital glycosylation disease" in every new clinical presentation and also in all known clinical syndromes in which the basic defect remains unknown.

Treatment

A serious problem for CDG and other glycogene-deficient patients, many of whom are desperately non-functional, is the lack of effective treatments. Only two CDG subtypes, CDG-Ib and CDG-IIc, have been treated successfully [107]. In CDG-Ib, alimentary addition of mannose bypasses the defective step (conversion of fructose-6-phosphate to mannose-6-phosphate) by allowing for formation of mannose-6-phosphate via the action of hexokinase. These children show remarkable improvement with therapy, probably because there are no detectable neuronal abnormalities in this disease. CDG-IIc, also known as leukocyte adhesion deficiency type II (LAD-II), stems from a defective membrane transport of GDP-L-Fuc. Alimentary supplementation with L-fucose in one CDG-IIc patient corrected the immunological defect and, surprisingly, also improved the neurological symptoms. However, treatment was ineffective in three other CDG-IIc patients probably due to differences in mutations between the patients.

Although mannose treatment of fibroblasts from CDG-Ia patients, the most common form of CDG, corrects altered *N*-glycosylation due to the absence of phosphomannomutase (the enzyme that converts Man-6-phosphate to Man-1-phosphate) [90,91,108], oral administration of Man to these patients is unfortunately not effective

[107]. Oral administration of Man-1-phosphate is also not effective because this material is not transported across the cell membrane. Attempts have been made to synthesize cell-permeable compounds that would be converted to free Man-1-phosphate upon entry into the cell [107]. Although such compounds correct the biochemical phenotype of CDG-Ia fibroblasts, the compounds synthesized to date are too unstable and too toxic to be useful in the clinic. Another approach to therapy is enzyme replacement, i.e., systemic delivery of normal versions of the mutant enzyme (e.g., phosphomannomutase) [107].

There is currently a lack of Type I CDG animal models that can be used to test putative therapeutic agents. Complete lack of *N*-glycosylation is lethal in all eukaryotes and null mutations in the glyco-genes defective in Type I CDGs are embryonic lethal in humans and mice. All Type I CDG patients have hypomorphic mutations and retain the ability to synthesize reduced amounts of normal *N*-glycans. Animal models for the Type I CDGs would therefore need to be hypomorphic mutants.

Therapy of CDG-Ib patients is effective partly because these patients do not have the severe abnormalities present in most other forms of Type I CDG (psychomotor retardation, retinopathy, and muscular hypotonia). This damage is probably established during fetal development and therefore may not be reversible with postpartum treatment. However, recent studies on neuroplasticity suggest that the brain and nervous system are capable of considerable repair in both children and adults.

Hyperglycosylation strategies have been proposed as therapeutic interventions in the CMDs (α -dystroglycanopathies) [20,109-111]. Recent work has demonstrated that the overexpression of either one of two related glyco-genes, LARGE and LARGE2, results in the hyperglycosylation of α -dystroglycan and resultant restoration of normal α -dystroglycan ligand binding. The mechanism of this important therapeutic effect has not been determined.

Conclusions

We have attempted in this relatively brief review to present a picture of the highly complicated nature of glycan structure and assembly and the devastating effects of glyco-gene malfunctions on the human body. Whereas spectacular advances have been made in recent years in the discovery of new glyco-genes and the phenotypes of the diseases resulting from defects in these genes, a great deal of work remains to be done especially in the areas of diagnosis and treatment.

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