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Special article

Alteration of protein glycosylation in liver diseases☆

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Chronic liver diseases are a serious health problem worldwide. The current gold standard to assess structural liver damage is through a liver biopsy which has several disadvantages. A non-invasive, simple and non-expensive test to diagnose liver pathology would be highly desirable. Protein glycosylation has drawn the attention of many researchers in the search for an objective feature to achieve this goal. Glycosylation is a posttranslational modification of many secreted proteins and it has been known for decades that structural changes in the glycan structures of serum proteins are an indication for liver damage. The aim of this paper is to give an overview of this altered protein glycosylation in different etiologies of liver fibrosis / cirrhosis and hepatocellular carcinoma. Although individual liver diseases have their own specific markers, the same modifications seem to continuously reappear in all liver diseases: hyperfucosylation, increased branching and a bisecting *N*-acetylglucosamine. Analysis at mRNA and protein level of the corresponding glycosyltransferases confirm their altered status in liver pathology. The last part of this review deals with some recently developed glycomic techniques that could potentially be used in the diagnosis of liver pathology.
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1. Introduction

Over the years it has become apparent that changes in protein glycosylation play an important role in the pathogenesis and progression of various liver diseases. In order to comprehend the relationship between glycosylation and liver diseases, some basic insight into this complex phenomenon is necessary. Therefore, a short introduction is provided, which covers basic biochemical aspects of glycosylation (see Fig. 1).

In general, glycosylation consists of co- and post-translational modification steps, in which individual glycans are added to proteins translated into the endoplasmic reticulum (ER), forming oligosaccharide chains. This is an enzyme-directed and a site-specific process. Two types of protein glycosylation exist: *N*-glycosylation to the amide nitrogen of asparagine (Asn) side chains and *O*-glycosylation to the hydroxyl groups of serine (Ser) and threonine (Thr) side chains. Most proteins in human serum contain one or more *N*-linked glycans, with the exception of albumin and C-reactive

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Abbreviations: ER, endoplasmic reticulum; Asn, asparagine; Ser, serine; Thr, threonine; GlcNAc, *N*-acetylglucosamine; HCC, hepatocellular carcinoma; ALD, alcoholic liver diseases; CDT, carbohydrate-deficient transferrin; ST6GalI, β-galactoside α2,6 sialyltransferase; TSA, total sialic acid; FSA, free sialic acid; Hp, haptoglobin; Con A, Concanavalin A; Apo E, Apolipoprotein E; GnT-III, *N*-acetylglucosaminyltransferase III; LAL, lysosomal acid lipase; HPLC, high performance liquid chromatography; MALDI-TOF, matrix assisted laser desorption/ionization time-of-flight; AGP, α1-acid glycoprotein; GnT-V, *N*-acetylglucosaminyltransferase V; HBx, HBV x-protein; α1-6 FT, α1-6 fucosyltransferase; LCA, lens culinaris agglutinin; E-PHA, Phaseolus vulgaris: erythroagglutinating; L-PHA, Phaseolus vulgaris: leuco-agglutinating; AAT, α-1-antitrypsin; TF, transferrin; DEN, diethylnitrosamine; DSA-FACE, DNA sequencer-assisted fluorophore-assisted carbohydrate electrophoresis; IgG, immunoglobulin G.

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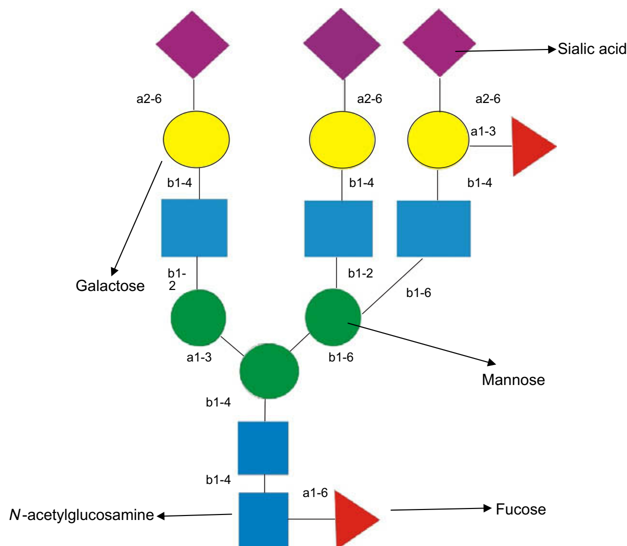

Fig. 1. *N*-Glycan with indication of the individual monosaccharides and the different binding types between the monosaccharides. a1–3: alpha 1–3 binding; a1–6: alpha 1–6 binding; a2–6: alpha 2–6 binding; b1–2: beta 1–2 binding; b1–4: beta 1–4 binding; b1–6: beta 1–6 binding.

protein. *O*-glycans are found in mucins, which are abundantly present on mucosal surfaces and saliva. Most modifications of glycosylation in liver diseases that have been studied affect *N*-glycosylated proteins and these will primarily be discussed. The *N*-oligosaccharide chain is attached to asparagine occurring in the tripeptide sequence Asn-X-Ser, in which X could be any amino acid except proline [1–4].

The biosynthesis of *N*- and *O*-glycans take place in the ER and the Golgi apparatus and it can be roughly divided in three steps [5]. The first step in *N*-glycosylation is carried out in the ER and consists of the formation of an oligosaccharide-lipid complex containing three glucoses, nine mannoses and two *N*-acetylglucosamines (GlcNAc). The lipid portion (dolichol) acts as a carrier molecule. The second step is the transfer of the oligosaccharide portion to a growing nascent polypeptide and the simultaneous removal of the three glucose residues and 1 mannose residue. The premature glycoprotein is then mediated to the Golgi apparatus where residual monosaccharides are removed until a $(mannose)_5(GlcNAc)_2$ heptasaccharide chain is formed. From here on, specific glycosyltransferases (Table 1 and [9–11]) and glycosidases will further modify the core-structure by adding or removing monosaccharides, respectively [6]. Glycosyltransferases make use of nucleotides sugars (donors) in order to incorporate monosaccharides into the *N*-glycan. Glycosidases on the other hand, catalyze the hydrolysis of the glycosidic linkage. In addition, glycans can have various branches (2–5) and are termed bi-, tri-, tetra- and penta-antennary, respectively. The enzymatic addition and removal of monosaccharides allow the formation of glycans with various length, composition and structure [7,8].

The functional role(s) of the *N*-linked carbohydrate moieties of glycoproteins is/are often not well understood. However, glycosylation is a necessity in the correct folding of certain proteins. Aberrant protein folding affects various physiochemical and functional properties of proteins: protein stability, protein solubility, protein inter-/intracellular transport and half-life in blood. The opposite can also be true. Carbohydrate moieties on glycoproteins also fulfill a role in intercellular contact and communication, which is an important aspect of host immunity as well as cancer [12–15].

The liver contains various receptors on sinusoidal and hepatocyte surfaces. A lot of proteins that bind to these receptors rely on their carbohydrate moieties. Besides changes in glycosylation patterns, the changes in receptor concentration and distribution also occur in various chronic liver diseases (cirrhosis, hepatocellular carcinoma (HCC) and alcoholic liver diseases

Table 1
Glycosyltransferases that are important in the modification of *N*-glycans on serum proteins.

Glycosyltransferase family	Mammalian glycosyltransferases	Substrate specificity
Fucosyltransferases [9]	α1,2-Fucosyltransferase*	α1,2 Linkage to the terminal Gal residue in *N*- or *O*-glycans
	α1,3/4-Fucosyltransferase*	α1,3 or α1,4 Linkage to GlcNAc in GlcNAc-Gal structures
	α1,6-Fucosyltransferase	α1,6 Linkage to the innermost (core) GlcNAc in *N*-glycans
N-Acetylglucosaminyltransferases [10]	*N*-Acetylglucosaminyltransferase III	GnT-III catalyzes the addition of GlcNAc via β1-4 linkage to the β-mannose core of *N*-glycans
	N-Acetylglucosaminyltransferase IV*	GnT-IV catalyzes the formation of GlcNac-β1-4 branches at the Man α1-3 side of the trimannosyl core of *N*-glycans
	N-Acetylglucosaminyltransferase V	GnT-V catalyzes the formation of GlcNAc-β1-6 branches at the Man α1-6 side of the trimannosyl core of *N*-glycans
Sialyltransferases [11]	α2,6-Sialyltransferase*	ST6GalI mediates the transfer of sialic acid residue with an α2,6-linkage to a terminal Gal residue
	α2,3-Sialyltransferase*	ST3GalI mediates the transfer of sialic acid to a Gal residue of a terminal Galβ1-3GalNAc oligosaccharide

* Different glycosyltransferases of this class are known.

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